159–160 °C, on recrystallization from EtOAc–petroleum ether. Anal. ($C_6H_5N_3O_3$) C, H, N.

Acknowledgment. We wish to express our gratitude to Dr. Ko Arima, Director of these Laboratories, and to Dr. K. Murayama, Assistant Director, for their encouragement and discussion. We are also indebted to Messrs. T. Sakamoto and K. Sato and Mrs. F. Saito for their technical assistance.

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3-Aminotetrahydrocarbazoles as a New Series of Central Nervous System Agents

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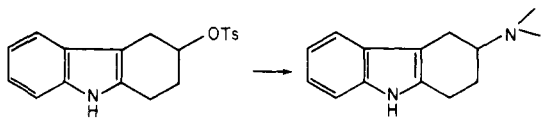
3-Dimethylamino-1,2,3,4-tetrahydrocarbazole, a structurally modified tryptamine, prevented amphetamine-induced stereotyped behavior in rats and prevented reserpine-induced ptosis in mice. Further study of this compound and a number of substituted derivatives indicated that either imipramine-like or chlorpromazine-like profiles were obtainable by changing substituents and their positions.

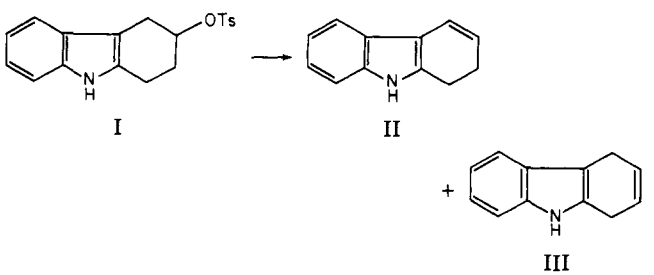
Our work began with the premise that 3-aminotetrahydrocarbazoles might have central nervous system activity paralleling the tryptamine types. The basic nitrogen present in these compounds is fixed neither "up" as in lysergic acid nor "down" as in reserpine.[1] Our first compound, 3-dimethylamino-1,2,3,4-tetrahydrocarbazole, was interesting because it prevented reserpine-induced ptosis in mice and amphetamine-induced stereotyped behavior in rats. Additional work suggests that the compound exhibited imipramine-like effects on cortical evoked potentials in cats and antidepressant activity in man.[2] We elaborated on the series and found that some of the members exhibited only imipramine-like activity, whereas others exhibited only chlorpromazine-like activity.

Synthesis. 3-Substituted amino-1,2,3,4-tetrahydrocarbazoles have been prepared by the usual Fischer cyclization. In order to prepare a number of N-substituted derivatives for a study of the effect of varying the side chain, the initial synthetic approach involved displacement of the 3-tosyloxy group with a base. This enabled us to

method A



prepare a variety of N-substituted 3-aminotetrahydrocarbazoles; the compounds thus prepared are included in Table I. This method suffers from the drawback that elimination in varying amounts also occurs in both possible directions. Compound II was presumed to be formed since



I II III

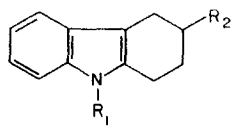
Table I. Comparison of Profiles of Activity of 3-Dimethylaminotetrahydrocarbazoles with Chlorpromazine and Imipramine

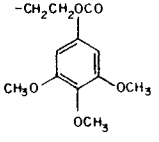
	Prevention of reserpine-induced ptosis, mg/kg ip	Prevention of *d*-amphetamine stereotyped behavior in rats, mg/kg po
3-Dimethylamino-tetrahydrocarbazole (3)	Active at 10, 30, 50	Active, ED_{50} = 10.3 (7.9-13.9)
3-Dimethylamino-5-methyltetrahydro-carbazole (60)	Active at 10, 30, 50	Inactive at 32
3-Dimethylamino-6,8-difluorotetrahydro-carbazole (48)	Inactive at 30, 50	Active, ED_{50} = 1.4 (0.8-2.4)
Chlorpromazine	Inactive at 1, 10, 30, 50	Active, ED_{50} = 8.6 (5.6-13.3)
Imipramine	Active at 10, 30, 50	Inactive at 32

during isolation of these side products, highly colored oils finally result in a stable crystalline mixture on which a mass spectrum shows mass ions for both carbazole (*m/e* 167) and dihydrocarbazole (*m/e* 169). The NMR spectrum shows four allylic hydrogens and two ethylenic hydrogens and an excess of aromatic hydrogens approximating 20% of carbazole in the mixture. The UV spectrum of the mixture run against a blank containing 20% carbazole is similar to 2,3-dimethylindole, indicating that the predominant component in the mixture is III. Evidently any II which is formed is oxidized to carbazole during the work-up giving a mixture of 80% III and 20% carbazole, indicating that elimination of the tosyloxy group leads preferentially to III.

It became apparent that **3** (Table II) was the most interesting CNS compound in the series and this compound was studied in great detail. For reasons outlined below, in our continuing synthetic work the basic ketone used was generally 4-dimethylaminocyclohexanone (IV)[3]

Table II. Tetrahydrocarbazoles Unsubstituted on the Aromatic Ring

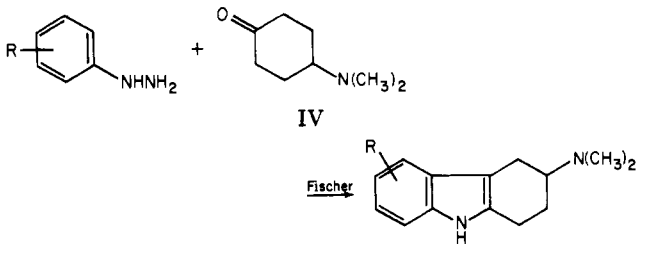


No.	R_1	R_2	Mp, °C	Formula	Method	% yield	Recrystn solvent	Ptosis prevention in mice, MED, mg/kg ip
1	H	$-NH_2$	298-299	$C_{12}H_{14}N_2 \cdot HCl$	B	50	Methanol	30, active
2	H	$-NHCH_3$	134-136	$C_{13}H_{16}N_2 \cdot HCl$	A	63	Ether	30, active
3	H	$-N(CH_3)_2$	138-142	$C_{14}H_{18}N_2$	B	81	Ether-hexane	10, active
4	H	$-NHC_2H_5$	128-129	$C_{14}H_{18}N_2$	A	20	Ether	10, inactive
5	H	$-NH$-*n*-C_3H_7	124-125	$C_{15}H_{20}N_2$	A	43	Ether	10, inactive
6	H	$-NH$-*n*-C_4H_9	110-111	$C_{16}H_{22}N_2$	A	45	Ether	10, inactive
7	H	$-NHCH_2C_6H_5$	109-115	$C_{19}H_{20}N_2$	A	46	Ether-pentane	*a*
8	H	-c-NC_4H_8	200-205	$C_{16}H_{20}N_2$	A	32	DMF-ether	50, inactive
9	H	-c-NC_5H_{10}	104-115	$C_{17}H_{22}N_2$	A B	54 70	Ether	50, inactive
10	H	-c-$N(CH_2CH_2)_2O$	131-134	$C_{16}H_{20}N_2O$	A	51	Trituration with ether	50, inactive
11	H	-c-$N(CH_2CH_2)_2N$-C_6H_5	230-232 dec	$C_{22}H_{25}N_3$	A	78	Aqueous DMF	50, inactive
12	H	$-NHCH_2CH_2N(C_2H_5)_2$	106-107	$C_{18}H_{27}N_3$	A	40	2-Propanol-pentane	50, inactive
13	H	$-NHCOCH_3$	165-167	$C_{14}H_{16}N_2O$	B	35	Dilute alcohol	10, inactive
14	CH_3-	$-N(CH_3)_2$	300	$C_{15}H_{20}N_2 \cdot HCl$	A	41	Chromatography with ether-pentane	10, inactive
15	$C_6H_5CH_2-$	$-N(CH_3)_2$	81-83	$C_{21}H_{24}N_2$	A	24	Chromatography with ether-pentane	10, inactive
16	*p*-$ClC_6H_4CH_2-$	$-N(CH_3)_2$	107-109	$C_{21}H_{23}ClN_2$	D	47	Ether-hexane	10, inactive
17	$(CH_3)_2NCH_2CH_2-$	$-N(CH_3)_2$	270 dec	$C_{18}H_{27}N_3 \cdot HCl$	A	60	MeOH-*i*-PrOH	10, inactive
18	$(CH_3)_2NCH_2CH_2CH_2-$	$-N(CH_3)_2$	302-305 dec	$C_{19}H_{29}N_3 \cdot 2HCl$	D	81	Methanol	10, inactive
19		$-N(CH_3)_2$	127-131	$C_{26}H_{32}N_2O_5$	D	17	Ethyl acetate	50, inactive
20	$-CH_2COOC_2H_5$	$-N(CH_3)_2$	242-243	$C_{18}H_{24}N_2O_2 \cdot HCl$	D	28	2-Propanol	10, active
21	$-CH_2COOH$	$-N(CH_3)_2$	316-319	$C_{16}H_{20}N_2O_2 \cdot HCl$	Acid hydrol	74	Ethanol-water	50, inactive
22	$-C_2H_5$	$-N(CH_3)_2$	292-293 dec	$C_{16}H_{22}N \cdot HCl$	C	75	Ethanol-methanol	30, active
23	$-CH_2CH{=}CH_2$	$-N(CH_3)_2$	277-279	$C_{17}H_{22}N_2 \cdot HCl$	C	58	Methanol	50, inactive
24	$-CH_2CH_2COOC_2H_5$	$-N(CH_3)_2$	259-261	$C_{19}H_{26}N_2O_2 \cdot HCl$	C	70	Ethanol-water	50, inactive
25	$-CH_2CH_2COOH$	$-N(CH_3)_2$	304-305	$C_{17}H_{22}N_2O_2 \cdot HCl$	*b*	35	Ethanol	50, inactive

[a] No testing done. [b] KOH hydrolysis of nitrile.

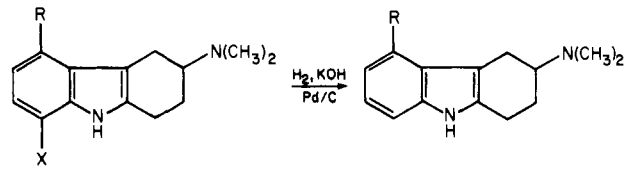
while a variety of substituents was put on the benzene ring moiety. This was for the most part quite simple synthetically since many substituted phenylhydrazines are readily available. These compounds are presented in the accompanying tables. The 6-hydroxy compound **32**, a

method B

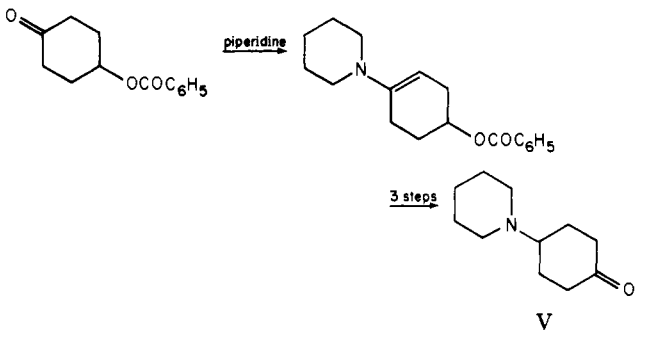


bufotenine analogue, was made through the 6-benzyloxy compound **29** by debenzylation. Using method B, ortho-substituted hydrazines gave 8-substituted tetrahydrocarbazoles while para-substituted hydrazines gave 6-substituted derivatives. With meta-substituted hydrazines, a mixture of 5 and 7 derivatives resulted in about a 1:2 ratio. These were separable by successive recrystallizations of either the bases or the hydrochlorides or both, the success of the separation being readily followed with gas chromatography. This difficulty was circumvented by blocking one of the ortho positions by means of halogen. Dehalogenation then afforded the pure 5-substituted isomer.

method C



The procedure of method B was used only with three other amino ketones—4-(1-piperidyl)cyclohexanone (V), 4-acetamidocyclohexanone (VI), and *N*-methyl-4-benzamidocyclohexanone (VII). The former (V) was made through the enamine. The latter two (VI and VII) were prepared by oxidation of the respective cyclohexanols with



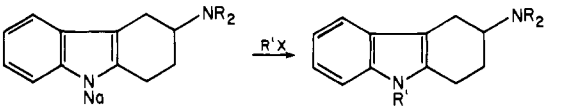
V

chromium trioxide. Table IV contains compound made with these ketones.

In Table II are also shown 9-substituted derivatives (**15–25**). These were made by method A where properly substituted phenylhydrazines were available. A 9-substituted 3-tosyloxy derivative was made and the tosyloxy group was replaced with a base. Otherwise the 3-substituted aminotetrahydrocarbazole was treated with sodium hydride in dimethylformamide and alkylated (method D).

Another synthetic approach which we had hoped to pursue was dependent on the oxidation of 3-hydroxytetrahydrocarbazole to 3-oxotetrahydrocarbazole. Procedures previously used[4] for the preparation of this ketone had not proved particularly satisfactory. Out of our work, there was developed a moderately successful procedure using cyclohexanone in the presence of Raney nickel;[5] this is described below. Further, one of our oxidation attempts which gave rather surprising results was oxidation of the alcohol with chlorosuccinimide. This resulted in a vigorous and rapid oxidation of a 3-hydroxytetrahydrocarbazole to a carbazole.

method D



Results and Discussion

Table I shows results for three interesting tetrahydrocarbazoles, imipramine, and chlorpromazine. 3-Dimethylaminotetrahydrocarbazole (**3**) prevented both reserpine-induced ptosis and amphetamine-induced stereotyped behavior. The 5-methyl derivative (**60**) prevented reserpine-induced ptosis but did not prevent amphetamine-induced stereotyped behavior. 6,8-Difluoro-3-dimethylaminotetrahydrocarbazole (**48**) prevented *d*-amphetamine-induced stereotyped behavior but did not prevent reserpine-induced ptosis. In the amphetamine test, the 6,8-difluoro compound (**48**) was about twice as potent as either of the monosubstituted derivatives (**33** and **35**). We see that some of the compounds appear to exhibit both chlorpromazine-like and imipramine-like activity, others only chlorpromazine-like, and others only imipramine-like activity.

Tables II–V show the effects of tetrahydrocarbazoles in preventing reserpine-induced ptosis in mice. Table II shows 3-aminotetrahydrocarbazoles where the aromatic ring is unsubstituted. Amino, methylamino, and dimethylamino were the basic side chains yielding greatest potency (compounds 1–**3**). Other basic side chains such as phenylpiperazine (11) which give potent compounds in the tryptamine series[6] were inactive in the tetrahydrocarbazole series. Substitution on the indole nitrogen for the most part decreased the potency of the 3-dimethylamino compounds.

Table III shows 3-dimethylaminotetrahydrocarbazoles with substituents in the 6 and 8 positions. Substitution of hydroxy, methoxy, and fluoro substituents (e.g., **32**, **28**, and **33**) on the benzene ring resulted in loss of potency. With the exception of the 8-ethyl (**34**) and 8-propyl (**44**) substituted compounds, none of the 3-dimethylaminotetrahydro compounds were as potent as the original unsubstituted 3-dimethylaminotetrahydrocarbazole (**3**).

Table IV shows 6,8-difluorotetrahydrocarbazoles with different substitutents on the 3 position. None of the compounds were active.

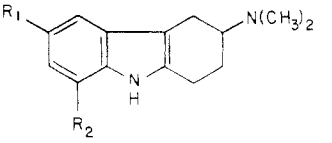
Table V shows 3-dimethylaminotetrahydrocarbazoles and 3-monomethylaminotetrahydrocarbazoles with substituents in the 5, 7, or 8 positions. None of the compounds were more potent than the original unsubstituted 3-dimethylaminotetrahydrocarbazole (**3**).

Experimental Section

All melting points were determined in an open capillary tube in a bath and are uncorrected. Gas chromatographic work was done on a Hewlett-Packard 5750 using an OV 17 column at 160 °C. All analyses (C, H, and N) were within ±0.4% of the theoretical values.

1,2,3,4-Tetrahydro-3-tosyloxycarbazole (I). A mixture of 9.3 g of 1,2,3,4-tetrahydro-3-hydroxycarbazole (0.05 mol), 10.5 g of *p*-toluenesulfonyl chloride (0.055 mol), and 25 mL of pyridine was shaken together with moderate external cooling so that the

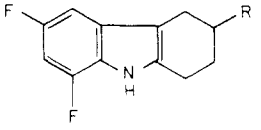
Table III. 3-Dimethylaminotetrahydrocarbazoles with Substituents in the 6 and 8 Positions



No.	R_1	R_2	Mp, °C	Formula	Method	% yield	Recrystn solvent	Ptosis prevention in mice, MED, mg/kg ip
26	Me	H	116-118	$C_{15}H_{20}N_2O$	A	7	Ether-pentane	50, inactive
27	OCH_3	H	126-128	$C_{15}H_{20}N_2O$	B	65	Ethyl acetate	10, inactive
28	OCH_3	7-OCH_3	167-169	$C_{16}H_{22}N_2O_2$	B	10	Ethyl acetate	50, inactive
29	$OCH_2C_6H_5$	H	209-212	$C_{21}H_{24}N_2O\cdot HCl$	B	67	Ethanol	50, inactive
30	H	Me	285-287	$C_{15}H_{20}N_2\cdot HCl$	B	27	Ethanol	50, inactive
31	H	Cl	154-157	$C_{14}H_{17}ClN_2$	B	30	Ethyl acetate	50, inactive
32	OH	H	202-204	$C_{14}H_{18}N_2O$	Pd redn	50	Ethyl acetate	50, active
33	F	H	264-268	$C_{14}H_{17}FN_2\cdot HCl$	B	68	2-Propanol	50, inactive
34	H	C_2H_5	282-285	$C_{16}H_{22}N\cdot HCl$	B	38	Ethanol	10, active
35	H	F	298-302	$C_{14}H_{17}FN\cdot HCl$	B	44	2-Propanol	50, inactive
36	CH_3	CH_3	312-314	$C_{16}H_{22}N_2\cdot HCl$	B	75	Methanol	50, inactive
37	OC_6H_5	H	235-240 dec	$C_{20}H_{22}N_2O\cdot HCl$	B	74	2-Propanol	50, inactive
38	Cl	Cl	192-194	$C_{14}H_{16}Cl_2N_2$	B	64	Toluene	50, inactive
39	H	Br	136-137	$C_{14}H_{17}BrN_2$	B	75	Heptane	50, inactive
40	H	C_6H_5	131-134	$C_{20}H_{22}N_2$	B	65	2-Propanol	50, active
41	H	CF_3	77-80	$C_{15}H_{17}F_3N_2$	B	41	Heptane	50, inactive
42	H	OCH_3	194-195	$C_{15}H_{18}N_2O_2$	B	51	2-Propanol	50, inactive
43	COOH	H	315	$C_{15}H_{18}N_2O_2$	B	62	2-Propanol	50, inactive
44	H	*n*-Pr	242-244	$C_{17}H_{24}N\cdot HCl$	B	40	2-Propanol	10, active
45	H	SCH_3	136-139	$C_{15}H_{20}N_2S$	B	67	2-Propanol	50, inactive
46	H	$OCH_2C_6H_5$	252-254	$C_{21}H_{24}N_2O\cdot HCl$	B	74	Ethanol	50, inactive
47	H	OH	315-318	$C_{14}H_{18}N_2O\cdot HCl$	Pd redn	93	H_2O-ethanol	50, inactive
48	F	F	181-183	$C_{14}H_{16}F_2N_2$	B	45	Ethyl acetate	30, inactive
49	5-CH_3	F	182-184	$C_{15}H_{19}FN_2\cdot HCl$	B	18	2-Propanol	10, active
50	7-F	F	200-202	$C_{14}H_{16}F_2N_2$	B	26	Ethyl acetate	*a*
51	CH_3	7-CH_3	183-187	$C_{16}H_{22}N_2$	B	22	Hexane	50, active

[a] No testing done.

Table IV. 6,8-Difluorotetrahydrocarbazoles with Varying 3-Substituents



No.	R	Mp, °C	Formula	Method	% yield	Recrystn solvent	Ptosis prevention in mice, MED, mg/kg ip
52	$-NH_2$	300	$C_{12}H_{12}F_2N_2\cdot HCl$	B to produce acetamide followed by H_2SO_4 (20%) hydrol	27	2-Propanol	50, inactive
53	$-NHCH_3$	135-138	$C_{13}H_{14}F_2N_2$	B	35	Ethyl acetate	50, inactive
54	-c-NC_5H_{10}	290	$C_{17}H_{20}F_2N_2\cdot HCl$	B	40	Ethanol	50, inactive
55	$-N(CH_3)COC_6H_5$	212-214	$C_{20}H_{18}F_2N_2O$	B	40	2-Propanol	50, inactive
56	$-N(CH_3)CH_2C_6H_5$	137-139	$C_{20}H_{20}F_2N_2$	$LiAlH_4$ redn	84	2-Propanol	50, inactive

temperature did not rise above 35 °C. After standing 16 h, the reaction mixture was quenched in ice water and the product filtered off and washed with water, 2-propanol, and ether to give a compound: mp 148–151 °C; 16.0 g (94%). Anal. ($C_{19}H_{19}NO_3S$).

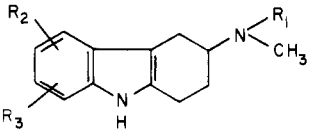
1,2,3,4-Tetrahydro-3-methylaminocarbazole (2). Method A. A mixture of 17.1 g (0.05 mol) of 1,2,3,4-tetrahydro-3-tosyloxycarbazole, 25.0 g of 40% aqueous methylamine, 200 mL of cellosolve, and 5.0 g of sodium bicarbonate was heated and stirred on a steam bath for 1 h. Removal of the solvent in vacuo followed by ether extraction and evaporation of the extract gave a solid residue. This was triturated with ether containing a small amount of pentane to give a product which was filtered off and thoroughly washed with ether: 5.1 g; mp 134–136 °C.

3-Dimethylamino-1,2,3,4-tetrahydrocarbazole (3). Method B. A suspension of 17.8 g (0.1 mol) of 4-dimethylaminocyclohexanone hydrochloride (IV) and 15.2 g (0.105 mol) of phenylhydrazine hydrochloride in 200 mL of absolute alcohol was stirred on a steam bath for 3 h. After cooling, the solids were filtered off and dissolved in water. The solution was made alkaline and extracted with ether. Most of the ether was removed in vacuo and the product precipitated with a little hexane. Filtering followed by hexane washing gave 18.2 g (85%), mp 138–141 °C.

Method A. A mixture of 91.2 g of 1,2,3,4-tetrahydro-3-tosyloxycarbazole (I) and 400 mL of liquid dimethylamine was heated in a shaking autoclave at 80–100 °C for 18 h. The reaction mixture was evaporated to remove excess base and the residue extracted with ether. Acidification of the extract with ethereal hydrogen chloride precipitated the salt which was filtered off. The filtrate was saved for further work-up. From the hydrochloride salt there was obtained 27.3 g of free base, mp 135–139 °C.

1,4-Dihydrocarbazole (III). Evaporation of the filtrate obtained above left 7.7 g of a nonbasic oil. This was redissolved

Table V. 3-Di- (or mono-) methylaminotetrahydrocarbazoles with Substituents in the 5 and 7 or 8 Positions



No.	R_1	R_2	R_3	Mp, °C	Formula	Method	% yield	Recrystn solvent	Ptosis prevention in mice, MED, mg/kg ip
57	CH_3	5-CH_3	8-CH_3	138–140	$C_{16}H_{22}N_2$	B	40	2-Propanol	30, active
58	CH_3	7-Cl	8-Cl	181–183	$C_{14}H_{16}Cl_2N_2$	B	69	2-Propanol	50, active
59	CH_3	5-Cl	8-OCH_3	304–307	$C_{15}H_{19}ClN_2O\cdot HCl$	B	37	Water	30, active
60	CH_3	5-CH_3	H	203–204	$C_{15}H_{20}N_2$	C	85[a]	Xylene	10, active
						B	17[b]		
61	CH_3	7-CH_3	H	134–138	$C_{15}H_{20}N_2$	B	34[b]	Ether	10, active
62	CH_3	5-CH_3	8-Cl	154–156, 167–169	$C_{15}H_{19}ClN_2$	B	40	2-Propanol	50, active
63	CH_3	5-F	H	168–170	$C_{15}H_{19}FN_2$	C	95	Benzene	10, active
64	CH_3	7-F	H	174–176	$C_{14}H_{17}FN_2$	B	58	2-Propanol	50, inactive
65	CH_3	5-CH_3	9-CH_3	318–320	$C_{16}H_{22}N\cdot HCl$	D	30	Water	50, active
66	CH_3	5-CH_3	7-CH_3	124–128	$C_{16}H_{22}N_2$	B	64	Heptane	50, active
67	CH_3	7-OH	H	286–288	$C_{14}H_{18}N_2O\cdot HCl$	B	48	Water–methanol	50, inactive
68	CH_3	5-C_2H_5	H	157–161	$C_{16}H_{22}N_2$	B	14	Cyclohexane	50, active
69	CH_3	5-CF_3	H	222–225	$C_{15}H_{17}F_3N_2$	B, C	70	None necessary	30, active
70	CH_3	5-CH_3	7-Cl	192–196	$C_{15}H_{19}ClN_2$	B	12	Ether	30, active
71	CH_3	5-Cl	7-CH_3	179–183	$C_{15}H_{19}ClN_2$	B	8	Ethyl acetate	10, active
72	CH_3	H	7-OCH_3	100–105	$C_{15}H_{20}N_2O$	B	22	Ether	30, active
73	CH_3	5-COOEt	H	114–116	$C_{17}H_{22}N_2O_2$	B	32	Heptane	30, active
74	H	H	7-CH_3	163–166	$C_{14}H_{18}N_2$	B	29[c]	Ether	50, active
75	H	5-CH_3	H	187–190	$C_{14}H_{18}N_2$	B	13[c]	Ethyl acetate	10, active

[a] Yield in catalytic dehalogenation. [b,c] Both compounds obtained from the same reaction mixture.

in ether and shaken with activated alumina and then with charcoal. The filtered ethereal solution was concentrated to a small volume and the precipitated crystals were collected and washed with cold ether giving 5.5 g of solid, mp 210–215 °C. Recrystallization from benzene afforded 5.0 g of solid, mp 222–224 °C. Spectral analysis indicated the product to be contaminated with approximately 20% carbazole: mass spectrum m/e 169 (M^+), 168 ($M^+ - 1$), 167 (M^+ carbazole); NMR (Me_2SO-d_6) 3.38 (m, 4, H at C_1 and C_4), 6.03 (m, 2, H at C_2 and C_3), 6.85–8.34 (m, 6, aromatic protons of B and 20% carbazole impurity), 10.7–11.3 (br, 1, NH); UV (95% C_2H_5OH) (the reference cell contained authentic carbazole in a concentration equal to 20% of the concentration of the sample) 226.5 nm (ε 31 730), 283 (6483), 290 (5495).

3-Dimethylamino-1,2,3,4-tetrahydro-5-methylcarbazole (60). A mixture of 2.0 g of 8-bromo-3-dimethylamino-1,2,3,4-tetrahydro-5-methylcarbazole, 1.0 g of potassium hydroxide in 2 mL of water, and 1.0 g of 10% palladium on carbon in 100 mL of methanol was shaken on a Parr hydrogenator for 0.5 h under 50 psi of hydrogen pressure. Filtration and evaporation gave a solid which was water washed and recrystallized from toluene giving 1.3 g of product, mp 202–204 °C. The chloro compound dehalogenated equally well.

3-Dimethylamino-1,2,3,4-tetrahydro-5- (and 7-) methylcarbazole (60 and 61). A Fischer cyclization was run in the usual way with *m*-tolylhydrazine hydrochloride (0.2 mol) and 4-dimethylaminocyclohexanone hydrochloride in alcohol. An ether extract of the product base was evaporated to give an oil which soon crystallized to a solid: 6.4 g; mp 130–160 °C. Trituration with ether left a solid, mp 190–203 °C, which on chromatographic purification on alumina using ether–chloroform combinations gave a material which melted at 202–204 °C. This was identical with **60** obtained above. The ether extract was also purified on alumina giving 12.5 g (**61**), mp 134–138 °C. GC showed this to be contaminated with 6% of **60**.

3-(Dimethylamino)-9-(dimethylaminoethyl)-1,2,3,4-tetrahydrocarbazole (17). To 6.7 g (0.031 mol) of **3** in 75 mL of dry DMF was added 1.35 g of 56% sodium hydride. The mixture was stirred and heated on a steam bath while 3.37 g of dimethylaminoethyl chloride in 10 mL of benzene was dripped in. After heating 2 h, the reaction mixture was cooled, diluted with water, and extracted with ether. The ether solution was decolorized on an alumina column. The elute was treated with ethereal hydrogen chloride and the precipitate dissolved in methanol. It was crystallized by adding ethanol and boiling off the methanol yielding 5.7 g as the hydrochloride decomposing at 270 °C.

4-Piperidinylcyclohexanone (V). Equimolar amounts of piperidine and 4-benzoyloxycyclohexanone were refluxed under a Dean-Stark trap until no more water was evolved. The solvent was removed and the enamine was reduced in alcohol using 10% palladium on carbon. Reduction was rapid and complete. The oil which resulted was hydrolyzed with 20% aqueous alcoholic potassium hydroxide. The nearly theoretical crude piperidinocyclohexanol resulting at this point was oxidized with chromic oxide in dilute acetic acid at room temperature overnight. Extraction of the product gave an overall yield of 24.2 g, bp 143–153 °C (10 mm), from a 0.2-mol run. However, the mass spectrum showed this to be approximately 75% ketone and 25% alcohol. This mixture was used in the Fischer reaction.

Carbazole from 3-Hydroxy-1,2,3,4-tetrahydrocarbazole. A mixture of 1.87 g of 3-hydroxy-1,2,3,4-tetrahydrocarbazole and 1.34 g of *N*-chlorosuccinimide in 15 mL of acetone was shaken to give an immediate and vigorous reaction. Water was added and crystals were filtered off. These crystals (1.55 g) melted at 235 °C and after recrystallization from benzene, the melting point rose to 242 °C. This was identical with carbazole.

1,2,3,4-Tetrahydro-3-oxocarbazole. Raney nickel (30 g) was well washed to remove base and then azeotroped with toluene (500 mL) to remove water.[5] There was added 1,2,3,4-tetrahydro-3-hydroxycarbazole (23.5 g) dissolved in cyclohexanone (250 mL) and the mixture was stirred at reflux for 20 h. After cooling and filtering, the filtrate was washed with dilute sodium hydroxide to remove 3-hydroxycarbazole. The toluene was taken off and pentane was added, precipitating 10 g of 1,2,3,4-tetrahydro-3-oxocarbazole contaminated with 10% of the starting alcohol.

Biological Methods. Biological prevention of reserpine-induced ptosis in mice was used an an index of antidepressant activity.[7] Male Swiss-Webster mice, 18–24 g, were injected intraperitoneally with test compounds at doses of 50, 30, 10, 1, and 0.5 mg/kg of the free base. An active compound was defined as one that produced a statistically significant decrease in reserpine-induced ptosis ($p < 0.05$, two-tailed value), whereas an inactive compound was defined as one that did not do so. For active compounds, the dose was decreased until an inactive dose was obtained. The lowest active dose was reported and was

defined as the minimum effective dose (MED). For inactive compounds, the highest inactive dose tested was reported.

Prevention of *d*-amphetamine-induced stereotyped behavior in rats was used as an index of antipsychotic activity. The test was a modification of that described previously.[8] Male Sprague–Dawley rats, 100–130 g, from Russell Roberts Farms were medicated orally with graded doses of test drugs 4 h before subcutaneous injection of *d*-amphetamine sulfate, 3.7 mg/kg of the free base. Oral dosing began at 32 mg/kg of the free base. One-minute observations were conducted 90, 100, and 110 min after injection of amphetamine. A rat was scored as affected by amphetamine if it exhibited licking, gnawing, biting, or repetitive head movements during any of the three observation periods. The ED_{50} values and confidence limits for antagonism were calculated.[9]

Pilot work was performed to obtain supplementary indexes of antipsychotic activity. To determine whether the compounds prevented apomorphine-induced emesis in dogs, a modification of a method described previously was used.[10] Compounds were injected intravenously 30 min before intravenous injection of apomorphine hydrochloride, 0.05 mg/kg of the free base.

Rhesus monkeys were medicated orally to determine whether the compounds produced a chlorpromazine-like pattern of activity consisting of catalepsy, ptosis, and taming.[6] Although accurate quantitative estimates of activity were not obtained in monkeys and dogs, results were consistent with those reported for the amphetamine test.

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Combined High Oxytocic with Negligible Antidiuretic and Pressor Activities in Multisubstituted Oxytocins

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Received August 24, 1976

Oxytocin analogues which combine high oxytocic activities with negligible antidiuretic and pressor activities have been studied. [4-Threonine,7-glycine]oxytocin, [1-(L-2-hydroxy-3-mercaptopropionic acid),4-threonine,7-glycine]oxytocin, and [1-(L-2-hydroxy-3-mercaptopropionic acid)]oxytocin were found to possess the following specific biological activities respectively: rat uterotonic, 270 ± 10, 337 ± 23, 1542 ± 18; avian vasodepressor, 8.6 ± 0.2, 50 ± 4, 1778 ± 25; rat pressor, mixed depressor/pressor, mixed depressor/pressor, 23.7 ± 0.4; rat antidiuretic, 0.002 ± 0.0008, 0.048 ± 0.005, 40.3 ± 2.4. The results are analyzed from a conformation–activity viewpoint in a continued attempt to evaluate the scope and limitations of this approach in comparison to structure–activity studies.

The amino acid residues in positions, 3, 4, 7, and 8 of neurohypophyseal hormones, oxytocin and vasopressin, comprise the corner positions of the two β turns which are important features of the peptide backbone structure in the proposed solution conformation of the hormones.[1] Consistent with the proposal that modifications of these corner positions would lead to the most dramatic as well as selective alterations of the biological activity profile of the hormones,[2] oxytocin analogues with substitutions in position 4 (e.g., ref 3 and 4) or 7 (ref 5a and references cited therein) show a marked dissociation of the smooth muscle and antidiuretic activities. Particularly noteworthy is the high ratio of rat uterotonic to antidiuretic activities characteristic of these analogues and also of [4-threonine]oxytocin[6] ([Thr^4]oxytocin)[7] which possesses an enhanced specific uterotonic activity as compared to oxytocin. This trend in the biological activity profile not only suggests that such analogues might be superior to oxytocin for the induction of labor in women ([Asu^{1,6},Gly^7]oxytocin is already being used under the name Statocin in Japan for this purpose[8]) but also raises expectations for the use of such analogues as contraceptive agents. The latter suggestion assumes, first, that the capacity of oxytocin to selectively stimulate the contractility of the human Fallopian tube in vivo at concentrations not affecting the nongravid uterus[9,10] can be extended to oxytocin analogues and, second, that the enhanced tubal muscular activity, which will increase the rate of ovum transport, will decrease the probability of successful fertilization and implantation.[11] Furthermore, any potentially useful analogue must totally lack or exhibit only negligible antidiuretic activity in order to prevent overhydration upon prolonged administration.

From a conformation–activity viewpoint, substitutions at more than one position in oxytocin—each substitution involving only a corner position of the β turns in the hormone—should result in selective modifications of the biological activity profile that reflect a summation of the changes seen with the individual monosubstituted compounds. However, substitutions at noncorner positions should not show this kind of selective additivity. In light of this assumption, with the high oxytocic activity of [Thr^4]oxytocin[6] and the negligible antidiuretic activity of [Gly^7]oxytocin,[5b] the synthesis and pharmacological study of [4-threonine,7-glycine]oxytocin ([Thr^4,Gly^7]oxytocin, **2**) appeared worthwhile. It should be noted that Manning had proposed earlier the synthesis of this compound on the basis of structure–activity studies.[12] Should the conformation–activity viewpoint be valid, [1-(L-2-hydroxy-3-mercaptopropionic acid),4-threonine,7-glycine]oxytocin ([Hmp^1,Thr^4,Gly^7]oxytocin, **4**), which has one additional structural change in a noncorner position (the hydroxyl group in position 1 when substituted into oxytocin causes an increase in all biological activities tested),