1,4,4a,10b-Tetrahydro-*N,N*-dimethyl-4-phenanthridinamines and 1,4,4a,5,6,10b-Hexahydro-*N,N*-dimethyl-4-phenanthridinamines

George Bobowski*, Barbara West and Diana Omecinsky

Parke-Davis Pharmaceutical Research Division,
Warner-Lambert Company,
2800 Plymouth Road,
Ann Arbor, Michigan 48105

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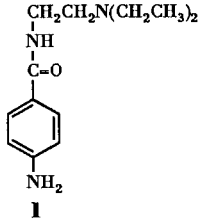
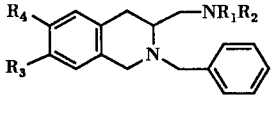
Synthetic procedures to prepare the title compounds are described. Diels-Alder cycloaddition of β-nitrostyrene derivatives **5** to *N,N*-dimethyl-1,3-butadien-1-amine, **6**, gave 5-aryl-*N,N*-dimethyl-6-nitro-2-cyclohexen-1-amines **7**. Reduction of **7** with zinc in acetic acid gave the diamino derivatives **8**. Schotten-Baumann acylation of **8** gave amides **9**. Treatment of **8** with alkyl isocyanates gave the aminourea derivatives **10**. Bischler-Napieralski cyclodehydration procudure of **9** and **10** gave 1,4,4a,10b-tetrahydrophenanthridinamines **3** and N^6-alkyl-1,4,4a,10b-tetrahydro-N^4,N^4-dimethyl-4,6-phenanthridinediamines **11**, respectively. Condensation of diamines **8** with aryl aldehydes under azeotropic conditions gave imines **12** which on treatment with acids yielded 6-aryl-1,4,4a,5,6,10b-hexahydro-*N,N*-dimethyl-4-phenanthridinamines **4**. The stereochemistry of these materials is assigned from the proton magnetic resonance studies.

J. Heterocyclic Chem., **29**, 33 (1992).

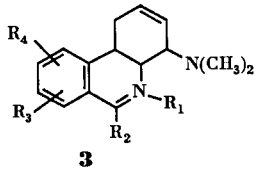
In the course of research on drugs with antiarrhythmic activity, it was found in our laboratories that 1,2,3,4-tetrahydro-*N*-alkyl-2-(phenylmethyl)-3-isoquinolinemethanamines **2** [1] exhibited good potency. Procainamide, **1** [2], one of the reference antiarrhythmic agents bears partial resemblance (at least in relation to the ethylenediamino fragment) to compound **2**. It was of interest to synthesize a series of compounds having general structures **3** and **4** which would incorporate the skeleton of **2** with the hope of enhancing biological activity.



1



2, R_1R_2 = H or alkyl
R_3R_4 = H, alkyl or alkoxy



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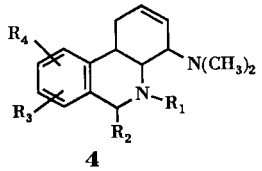
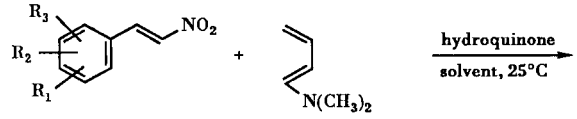
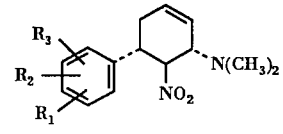


4

This paper describes synthetic methods for the target compounds **3** and **4** using readily obtainable starting materials and intermediates. The general method represents a Diels-Alder type [3] cycloaddition of β-nitrostyrenes **5** to *N,N*-dimethyl-1,3-butadien-1-amine **6** [4] in the presence of catalytic amounts of hydroquinone to give adducts **7** (Table I).

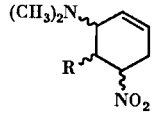


5 **6**



7

Theoretically, there is a possibility of the formation of other positional isomers (R = aromatic), such as **13**. In



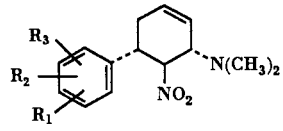
13

such a case, however, the ^{1}H nmr signal of the proton on the nitro-bearing carbon would be a complex multiplet instead of the doublet of doublets actually seen.

Reduction of the nitro group of **7** was effected using excess zinc dust either in glacial acetic acid (method A) or in methanolic hydrochloric acid (method B) [5] to give diamines **8** in fair yields (Table II). That the reduction proceeded through the expected hydroxylamine stage was demonstrated by the isolation of **14** in high yield when only one equivalent of zinc was used.

Table I

N,N-Dimethyl-6-nitro-5-(substituted phenyl)-2-cyclohexen-1-amines **7**

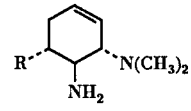


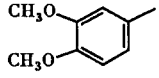
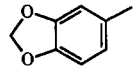
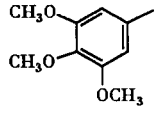
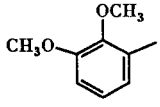
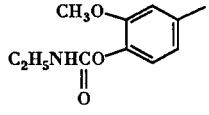
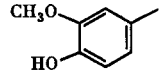
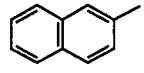
Compound	R_1	R_2	R_3	Mp °C	Crystallization Solvent	Yield	Formula	Analysis % Calcd./Found C	H	N
7a	3-OCH_3	4-OCH_3	H	143-144	Methanol	82	$C_{16}H_{22}N_2O_4$	62.72	7.24	9.14
								62.71	7.32	9.06
7b	3,4-OCH_2O-		H	147-148	Methanol	60	$C_{15}H_{18}N_2O_4$	62.05	6.25	9.65
								62.00	6.13	9.88
7c	3-OCH_3	4-OCH_3	5-OCH_3	150-151	2-Propanol	46	$C_{17}H_{24}N_2O_5$	60.70	7.19	8.33
								60.74	7.33	8.04
7d	2-OCH_3	3-OCH_3	H	133-134	2-Propanol	66	$C_{16}H_{22}N_2O_4$	62.72	7.24	9.14
								62.92	7.21	8.93
7e	3-OCH_3	4-$OCONHC_2H_5$	H	150-151	2-Propanol	40	$C_{18}H_{25}N_3O_5$	59.49	6.93	11.56
								59.40	7.00	11.42
7f	3-OCH_3	4-OH	H	152-153	Ethyl acetate	46	$C_{15}H_{20}N_2O_4$	61.63	6.90	9.58
								61.57	6.89	9.55
7g	3,4-		H	169-170 [a]	Methanol	62	$C_{18}H_{20}N_2O_2$	72.95	6.80	9.45
								72.73	6.84	9.59

[a] Melts with decomposition.

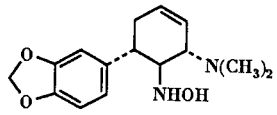
Table II

6-Aryl-N^2,N^2-dimethyl -3- cyclohexene-1,2-diamines **8**



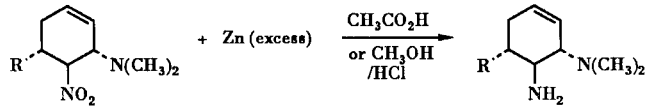
Compound	R	Mp °C	Crystallization Solvent	Yield	Method	Empirical Formula	Analysis % Calcd./Found C	H	N	Cl
8a		137-138	acetonitrile	75	A	$C_{16}H_{24}N_2O_2$	69.53	8.75	10.14	
							69.31	8.84	9.86	
8b		89-90	isopropyl ether	66	A	$C_{15}H_{20}N_2O_2$	69.20	7.74	10.76	
							69.37	7.84	10.61	
8c		88-89	isopropyl ether	49	A,B [b]	$C_{17}H_{26}N_2O_3$	66.64	8.55	9.14	
							66.35	8.54	9.02	
8d		245-246 [a]	2-propanol	51	A	$C_{16}H_{24}N_2O_2$• 2HCl	55.02	7.50	8.02	20.30
							55.26	7.51	7.96	20.05
8e		192-193 [a]	ethanol	76	A	$C_{18}H_{27}N_3O_3$• 2HCl•2H_2O [c]	48.87	7.52	9.50	16.03
							48.73	7.34	9.53	16.14
8f		122-123	acetonitrile	46	A,C	$C_{15}H_{22}N_2O_2$	66.87	8.45	10.68	
							68.45	8.22	10.97	
8g		266-267 [a]	acetonitrile	50	A	$C_{18}H_{22}N_2$• 2HCl	63.72	7.13	8.26	20.90
							63.47	7.32	8.21	20.78

[a] Melts with decomposition. [b] Yield of product **8c** by method B was 47%. [c] Determined by Karl Fischer method, 7.76% water (theoretical: 8.14%).



14

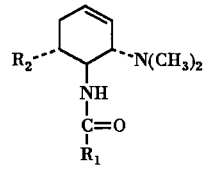
Schotten-Baumann acylation of diamines **8** gave amides **9**. Reaction of **8** with alkyl isocyanates gave urea derivatives **10** (Table III). Bischler-Napieralski cyclodehydration [6] of **9** and **10** in refluxing phosphorus oxychloride gave tetrahydrophenanthridines **3** and **11**, respectively (Scheme I, Table IV).

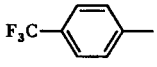
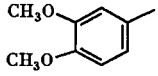
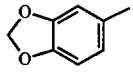
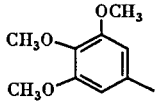
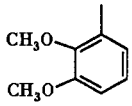
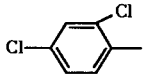
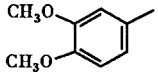
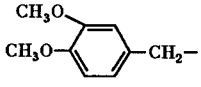
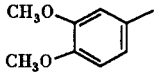
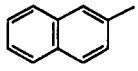
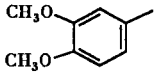
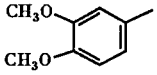
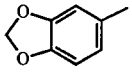


7, R = Aryl **8**

Table III

N-[(6-Aryl)-2-(dimethylamino)-3-cyclohexen-1-yl]amides **9** and *N*-[(6-Aryl)-2-(dimethylamino)-3-cyclohexen-1-yl]ureas **10**

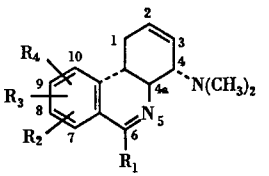


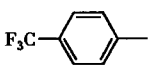
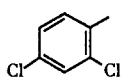
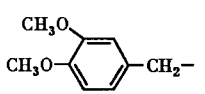
Compound	R_1	R_2	Mp °C	Crystallization Solvent	Yield %	Empirical Formula	Analysis % Calcd./Found C	H	N
9a			152-153	[a]	62	$C_{24}H_{26}F_3N_2O_3$ [c]	64.28 64.57	6.07 6.16	6.25 6.19
9b	C_6H_5		206-207	[a]	75	$C_{22}H_{24}N_2O_3$	72.50 72.53	6.64 6.72	7.69 7.55
9c	C_6H_5		157-158	[a]	88	$C_{24}H_{30}N_2O_4$	70.22 70.46	7.37 7.37	6.82 6.85
9d	C_6H_5		206-207	[a]	78	$C_{23}H_{28}N_2O_3$	72.61 72.89	7.42 7.48	7.36 7.14
9e			193-194	[a]	67	$C_{23}H_{26}Cl_2N_2O_3$ [d]	61.47 61.41	5.83 5.82	6.23 6.14
9f			144-145	[b]	55	$C_{26}H_{34}N_2O_5$	68.70 68.45	7.54 7.50	6.16 6.10
9g	C_6H_5		176-177	[a]	50	$C_{25}H_{26}N_2O$	81.04 80.94	7.07 7.10	7.56 7.45
10a	C_2H_5NH-		138-139	[a]	92	$C_{19}H_{29}N_3O_3$	65.68 65.92	8.41 8.38	12.10 11.87
10b	$(CH_3)_2CHNH$-		131-132	[a]	91	$C_{20}H_{31}N_3O_3$	66.45 66.16	8.64 8.56	11.62 11.73
10c	C_2H_5NH-		156-157	[a]	92	$C_{18}H_{25}N_3O_3$	65.23 65.00	7.60 7.60	12.68 12.66

[a] Ethyl acetate. [b] Acetonitrile. [c] Calcd: F, 12.71; Found: F, 12.69. [d] Calcd: Cl, 15.77; Found: Cl, 15.85.

Table IV

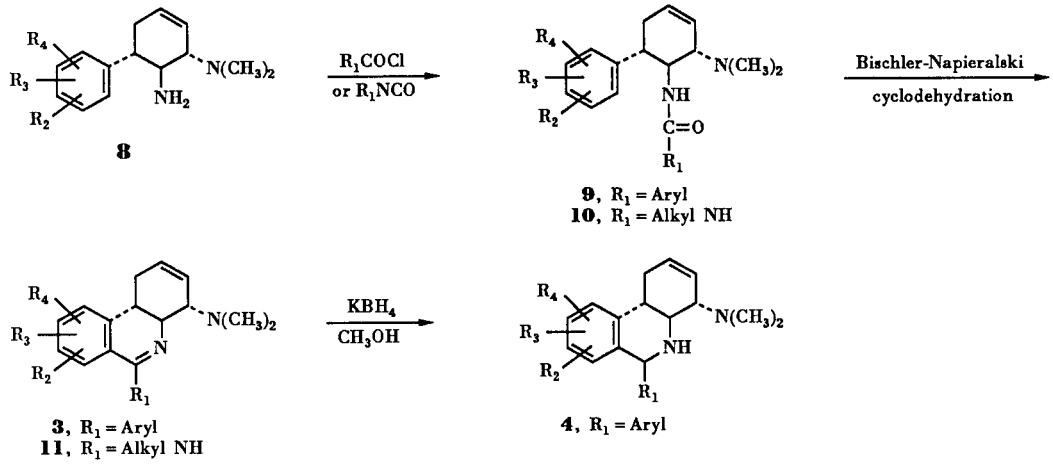
4-(Dimethylamino)-1,4,4a,10b-tetrahydro-6-aryl(alkyl)phenanthridines **3** and 4-(Dimethylamino)-1,4,4a,10b-tetrahydro-6-(alkylamino)phenathridines **11**



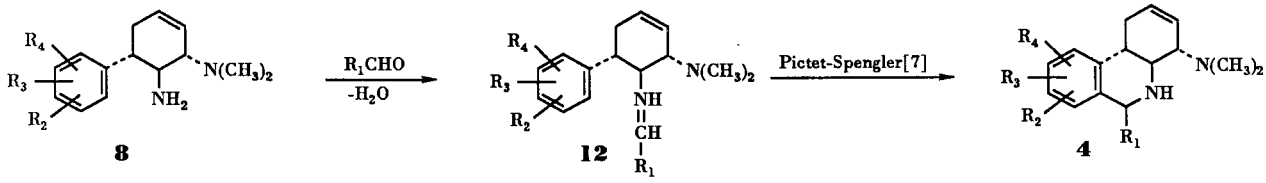
Compound	R_1	R_2	R_3	R_4	Mp °C	Yield %	Empirical Formula	Crystallization Solvent	Analysis % Calcd./Found C	H	N	Halogen
3a		H	8-OCH_3	9-OCH_3	174-175	48	$C_{24}H_{25}F_3N_2O_2$	Acetonitrile	66.96 66.75	5.85 5.89	6.51 6.59	F, 13.24 13.19
3b		H	9-OCH_3	10-OCH_3	229-230 [a]	40	$C_{23}H_{26}N_2O_2$• HCl	Acetonitrile	69.25 69.42	6.82 6.99	7.02 7.01	Cl^-, 8.89 8.79
3c		7-OCH_3	8-OCH_3	9-OCH_3	208-210 [a]	53	$C_{24}H_{28}N_2O_3$• HCl	2-Propanol	67.19 67.08	6.81 6.93	6.53 6.19	Cl^-, 8.27 8.18
3d		H	8-OCH_3	9-OCH_3	147-148	28	$C_{23}H_{24}Cl_2N_2O_2$	Acetonitrille	64.04 63.92	5.61 5.56	6.49 6.56	Cl, 16.44 16.40
3e		H	8-OCH_3	9-OCH_3	129-130	78	$C_{26}H_{32}N_2O_4$	*tert*-butyl alcohol	71.53 71.33	7.39 7.33	6.42 6.28	
3f		H	8,9- 		199-200	60	$C_{25}H_{24}N_2$	2-Propanol	85.19 84.91	6.86 6.84	7.95 7.95	
11a	C_2H_5NH-	H	8-OCH_3	9-OCH_3	260-261 [a]	75	$C_{19}H_{27}N_3O_2$• 2HCl•C_2H_6O [b]	Ethanol	56.25 56.22	7.87 7.68	9.37 9.08	Cl^-, 15.81 15.93
11b	$(CH_3)_2CHNH$-	H	8-OCH_3	9-OCH_3	145-146	70	$C_{20}H_{29}N_3O_2$	Isopropyl ether	69.94 70.07	8.51 8.81	12.23 12.37	
11c	C_2H_5NH-	H	8,9-OCH_2O		136-137	85	$C_{18}H_{23}N_3O_2$	Hexane	68.98 68.91	7.40 7.30	13.41 13.56	

[a] Melts with decomposition. [b] Contains one mole of ethanol as crystallization solvent.

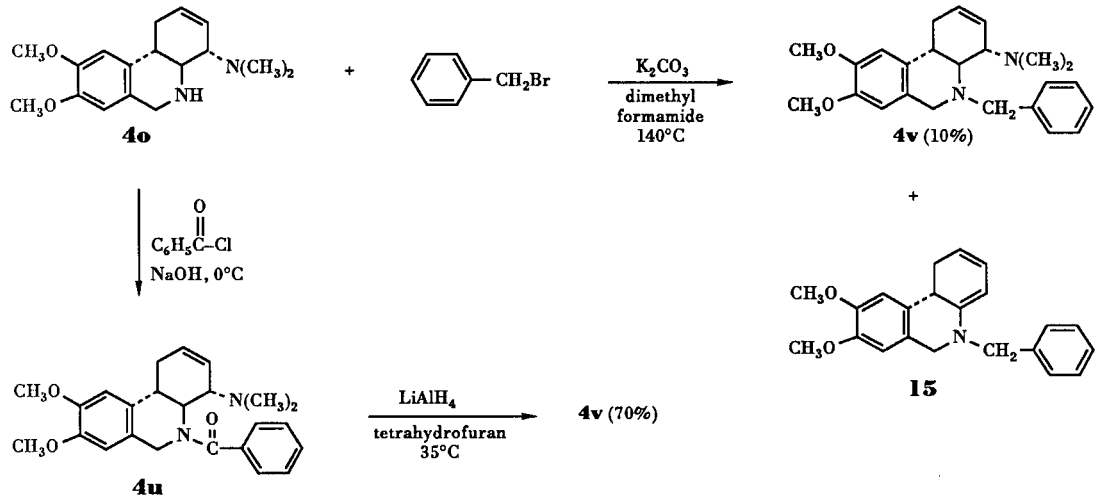
Scheme I



Scheme II



Scheme III



Some of the tetrahydrophenanthridines **3** were reduced by potassium borohydride in methanol at room temperature to the corresponding hexahydrophenanthridines **4** as single products (Scheme I, Table V).

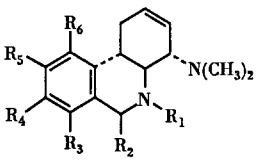
Condensation of diamines **8** and aryl aldehydes with azeotropic removal of water gave imines **12**. The latter, on treatment with trifluoroacetic acid [7] were converted to hexahydrophenanthridines **4** (Scheme II, Table V), identical to those obtained from tetrahydrophenanthridines **3** by borohydride reduction.

The 6-unsubstituted hexahydrophenanthridine hydrochlorides **4** (R = H) were obtained directly from the dihydrochlorides of **8** by refluxing with excess paraformaldehyde in methanol or ethanol [8] (Table V).

The synthesis of *N*-benzyl derivative **4v** was desired since it resembles more closely the structure of biologically active **2**. Alkylation of **4o** with benzyl bromide in the presence of potassium carbonate, however, was not a practical method. Because of the stringent conditions required, the desired compound (10%) was contaminated

Table V

4-(Dimethylamino)-1,4,4a,5,6,10b-hexahydrophenanthridines **4**



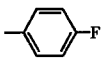
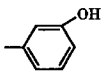
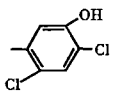
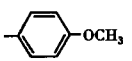
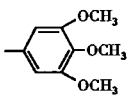
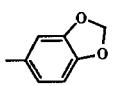
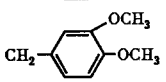
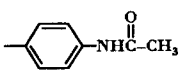
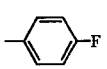
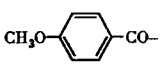
Compound	R_1	R_2	R_3	R_4	R_5	R_6	Mp °C	Yield %	Empirical Formula	Method	Cyclization Temp., °C, Time	Crystallization Solvent	Analysis % Calcd./Found C	H	N	Halogen
4a	H	C_6H_5	H	OCH_3	OCH_3	H	184-185	70	$C_{23}H_{28}N_2O_2$	A	25, 24 hours	2-propanol	75.79 76.07	7.74 7.86	7.69 7.50	
4b	H	C_6H_5	H	H	OCH_3	OCH_3	159-160	74	$C_{23}H_{28}N_2O_2$	B	73, 2 hours	2-propanol	75.79 75.86	7.74 7.72	7.69 7.73	
4c	H	C_6H_5	OCH_3	OCH_3	OCH_3	H	126-127	79	$C_{24}H_{30}N_2O_3$	A,B	73, 2 hours	2-propanol	73.06 73.03	7.67 7.71	7.10 7.01	
4d	H		H	OCH_3	OCH_3	H	189-190	59	$C_{23}H_{27}FN_2O_2$	A	25, 24 hours	2-propanol	72.23 73.13	7.11 7.23	7.32 7.23	F, 4.96 4.73
4e	H		H	OCH_3	OCH_3	H	228-229	63	$C_{23}H_{28}N_2O_3$	A	73, 4 hours	2-propanol	72.61 72.48	7.42 7.47	7.36 7.11	
4f	H		H	OCH_3	OCH_3	H	219-220 [a]	80	$C_{23}H_{28}Cl_2N_2O_3$	A	73, 1.4 hours	ethyl acetate	61.47 61.34	5.83 5.82	6.23 5.93	Cl, 15.78 15.84
4g	H		H	OCH_3	OCH_3	H	156-157	36	$C_{24}H_{30}N_2O_3$	A	73, 4 hours	2-propanol	73.06 73.26	7.67 7.66	7.10 6.96	
4h	H		H	OCH_3	OCH_3	H	144-145	56	$C_{26}H_{34}N_2O_5$	A	25, 24 hours	2-propanol	68.70 68.49	7.54 7.54	6.16 5.97	
4i	H		H	OCH_3	OCH_3	H	151-153	62	$C_{24}H_{28}N_2O_4$	A	73, 4 hours	2-propanol	70.56 70.42	6.91 6.84	6.86 6.82	
4j	H		H	OCH_3	OCH_3	OCH_3	221-222 [a]	47	$C_{26}H_{34}N_2O_4 \cdot 2HCl$	B		ethanol	61.05 61.19	7.09 7.24	5.48 5.21	Cl^-, 13.86 13.67
4k	H	C_6H_5	H	OH	OCH_3	H	169-170	53	$C_{22}H_{26}N_2O_2$	A	73, 1.5 hours	Acetonitrile	75.40 75.29	7.48 7.49	7.99 7.96	
4l	H		H	R4,5-OCH_2O-		H	227-228 [a]	69	$C_{24}H_{27}N_3O_3$	A	73, 3 hours	ethyl acetate	71.09 70.88	6.71 6.82	10.36 10.17	
4m	H	C_6H_5	H	R4,5- 		H	167-168	56	$C_{25}H_{26}N_2$	A,B	25, 2 hours	2-propanol	84.70 84.74	7.39 7.67	7.90 7.80	
4n	CH_3		H	OCH_3	OCH_3	H	110-111	52	$C_{24}H_{29}FN_2O_2$	E-C [b]		2-propanol	72.70 72.80	7.37 7.41	7.06 7.05	F, 4.79 4.53

Table V (Continued)

Compound	R_1	R_2	R_3	R_4	R_5	R_6	Mp °C	Yield %	Empirical Formula	Method	Cyclization Temp., °C, Time	Crystallization Solvent	Analysis % Calcd./Found C	H	N	Halogen
4o	H	H	H	OCH_3	OCH_3	H	155-156	71	$C_{17}H_{24}N_2O_2$	C	E, 2 hours	ethyl acetate	70.80 71.03	8.39 8.59	9.71 9.74	
4p	H	H	H	$-OCONHC_2H_5$	OCH_3	H	164-165	50	$C_{19}H_{27}N_3O_3$	C	E, 0.5 hours	aceto-nitrile	66.06 65.78	7.88 7.92	12.17 12.02	
4q	H	H	H	H	OCH_3	OCH_3	206-207 [a]	75	$C_{17}H_{24}N_2O_2 \cdot 2HCl \cdot C_2H_4O_2$ [c]	C	P, 5 hours	acetic acid	54.16 53.99	7.18 7.46	6.65 6.74	Cl^-, 16.83 16.72
4r	H	H	H	R_4,R_5-OCH_2O-		H	121-122	92	$C_{16}H_{20}N_2O_2$	C	M, 1 hour	isopropyl ether	70.56 70.74	7.48 7.43	10.29 10.28	
4s	H	H	OCH_3	OCH_3	OCH_3	H	186-187 [a]	87	$C_{18}H_{26}N_2O_3 \cdot 2HCl \cdot CH_3OH$ [d]	C	M, 2 hours	methanol	59.90 53.90	7.62 7.60	6.62 6.71	Cl^-, 16.75 16.59
4t		H	H	R_4,R_5-OCH_2O-		H	140-141	48	$C_{24}H_{26}N_2O_4$		S	benzene-cyclo-hexane	70.91 71.09	6.45 6.43	6.89 6.74	
4u	C_6H_5CO-	H	H	OCH_3	OCH_3	H	163-164	78	$C_{24}H_{28}N_2O_3$		S	ethyl acetate	73.44 73.52	7.19 7.17	7.14 7.38	
4v	$C_6H_5CH_2$-	H	H	OCH_3	OCH_3	H	100-101	77	$C_{24}H_{30}N_2O_2$		LAH	2-propanol	76.15 75.95	7.99 8.09	7.40 7.33	
4w	C_2H_5NHCO	H	H	R_4,R_5-OCH_2O-		H	176-177	89	$C_{24}H_{29}N_3O_3$			isopropyl ether	66.82 66.74	8.13 8.19	16.69 16.74	

[a] Melts with decomposition. [b] By Eschweiler-Clarke procedure. [c] Contains one mole of acetic acid as a solvent of cyrstallization. [d] Contains one mole of methanol as a solvent of cyrstallization. E, ethanol as a reaction solvent. M. methanol. P, *n*-propanol. S, Schotten-Baumann conditions. LAH, lithium aluminum hydride reduction.

with the elimination product **15**, and other intractable decomposition products. An indirect procedure, *via* the intermediate benzamido derivative **4u**, was much more effective (Scheme III).

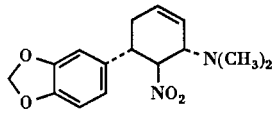
Discussion of Proton Magnetic Resonance Spectral Data.

All nitroamine adducts **7** exhibit similar patterns in their proton magnetic resonance (^{1}H nmr) spectra. The signal of the proton on the nitro-bearing carbon (H-6) is readily recognized because of the large deshielding effect of the nitro group. It appears as a closely-spaced doublet of doublets between δ 4.80 and δ 5.00. The proton geminal to the dimethylamino group (H-1) appears as a doublet of multiplets at about δ 4.00, and the proton geminal to the aryl group (H-5) is seen as a sextet or a multiplet between δ 3.35 and δ 3.50. Steric considerations suggest that the 1-C, 5-C and 6-C substituents on the cyclohexene ring should approach an all equatorial configuration as shown in **7b**. The H-1, H-5 and H-6 protons should therefore approach all axial and H-1 and H-5 should be approximately *trans* to H-6. This is roughly born out by the shifts and coupling constants of the three protons. If H-1 and H-5 were strictly *trans* to H-6, however, they would exhibit very similar coupling constants and H-6 should be a triplet. This situation where $J_{H\text{-}1,H\text{-}6} = J_{H\text{-}5,H\text{-}6}$ and H-6 is a triplet was demonstrated in the case of the cyclohexane derivative **16** [9]. In order to show the effect of the ring unsaturation on the coupling constants of H-1, H-6 and that of H-5, H-6 of compound **7b**, a detailed spectral study was carried out.

The proton magnetic resonance spectrum (^{1}H nmr) of **7b** in deuteriochloroform on a Varian XL300 shows a signal of the H-6 as a doublet (δ 4.83) with the coupling constants J = 11.6 and J = 9.8 Hz. Vinylic protons in all compounds exhibit variable but definite nonequivalency. In compound **7b** the H-2 appears at δ 5.74 as a doublet of narrow multiplets separated by about 10.0 Hz. The H-3 shows extensive multiplicity at δ 5.92 which collapsed to a doublet (J = 10.0 Hz) on decoupling of the neighboring methylene group (CH_2-4). The dioxymethylene group is shown as a sharp spike at δ 5.94, while the aromatic protons display a narrow multiplet centered at δ 6.72. The dimethylamino group resonates as a singlet at δ 2.34 and a multiplet of the methylene group of the cyclohexene ring appears at δ 2.40. Decoupling of H-1 by irradiation at δ 4.04 resulted in a doublet at δ 4.83 for H-6 with $J_{H\text{-}5,H\text{-}6}$ = 11.6 Hz. Irradiation of the benzylic proton (H-5) at δ 3.36 showed a doublet at δ 4.83 for H-6 with $J_{H\text{-}1,H\text{-}6}$ = 9.8 Hz. Thus, it was established that the larger coupling constant (J = 11.6 Hz) is that resulting from coupling between H-5 and H-6 as could be expected [10]. Decoupling of H-6 by irradiation at δ 4.83 showed a narrow multiplet for H-1. This would indicate some long-range coupling of the 1-proton with another olefinic proton (H-3) in addition to the vicinal proton (H-2).

Zinc reduction of the nitro group in **7** to give diamines **8** was not expected to cause conformational changes but this proved hard to demonstrate, because the 6- and 5-protons in **8** suffered an upfield shift resulting in a complex multiplet centered at about δ 3.10.

A much better model was the benzamido derivative **9b** where the critical protons are sufficiently separated. After the deuterium oxide exchange, the H-1 multiplet changed into a doublet of doublets centered at δ 4.48 with the coupling constants of J = 11.5 Hz and J = 9.6 Hz, respectively. Decoupling of H-6 by irradiation at δ 3.03 resulted in a doublet for H-1 (J = 9.6 Hz) at δ 4.48. Irradiation of H-2 at δ 3.50 resulted in a doublet (J = 11.5 Hz) for H-1



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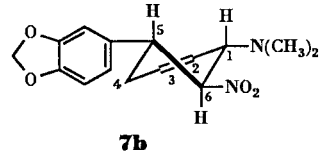
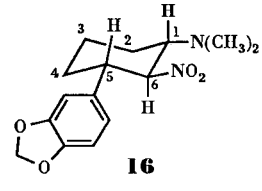
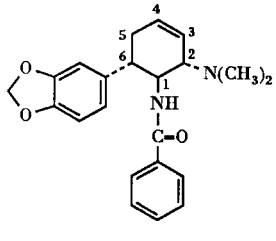


7b



16

H-6 = triplet
$J_{H\text{-}1,H\text{-}6} = J_{H\text{-}5,H\text{-}6} = 10.8$ Hz



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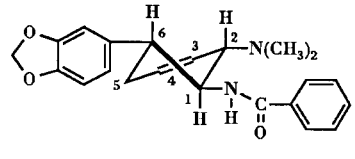
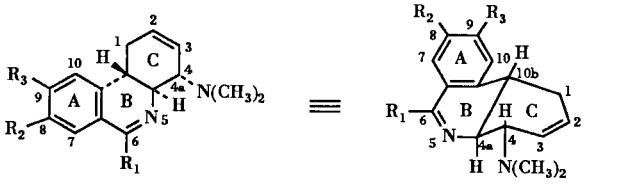


at δ 4.48. These data show clear analogy to the nitroamino precursor **7b**.

A two-dimensional ^{1}H nmr [11] confirms the stereochemical assignment for **9b**, shows unambiguously the *trans* relationship of H-2 and H-6 to H-1 and allows us to assign the exact position to each of the vinylic protons, H-3 (δ 5.70, m) and H-4 (δ 5.94, m).

The Bischler-Napieralski cyclization products, **3**, assume rather rigid structures with H-4a and H-10b in a roughly *trans* diaxial relationship approximately perpendicular to the aromatic ring. The aromatic substituent, R_1, is apparently in plane of the C=N bond and ring A.



3a, R_1 = —C$_6$H$_4$—CF$_3$, $R_2 = R_3 = OCH_3$

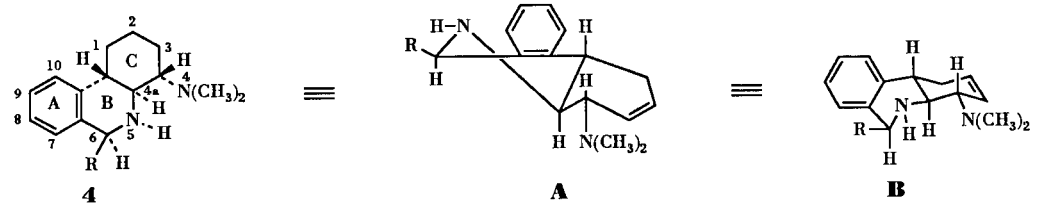
In contrast to the amide precursors **9**, the axial protons in **3** (H-4, H-4a and H-10b) experience upfield shifts and are spaced more closely. Also, the signals of some of the substituents on the A-ring as well as those on the 6-substituent itself undergo a downfield shift [12].

Compound **3a** may serve as an example [13]. The signal of the 7-proton underwent a downfield shift by 0.26 ppm at δ 6.88 and the signal of the 8-methoxy methyl was downshifted by 0.30 ppm to δ 3.98. The signals of other protons on the A-ring (9-methoxy methyl and H-10) remained unchanged. The signals of the 6-substituent protons experienced downfield shift of about 0.45 ppm, appearing as doublet of doublets (J = 8.2 Hz) at δ 7.70 and δ 7.80, respectively as compared to a narrow multiplet of the precursor **9a** centered at δ 7.28. The 9- and 10-dimethoxy analogue of **3a** (**3b**) exhibits similar characteristics. Thus, the ^{1}H nmr spectrum (perdeuteriomethanol) shows the 7-and 8-protons to be equivalent with the signal at lower field (δ 6.97), while all phenyl protons also experience a downfield shift as compared to the precursor amide **9d**.

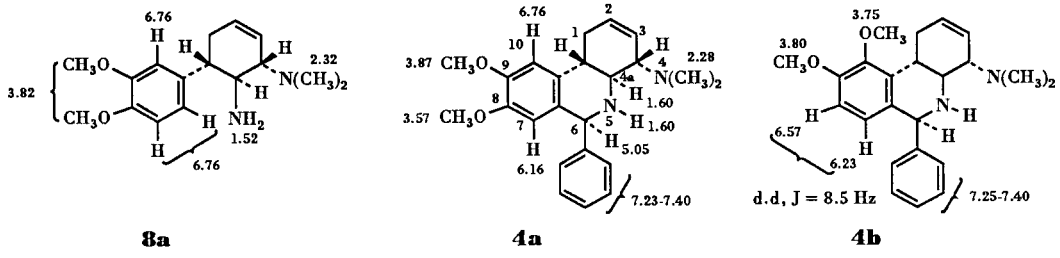
The somewhat more flexible hexahydrophenanthridines **4** with the B/C ring junction in *trans* orientation and the lone protons H-4, H-4a and H-10b in *trans* axial relationships could be represented in the forms **A** or **B**.

A priori, the substituents at C-6 could assume either the *pseudo*axial (α) or *pseudo*equatorial (β) relationship, but assuming the half-chair conformation of ring B, the large 6-substituent is expected to be in a *pseudo*equatorial orientation. Indeed, compounds **4** show only one ^{1}H nmr signal for the benzylic (H-6) proton at about δ 5.00 [14].

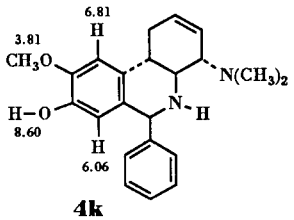
As expected, neither the olefinic protons nor the dimethylamino protons underwent any important change on cyclization from **8** to **4**. The most dramatic changes were considerable upfield shifts of the aromatic protons and substituents on the 7- and 8-positions of the A-ring due to introduction of the neighboring benzylic group. Thus, in going from **8a** to **4a** the signal of H-7 underwent an upfield shift of 0.60 ppm (δ 6.76 to 6.16) while that of H-10 (δ 6.76) remained unchanged. The chemical shift of the signal of 9-methoxy methyl remained unchanged while that of the 8-methoxy group shifted upfield by 0.30 ppm. To unambiguously determine the identity of these signals, a comparison was made to the transformation of **8d** to **4b**



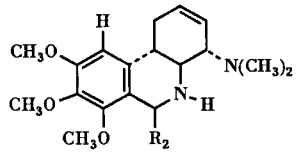
4 **A** **B**



8a **4a** **4b**



4k



4s, $R_2 = H$
4c, $R_2 = C_6H_5$

in which both dimethoxy methyl signals remained unchanged, while the H-7 and H-8 became doublets (J = 8.5 Hz) centered at δ 6.23 and δ 6.57, respectively. Additional proof is shown by the 8-hydroxy analogue of **4a** (**4k**) which displays a 9-methoxy methyl signal at δ 3.81, unchanged from **8f**. Again H-10 was practically unchanged at δ 6.81 while H-7 experienced an even larger upfield shift than that of **4a** (δ 6.16). Nuclear Overhauser studies (conducted in deuteriomethanol) further confirm the assignment of protons in **4k**. Irradiation of H-6 signal at δ 4.97 caused a significant increase in the intensity of H-7 at δ 6.06 with no effect on the H-10 singlet at δ 6.81. Irradiation of the 9-methoxy methyl signal at δ 3.81 caused a significant increase in the intensity of H-10 singlet at δ 6.81 with practically no effect on H-7. Conversely, irradiation of H-10 caused a considerable increase in the intensity of the 9-methoxy singlet.

In the 6-nor (6-unsubstituted) analogues **4** (R_2 = H), the changes in the ring A were observed to a much lesser degree than where a large 6-substituent is present. Compound **4s** (base) may serve as an example. The signal of H-10 remained unchanged from **8c** and all three methoxy methyls are overlapping each other (together with one proton of CH_2-6) at δ 3.80. However, the 7-methoxy group affected the methylene protons (CH_2-6), causing a separation of their signals by 0.32 ppm (J = 15.0 Hz). In sharp contrast to **4s**, its 6-phenyl homologue **4c** exhibits a dramatic upfield shift of the 7-methoxy methyl to δ 2.98, the 8- and 9-methoxy methyls resonating at δ 3.73 and δ 3.85, respectively [15].

While, in general, the methylene protons (vicinal to vinylic function) resonate as a moderately wide multiplet in open compounds **7**, **8** and **9**, they undergo for the most part a substantial separation of their signals in cyclized products **3** and **4**. The above discussed examples constitute rather general observations regarding the structural characteristics of intermediates **7**, **8** and **9** and final products **3** and **4**. More details, whenever available, will be described in the experimental section.

Tetrahydrophenanthridines **3** exhibited rather weak antiarrhythmic activity. Hexahydrophenanthridines **4** showed moderate activities. The best activities were shown by compounds **4j**, **4l**, **4t** and **4w** in the ouabain-induced arrhythmia test [16] (5-20 mg/kg) and in the coronary ligated Harris dog [17] test in the range of about 10 to 50 mg/kg.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet (uv, ethanol) and infrared (ir) spectra were obtained with a Beckman DK-1 spectrophotometer and a Baired Model 455 double-beam spectrograph, respectively. Proton nuclear magnetic resonance (^{1}H nmr) studies were performed on the Varian A-60 or Bruker WH-90 spectrometers. High-resolution, one- and two-dimensional proton spectra were acquired on the Bruker AM250 MHz and Varian XL300 MHz NMR spectrometers. Spectra were obtained on freshly prepared solutions in deuteriochloroform 10 mg/0.7 ml for 1D and 40 mg/0.7 ml for 2D experiments. Thirty-two or 64 transients were collected for the 1D proton and single frequency proton decoupled spectra. The ^{1}H, ^{1}H COSY spectra were recorded with the following parameters. Size in F2: 1K; number of experiments: 512; number of acquisitions: 128; window function in F1 and F2: sine bell. Chemical shift, integration, single frequency proton decoupling and 2D homonuclear chemical shift correlation data were used to make the proton signal assignments.

The mass spectra were recorded on a Finnigan 1015 Quadrupole Mass Spectrometer. The thin layer chromatography (tlc) was carried out on silica gel G (Stahl) or basic alumina (Woelm) plates and the chromatograms were developed in an iodine chamber. The detailed assignment of proton resonances was done whenever the signals were distinctly separated and there was sufficient resolution. In case of hexahydrophenanthridines, detailed spectral data are described for **4a**, **b**, **c**, **j**, **k**, **l**, **o**, **q**, **r**, **s**, **u**, **v** and **w** only, as representative compounds in that series. The starting materials **5** and **6** were prepared according to the literature procedures and no attempts were made to optimize the yields of intermediates **7**, **8** and **9** and final products **3** and **4**, respectively. The reactions of **5** and **6** to produce **7** were mildly exothermic and, occasionally, it was necessary to cool the reaction flask externally. Although most preparations of **7** were done in chloroform, other solvents like dichloromethane, tetrahydrofuran, methanol, or a combination of solvents were used depending on the solubility of starting styrene **5**.

General Procedure for the Preparation of 5-Aryl-*N*,*N*-dimethyl-6-nitro-2-cyclohexen-1-amines **7**. Table I.

Most of compounds **5** were prepared by using a modified procedure of Gairaud and Lappin [18]. The solution of aldehyde and catalytic amounts of ammonium acetate in excess nitromethane (which served both as a reactant and as a solvent) was refluxed for 0.5 to 2 hours and the resulting styrene **5** was usually obtained directly after cooling the reaction mixture. The preparation of **5a** will exemplify the general synthesis of styrenes **5**.

1,2-Dimethoxy-4-(2-nitroethenyl)benzene (**5a**).

A stirred solution of 66.4 g (0.4 mole) of 3,4-dimethoxybenzaldehyde and 163 g (eight-fold excess) of nitromethane was refluxed for 0.5 hour while light-yellow crystals of **5a** began to separate. After the mixture was allowed to stand overnight at 25°, the solid was collected, washed with 25 ml of acetic acid and allowed to dry in air giving 74.0 g (88% yield) of **5a** as light-yellow crystals, mp 141-142°. An analytical sample was obtained by recrystallization from glacial acetic acid, mp 142-143° [lit [18] mp 141-142°].

N,N-Dimethyl-1,3-butadien-1-amine (**6**).

A modified procedure of Hunig and Kahanek [3c] for the preparation of the *N,N*-diethyl-1,3-butadien-1-amine homologue was used. Freshly distilled crotonaldehyde (70.1 g, 1.0 mole) was added dropwise for 0.5 hour to a vigorously stirred mixture of 100.0 g (2.2 moles) of anhydrous dimethylamine and 70 g of anhydrous potassium carbonate in 170 ml of benzene under nitrogen at -10° to -5° until the turbidity of the supernatant liquid completely disappeared (1 hour). After the solid was removed by filtration, 0.5 g of phenanthrenequinone was added and the solution was concentrated *in vacuo* under roto-vap at 55°, while the solvent and excess dimethylamine were removed. The residual liquid was distilled *in vacuo* at 14 mm to give 6.5 g of the first fraction, bp 48-58°. The majority of material (76 g) was distilled at 59-66°/14 mm leaving behind 15 g of nondistillable residue. The main fraction was redistilled through the short Vigreaux column at 57-60°/9 mm to give 62.0 g (64% yield) of *N,N*-dimethyl-1,3-butadien-1-amine (**6**) as light-yellow liquid [lit [4] bp 95-105°/-250 mm]; uv (ethanol): λ nm (ε) 277 (28,500); ir (chloroform): 1638 cm^{-1}; n_D^{25} = 1.5228.

Anal. Calcd. for $C_6H_{11}N$: C, 74.17; H, 11.41; N, 14.42. Found: C, 73.92; H, 11.63; N, 14.71.

5-(3,4-Dimethoxyphenyl)-*N,N*-dimethyl-6-nitro-2-cyclohexen-1-amine (**7a**).

Twenty grams (0.2 mole) of *N,N*-dimethyl-1,3-butadien-1-amine (**6**) was added to a solution of 42.0 g (0.2 mole) of 3,4-dimethoxy-β-nitrostyrene (**5a**) and 0.05 g of hydroquinone in 300 ml of chloroform under nitrogen at 20°. The solution turned cherry-red instantaneously and gradually changed to light-brown as the temperature rose to 27°. After 20 hours at room temperature, the tlc (acetone:benzene:heptane, 2:2:1) showed complete reaction, the new product **7a** having slower mobility (R_f = 0.5) than the starting styrene **5a** (R_f = 0.6). The solution was evaporated under diminished pressure and the residue was crystallized from methanol to give 53.5 g (82% yield) of **7a** as white crystals, mp 143-144°; uv: λ max nm (ε) 228 (9920), 278 (2920); ir (chloroform): 1547 (NO_2), 1260, 1030 (OCH_3) cm^{-1}; ^1H nmr (deuteriochloroform): [19] δ 2.30 [s, 6H, $N(CH_3)_2$], 2.40 (m, 2H, CH_2), 3.35 (m, 1H, H-5), 3.77, 3.80 [ss, 6H, $(OCH_3)_2$], 4.05 (m, 1H, H-1), 4.83 (dd, J = 11.6 Hz and 9.8 Hz, 1H, H-6), 5.73 (m, 1H, H-2), 5.87 (m, 1H, H-3), 6.62-6.75 (m, 3H, aromatic); ms: m/z 306.

The above reaction was repeated using methanol as a reaction solvent to give **7a** (76%).

5-(1,3-Benzodioxol-5-yl)-*N,N*-dimethyl-6-nitro-2-cyclohexen-1-amine (**7b**).

The same procedure used for the preparation of **7a** was followed with exception being the use of dichloromethane instead of chloroform as the reaction medium; uv: λ max nm (ε) 232 (5140), 284 (4140); ir (chloroform): 1546 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): [19] δ 2.34 [s, 6H, $N(CH_3)_2$], 2.40 (m, 2H, CH_2), 3.36 (sextet, J = 11.6 Hz and 5.8 Hz, 1H, H-5), 4.04 (doublet of multiplets, 1H, H-1), 4.83 (dd, J = 11.6 Hz and 9.8 Hz, 1H, H-6), 5.74 (m, 1H, H-2), 5.92 (m, 1H, H-3), 5.94 (s, 2H, dioxymethylene group), 6.72 (m, 3H, aromatic); ms: m/z 290.

N,N-Dimethyl-6-nitro-5-(3,4,5-trimethoxyphenyl)-2-cyclohexen-1-amine (**7c**).

This compound had uv: λ max nm (ε) 262-270, plateau (1350); ^1H nmr (deuteriochloroform): [19] δ 2.33 [s, 6H, $N(CH_3)_2$], 2.45 (m, 2H, CH_2), 3.35 (m, 1H, H-5), 3.75 (s, 3H, 4'-OCH_3), 3.78 [s, 6H, 3',5'-$(OCH_3)_2$], 4.05 (doublet of multiplets, 1H, H-1), 4.85 (dd, J = 11.6 Hz and 9.8 Hz, 1H, H-6), 5.78 (m, 1H, H-2), 5.88 (m, 1H, H-3), 6.38 (s, 2H, aromatic); on decoupling of CH_2-4, the multiplet of H-3 collapsed to a doublet, J = 10.0 Hz; ms: m/z 336.

5-(2,3-Dimethoxyphenyl)-*N,N*-dimethyl-6-nitro-2-cyclohexen-1-amine (**7d**).

This compound had uv: λ max nm (ε) 228 (9925), 278 (2930); ir (chloroform): 1548 (s, NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): [19] δ 2.35 [s, 6H, $N(CH_3)_2$], 2.40 (m, 2H, CH_2), 3.80, 3.85 [ss, 6H, $(OCH_3)_2$], 4.02 (m, 1H, H-1), 5.15 (dd, J = 14.0 Hz and 10.5 Hz, 1H, H-6), 7.50, 7.80 (mm, 2H, vinylic protons), 6.70-7.00 (m, broad, 3H, aromatic).

4-[5-Dimethylamino)-6-nitro-3-cyclohexen-1-yl]-2-methoxyphenyl Ethyl Carbamate (**7e**).

The 4.9 g (0.05 mole) of **6** was added portionwise to a solution of 12.5 g (0.046 mole) of 3-methoxy-4-ethylcarbamoyl-β-nitrostyrene and 0.05 g of hydroquinone in 150 ml of tetrahydrofuran at 20°. After a period of two hours the solution was evaporated and the residue was crystallized to give **7e** as off-white crystals; uv: λ max nm (ε) 224 sh (20,530), 274 (4720), 280 (4360); ir (nujol): 3250 (NH), 1720 (C=O), 1693 (CONH), 1545 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.18 (t, J = 8.0 Hz, 3H, CH_2CH_3), 2.30 [s, 6H, $N(CH_3)_2$], 2.38 (m, 2H, CH_2-4), 3.24 (m, 3H, CH_2CH_3 and H-5), 3.78 (s, 3H, OCH_3), 4.05 (m, 1H, H-1), 4.85 (m, 2H, H-6 and NH), 5.75 (m, 2H, vinylic), 6.00-7.00 (m, 3H, aromatic).

4-[5-(Dimethylamino)-6-nitro-3-cyclohexen-1-yl]-2-methoxyphenol (**7f**).

A stirred solution of 24.9 g (0.07 mole) of 4-[5-(dimethylamino)-6-nitro-3-cyclohexen-1-yl]-2-methoxyphenyl ethyl carbamate (**7e**) in 400 ml of methanol was treated with 7.6 g (0.14 mole) of sodium methoxide at 15° and allowed to stand overnight at room temperature. The tlc (chloroform) showed complete hydrolytic transesterification, the new phenolic product having faster mobility (R_f = 0.15) than the starting carbamate (R_f = 0.1). The solution was adjusted to *p*H 7.0 with acetic acid and evaporated *in vacuo*. The residue was taken up with cold water and extracted twice with 200 ml of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated to dryness *in vacuo*. Crystallization of the residue from 2-propanol gave 9.4 g of 4-[(dimethylamino)-6-nitro-3-cyclohexen-1-yl]-2-methoxyphenol (**7f**) as off-white crystals, mp 151-152°. An analytical sample was obtained by recrystallization from ethyl acetate, mp 152-153°; uv: λ max nm (ε) 218-228 plateau (8390), 230 sh (8190), 278 (3070); ir (chloroform): 3565 (OH), 1547 (NO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.25 [m, 8H, CH_2 and $N(CH_3)$], 3.15 (m, 1H, H-5), 3.63 (s, 3H, OCH_3), 3.85 (m, 1H, H-1), 5.02 (dd, J = 12.0 Hz and J = 10.0 Hz, H-6), 5.68 (m, 2H, vinylic), 6.52, 6.82 (ms, 3H, aromatic), 8.76 (s, 1H, OH); ms: m/z 392.

N,N-Dimethyl-5-(2-naphthalenyl)-6-nitro-2-cyclohexen-1-amine (**7g**).

This compound had uv: λ max nm (ε) 256 sh (3850), 266 (5040), 276 (5050); ir (nujol): 1545 (NO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.30 [s, 6H, $N(CH_3)_2$], 2.45 (m, 2H, CH_2), 3.35 (m, 1H, H-5), 4.00 (m, 1H, H-1), 4.95 (dd, J = 11.5 Hz and J = 10.0 Hz, 1H, H-6), 5.75 (m, 2H, vinylic), 7.12-7.83 (m, 7H, aromatic).

6-(3,4-Dimethoxyphenyl)-N^2,N^2-dimethyl-3-cyclohexene-1,2-diamine (**8a**). (Method A). Table II.

This method [5] represents the general procedure for the preparation of **8a–8g**, **8k** and **8l** under mild conditions. To a vigorously stirred solution of 50 g (0.163 mole) of 5-(3,4-dimethoxyphenyl)-*N*,*N*-dimethyl-6-nitro-2-cyclohexen-1-amine (**7a**) in 300 ml of glacial acetic acid was added 75 g of zinc dust portionwise at 16-22° (ice-water cooling bath) over a period of one hour and allowed to stir for 20 hours at room temperature. The tlc (dioxane-methanol, 1:1) showed complete reaction, the new product having slower mobility (R_f = 0.22) than the starting **7a** (R_f = 0.5). The solid was filtered off and washed with 50 ml of acetic acid. The filtrate was evaporated under rotary evaporator. The residue was taken up with ice, made basic with aqueous ammonia and extracted twice with 300 ml of dichloromethane. The combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate and evaporated. Crystallization of the residue from 2-propanol gave 33.7 g of nearly white crystals, mp 136-137°. An analytical sample of **8a** was obtained by recrystallization from acetonitrile, mp 137-138°; uv: λ max nm (ε) 228.5 (9280), 278 (3200); ^{1}H nmr (deuteriochloroform): δ 1.52 (s, broad, 2H, deuterium oxide-exchangeable, NH_2), 2.20 (m, 2H, CH_2), 2.32 [s, 6H, N(CH_3)$_2$], 2.70 (m, 1H, H-6), 3.08 (m, 2H, H-1, H-2), 3.82 [s, 6H, (OCH_3)$_2$], 5.75 (m, 2H, vinylic), 6.76 (s, 3H, aromatic); ms: m/z 276.

6-(1,3-Benzodioxol-5-yl)-N^2,N^2-dimethyl-3-cyclohexene-1,2-diamine (**8b**).

This compound had uv: λ max nm (ε) 232 (5000), 286 (4330); ^{1}H nmr (deuteriochloroform): δ 1.50 (s, broad, 2H, NH_2), 2.16 (m, 2H, CH_2), 2.32 [s, 6H, N(CH_3)$_2$], 2.70 (m, 1H, H-6), 3.05 (m, 2H, H-1, H-2), 5.75 (m, 2H, vinylic), 5.85 (s, 2H, O-CH_2-O), 6.73 (s, 3H, aromatic).

Dihydrochloride of **8b**, recrystallized from ethanol, melted at 253-254°, dec.

Anal. Calcd. for $C_{15}H_{20}N_2O_2$·2HCl: C, 54.06; H, 6.66; N, 8.40. Found: C, 54.12; H, 6.76; N, 8.40.

6-(1,3-Benzodioxol-5-yl)-N^1-hydroxy-N^2,N^2-dimethyl-3-cyclohexene-1,2-diamine (**14**).

Zinc dust (3.3 g) was added portionwise to a stirred solution of 5-(1,3-benzodioxol-5-yl)-*N*,*N*-dimethyl-6-nitro-2-cyclohexen-1-amine (5.8 g, 0.02 mole) in 50 ml of methanol and 25 ml of glacial acetic acid over a period of 10 minutes at 20-25° and stirred for 20 hours at 25°. The solid was filtered off, washed with acetic acid, and the filtrate was evaporated at 35° *in vacuo*. The residue was made basic at 10° with aqueous ammonia and extracted twice with 75 ml of ethyl acetate. The combined extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated *in vacuo*. Crystallization of the residue from 2-propanol gave 4.4 g (85%) of **14** as nearly white crystals, mp 173-174°, dec. An analytical sample, melting at 174-175° dec, was obtained by recrystallization from acetonitrile; uv: λ max nm (ε) 236 (14,000), 280 (4620); ^{1}H nmr (DMSO-d_6): δ 2.15 (m, 2H, CH_2), 2.26 [s, 6H, N(CH_3)$_2$], 2.80-3.05 (m, broad, 3H), 3.25 (m, 1H, deuterium oxide-exchangeable), 3.50 (m, 1H), 5.75 (m, 2H, vinylic), 5.88 (s, 2H, O-CH_2-O), 6.73, 6.85 (2H, 1H, J = 8.5 Hz, aromatic); ms: m/z 276.

Anal. Calcd. for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.26; H, 7.30; N, 10.21.

N^2,N^2-Dimethyl-6-(3,4,5-trimethoxyphenyl)-3-cyclohexene-1,2-diamine (**8c**). (Method A).

This compound had uv: λ max nm (ε) 222 sh (10,420), 269 (850), 279 sh (600); ^{1}H nmr (deuteriochloroform): δ 1.53 (2H, NH_2), 2.20 (m, 2H, CH_2), 2.30 [s, 6H, N(CH_3)], 3.05 (m, 2H), 3.78 (s, 3H, 4′-OCH_3), 3.81 [s, 6H, 3′,5′-(OCH_3)$_2$], 5.74 (vinylic), 6.46 (s, 2H, aromatic).

Method B.

A rapidly stirred solution of 16.8 g (0.05 mole) of **7c** in 125 ml of absolute methanol, saturated with hydrogen chloride (*p*H 1.0), was treated with 40.0 g of zinc dust portionwise over a period of 15 minutes at 20° and allowed to stir for six hours at room temperature. The solids were filtered off, washed with 50 ml of methanol and the filtrate was evaporated *in vacuo*. The residue was taken up with ice-water, made basic with aqueous ammonia and extracted twice with 150 ml of ethyl acetate. The combined extracts were washed, dried over sodium sulfate and evaporated *in vacuo*. Crystallization of the residue from a mixture of *tert*-butyl alcohol and isopropyl ether gave 7.2 g of **8c**, mp 88-89°.

6-(2,3-Dimethoxyphenyl)-N^2,N^2-dimethyl-3-cyclohexene-1,2-diamine, Dihydrochloride (**8d**).

Compound **8d** was obtained by method A from 30.0 g (0.098 moles) of **7d**. After the basic work-up, the dihydrochloride of **8d** was prepared by the addition of two equivalents of 2-propanolic hydrogen chloride to a cold solution of the base in 2-propanol giving 18.9 g of pure **8d** as nearly white crystals, mp 245-246°, dec; uv: λ max nm (ε) 219 (9000), 270-280 plateau (1600); ^{1}H nmr (deuterium oxide): δ 2.50 (m, 2H, CH_2), 3.00 [s, 6H, N(CH_3)$_2$], 3.60 (m, 1H, H-6), 3.78 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 6.90-7.25 (m, 3H, aromatic).

4-[6-Amino-5-(dimethylamino)-3-cyclohexen-1-yl]-2-methoxyphenyl Ethyl Carbamate, Dihydrochloride Dihydrate (**8e**).

Compound **8e** was prepared from 26.3 g (0.072 mole) of **7e** using method A. After acetic acid solution was evaporated, the residue was made basic with aqueous ammonia at 15°, and extracted three times with 150 ml of chloroform. The worked-up base was dissolved in 2-propanol and treated with hydrogen chloride to *p*H 2.0 giving 24.8 g of **8e**, mp 192-193°, dec. Recrystallization from 95% ethanol gave **8e** as a dihydrochloride dihydrate, mp 192-193°, dec; uv: λ max nm (ε) 216 (9400), 272 (2800), 278 sh (2600); ir (nujol mull): 3450, 3300 (NH), 1725 (C=O) cm^{-1}. The water of crystallization was confirmed by the Karl Fischer method giving 7.7% (8.14% theoretical).

4-[6-Amino-5-(dimethylamino)-3-cyclohexen-1-yl]-2-methoxyphenol (**8f**).

Compound **8f** was prepared by method A from 28.3 g (0.096 mole) of **7f**. The work-up was done using aqueous ammonia for the neutralization of the acetic residue and extraction three times with 350 ml of ethyl acetate. After the removal of solvent, the residue was triturated with ether to give 16.5 g of off-white crystals, mp 118-120°. Recrystallization from acetonitrile gave 11.6 g of pure **8f**.

Method C. *Via* Solvolysis of **8e**.

A stirred solution of 8.8 g (0.02 mole) of carbamate **8e** in 50 ml of methanol was treated with 8.0 g of sodium methoxide at 15° and allowed to stand overnight at room temperature. The solu-

tion was adjusted to *p*H 7.0 with acetic acid and evaporated *in vacuo*. The residue was taken up with water and extracted twice with 50 ml of ethyl acetate. The extracts were dried and concentrated to a low volume to give, upon cooling, 13.5 g of **8f**, mp 120-121°. Recrystallization from acetonitrile gave 2.5 g of pure **8f**; uv: λ max nm (ε) 230 (7870), 280 (3150); ir (chloroform): 3595 (OH), 3400 (NH_2) cm^{-1}.

*N*²,*N*²-Dimethyl-6-(2-naphthalenyl)-3-cyclohexene-1,2-diamine (**8g**).

Compound **8g** was prepared from 10.0 g (0.034 mole) of **7g** by method A and isolated as a dihydrochloride (5.8 g, mp 265-266° dec) from 2-propanol. An analytical sample, mp 266-267° dec, was obtained by recrystallization from acetonitrile; uv: λ max nm (ε) 228 (114,690), 259 sh (3390), 263 sh (4410), 272 (4750), 283 (3050).

General Procedure for the Synthesis of Amides **9a-e**, **9g**. Method A (Table III).

N-[6-(3,4-Dimethoxyphenyl)-2-(dimethylamino)-3-cyclohexen-1-yl]-4-(trifluoromethyl)benzamide (**9a**). Method A.

4-Trifluoromethylbenzoyl chloride (10.6 g, 0.055 mole) was added to a stirred mixture of 13.8 g (0.05 mole) of 6-(3,4-dimethoxyphenyl)-*N*²,*N*²-dimethyl-3-cyclohexene-1,2-diamine (**8a**) and 100 ml of 10% aqueous sodium hydroxide in 300 ml of chloroform dropwise at 10° over a period of 15 minutes. After the mixture was stirred for an additional 45 minutes at 10-15°, the chloroform phase was washed with water, dried over sodium sulfate and evaporated. The residue was crystallized from ethyl acetate to give 13.9 g (62% yield) of **9a** as white crystals, mp 152-153°; uv: λ max nm (ε) 220 (15,780), 272-276 plateau (3950); ir (nujol): 3275 (NH), 1630 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): 2.35 [m, 8H, CH_2 and $N(CH_3)_2$], 3.10 (m, 1H, H-6), 3.50 (m, 1H, H-2), 3.67, 3.73 [ss, 6H, $(OCH_3)_2$], 4.25 (m, 1H, H-1), 5.72 (m, 2H, vinylic), 5.95 (1H, NH), 6.65 (2H, H-2′, H-5′), 6.75 (J = 8.5 Hz, 1H, H-6′), 7.28 (m, narrow, 4H, aromatic). The above procedure (Method A) was used to prepare amides **9b-e**.

N-[6-(1,3-Benzodioxol-5-yl)-2-(dimethylamino)-3-cyclohexen-1-yl]-benzamide (**9b**).

This compound had uv: λ max nm (ε) 224 (12,200), 286 (3800); ir (chloroform): 3400 (NH), 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (m, 2H, CH_2-5), 2.39 [s, 6H, $N(CH_3)_2$], 3.08 (m, 1H, H-6), 3.49, 3.53 (d of multiplets, 1H, H-2), 4.44 (m, after deuterium oxide exchange: dd, J = 11.5 Hz and 9.8 Hz, 1H, H-1), 5.70 (d of multiplets, 1H, H-3), 5.79 (N*H*), 5.85 (s, 2H, OCH_2O), 5.89 (m, H-4), 6.77-8.10 (m, 3H, H-3′, H-4′, H-6′), 7.25-7.45 (m, 5H, C_6H_5CO protons); ^1H nmr (deuteriomethanol): 2.32 (m, 2H, CH_2-5), 2.39 [s, 6H, $N(CH_3)_2$], 3.03 (m, 1H, H-6), 3.59 (d of multiplets, 1H, H-2), 4.48 (dd, J = 11.5 Hz and 9.6 Hz), 5.70 (d of multiplets, 1H, H-3), 5.79 (s, 2H, OCH_2O), 5.94 (m, 1H, H-4), 6.30-6.80 (m, 3H, H-3′, H-4′, H-6′), 7.27-7.45 (m, 5H, C_6H_5CO protons).

N-[2-(Dimethylamino)-6-(3,4,5-trimethoxyphenyl)-3-cyclohexen-1-yl]benzamide (**9c**).

This compound had uv: λ max nm (ε) 220 (15,800), 273 (3960); ir (chloroform): 3380 (NH), 1655 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.28 (m, 2H, CH_2), 2.38 [s, 6H, $N(CH_3)_2$], 3.20 (m, 1H, H-6), 3.50 (m, 1H, H-2), 3.68 (s, 3H, 4′-OCH_3), 3.74 [s, 6H, 3′,5′-$(OCH_3)_2$], 4.50 (m, 1H, H-1), 5.75 (m, 2H, vinylic), 5.95 (1H, N*H*), 8.48 (s, 2H, H-2′, H-6′), 7.15-7.42 (m, 5H, C_6H_5CO).

N-[6-(2,3-Dimethoxyphenyl)-2-dimethylamino)-3-cyclohexen-1-yl]-benzamide (**9d**).

This compound had uv: λ max nm (ε) 218 sh (17,500), 270 (2660); ir (chloroform): 3390 (NH), 1645 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 [m, 8H, CH_2 and $N(CH_3)_2$], 3.30 (m, 1H, H-6), 3.50 (m, 1H, H-2), 3.67 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.45 (m, 1H, H-1), 5.75 (m, 2H, vinylic), 6.03 (1H, NH), 6.60 (m, 1H, H-4′), 6.85 (m, 2H, H-5′, H-6′), 7.08-7.45 (m, 5H, C_6H_5CO).

2,4-Dichloro-*N*-[6-(3,4-dimethoxyphenyl)-2-(dimethylamino)-3-cyclohexen-1-yl]benzamide (**9e**).

This compound had uv: λ max nm (ε) 222 sh (15,280), 274-280 plateau (4050); ir (chloroform): 3400 (NH), 1660 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.34 (m, 2H, CH_2), 2.40 [s, 6H, $N(CH_3)$], 3.00 (m, 1H, H-6), 3.50 (m, 1H, H-2), 3.83, 3.86 [ss, 6H, $(OCH_3)_2$], 4.48 (m, 1H, H-1), 5.82 (m, 3H, N*H* and two vinylic protons), 6.75-7.85 (m, 6H, aromatic).

N-[6-(3,4-Dimethoxyphenyl)-2-(dimethylamino)-3-cyclohexen-1-yl]-3,4-dimethoxybenzeneacetamide (**9f**).

Method B.

(3,4-Dimethoxyphenyl)acetyl chloride (11.8 g, 0.055 mole) was added dropwise to a stirred solution of 13.8 g (0.05 mole) of **8a** and 26.1 g (0.33 mole) of pyridine in 150 ml of chloroform at 0°. After one hour at 0-10°, the solution was evaporated *in vacuo*. The residue was taken up with aqueous sodium carbonate and extracted twice with 175 ml of dichloromethane. The combined extracts were washed, dried over sodium sulfate and evaporated. Crystallization of the residue from ethyl acetate gave 11.6 g of **9f** as fluffy, white crystals, mp 144-145°; uv: λ max nm (ε) 228-232 plateau (14,550), 276-282 (4460); ir (chloroform): 3360 (NH), 1632 (C=O) cm^{-1}.

N-[2-(Dimethylamino)-6-(2-naphthalenyl)-3-cyclohexen-1-yl]benzamide (**9g**).

This compound had uv: λ max nm (ε) 224 (47,360), 250-260 plateau (5920), 276 (5550), 288 sh (3330); ir (chloroform): 3400 (NH), 1645 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 [m, 8H, CH_2 and $N(CH_3)_2$], 3.25 (m, 1H, H-6), 3.50 (m, 1H, H-2), 4.55 (m, 1H, H-1), 5.75 (m, 2H, vinylic), 6.02 (m, NH), 6.70-7.70 (m, 12H, aromatic).

N-[6-(3,4-Dimethoxyphenyl)-2-(dimethylamino)-3-cyclohexen-1-yl]-*N*′-ethylurea (**10a**).

Ethyl isocyanate (2.35 g, 0.033 mole) was added dropwise to a solution of 8.65 g (0.03 mole) of 6-(3,4-dimethoxyphenyl)-*N*²,*N*²-dimethyl-3-cyclohexene-1,2-diamine (**8a**) in 125 ml of dichloromethane at 20° and allowed to stand overnight at room temperature. The tlc (silica gel G, dioxane-methanol, 1:1) showed complete reaction, the new product **10a** having faster mobility (R_f = 0.25) than the starting **8a** (R_f = 0.2). Methanol (0.5 ml) was added to destroy excess isocyanate and the solution was evaporated to dryness. Crystallization of the residue from ethyl acetate gave 9.9 g of pure **10a**, mp 138-139°; uv: λ max nm (ε) 229 (8350), 279 (2800), 286 sh (2400); ir (chloroform): 3380 (NH), 1648 (C=O), 1594 (NHC=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.95 (t, J = 8.0 Hz, 3H, CH_2CH_3), 2.15 (m, 2H, CH_2-5), 2.30 [s, 6H, $N(CH_3)_2$], 2.90 (m, 5H), 3.75, 3.79 [6H, $(OCH_3)_2$], 4.08 (m, 2H, H-1 and NH), 5.70 (m, 2H, vinylic), 6.45 (NH), 6.68 (m, 3H, aromatic).

Following the above procedure, compounds **10b** and **10c** were

prepared. Yields, melting points and solvents of crystallization are listed in Table III.

N-[6-(3,4-Dimethoxyphenyl)-2-(dimethylamino)-3-cyclohexen-1-yl]-*N'*-(1-methylethyl)urea (**10b**).

This compound had uv: λ max nm (ε) 229 (8300), 279 (2750); ir (chloroform): 3420, 3340 (NH), 1650 (C=O), 1590 (NHCO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.98 [d, J = 8.0 Hz, 6H, $CH(CH_3)$], 2.35 [8H, CH_2-5 and $N(CH_3)$], 2.60 (m, 1H), 3.35 (m, 1H), 3.75. 3.78 [m, 7H, H-1 and $(OCH_3)_2$], 4.00 (1H, N*H*), 5.45 (m, 1H, NH), 5.70 (m, 2H, vinylic), 6.65 (m, 3H, aromatic).

N-[6-(1,3-Benzodioxol-5-yl)-3-cyclohexen-1-yl]-*N'*-ethylurea (**10c**).

This compound had uv: λ max nm (ε) 234 (4400), 286 (4000); ir (chloroform): 3390, 3200 (NH), 1655 (C=O), 1690 (NHCO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.02 (t, J = 8.0 Hz, 3H, CH_2CH_3), 2.20 (m, 2H, CH_2-5), 2.35 [s, 6H, $N(CH_3)$], 2.60-3.75 (m, 5H), 4.15 (m, 1H, H-1), 5.85 (m, 4H, vinylic and O-CH_2-O), 6.68 (s, 3H, aromatic), 7.10 (m, 1H, NH).

Bischler-Napieralski Cyclodehydration Products, **3** and **11**. Table IV. General Procedure.

1,4,4a,10b-Tetrahydro-8,9-dimethoxy-*N*,*N*-dimethyl-6-[4-(trifluoromethyl)phenyl]-4-phenanthridinamine (**3a**).

A solution of 13.5 g (0.03 mole) of *N*-[6-(3,4-dimethoxyphenyl)-2-(dimethylamino)-3-cyclohexen-1-yl]-α,α,α-trifluorotoluamide (**9a**) in 75 ml of phosphorus oxychloride was refluxed under nitrogen for 90 minutes. The subsequent tlc (silica gel G, methanol) showed complete reaction. The contents were poured into crushed ice, made basic with sodium hydroxide and extracted three times with 250 ml of dichloromethane. The combined extracts were washed, dried over sodium sulfate and evaporated. The residue was crystallized from *tert*-butyl alcohol to give 6.2 g of off-white crystals, mp 173-174°. An analytical sample was recrystallized from acetonitrile, mp 174-175°; uv: λ max nm (ε) 236 (25,400), 276-282 plateau (5170), 308-312 plateau (5600); ^1H nmr (deuteriochloroform): δ 2.23 (m, 1H, H_{axial}-1), 2.57 [s, 6H, $N(CH_3)_2$], 2.78 (m, 2H, H_{eq}-1 and H-10b), 3.28 (m, 1H, H-4a), 3.76 (s, 3H, OCH_3), 3.82 (m, 1H, H-4), 3.98 (s, 3H, OCH_3), 5.82 (d of multiplets, $J_{2,3}$ = 10.2 Hz, H-3), 6.00 (m, 1H, H-2), 6.76 (s, 1H, H-10), 6.88 (s, 1H, H-7), 7.70 (d, J = 8.2 Hz, H-3', H-5'), 7.80 (d, J = 8.2 Hz, H-2', H-6'); ms: m/z 430.

1,4,4a,10b-Tetrahydro-9,10-dimethoxy-*N*,*N*-dimethyl-6-phenyl-4-phenanthridinamine, Hydrochloride (**3b**).

This compound had uv: λ max nm (ε) 234 (13,560), 280 (11,170), 294 (9970); ^1H nmr (deuteriomethanol, for the base): δ 2.25 (m, 1H, H_a-1), 2.37 [s, 6H, $N(CH_3)_2$], 2.88 (m, 1H, H_e-1), 3.16 (m, 1H, H-4a), 3.46 (m, 1H, H-10b), 3.63 (d of m, $J_{4,4a}$ = 9.1 Hz, 1H, H-4), 3.77 (3H, OCH_3), 3.88 (3H, OCH_3), 5.79 (m, 1H, H-3), 6.03 (m, 1H, H-2), 6.97 (s, 2H, H-7 and H-8), 7.43 (m, 3H, H-3', H-4', H-5'), 7.50 (m, 2H, H-2', H-6'); ms: m/z 362.

1,4,4a,10b-Tetrahydro-7,8,9-trimethoxy-*N*,*N*-dimethyl-6-phenyl-4-phenanthridinamine, Hydrochloride (**3c**).

This compound had uv: λ max nm (ε) 230 sh (20,160), 282 (9010); ^1H nmr (DMSO-d_6, for base): δ 2.25 (m, 1H, H_a-1), 2.36 [s, 6H, $N(CH_3)_2$], 2.85 (m, 1H, H_e-1), 3.15 (m, 1H, H-4a), 3.43 (m, 1H, H-10b), 3.65 (m, 1H, H-4), 3.24 (OCH_3), 3.64 (OCH_3), 3.85 (OCH_3), 5.75 (m, 1H, H-3), 6.05 (m, 1H, H-2), 6.75 (1H, H-10), 7.35 (m, 5H, phenyl protons).

6-(2,4-Dichlorophenyl)-1,4,4a,10b-tetrahydro-8,9-dimethoxy-*N*,*N*-dimethyl-4-phenanthridinamine (**3d**).

This compound had uv: λ max nm (ε) 226-230 plateau (22,430), 282 (6040), 308-314 plateau (5610); ^1H nmr (deuteriochloroform): δ 2.23 (m, 1H, H_a-1), 2.48 [s, 6H, $N(CH_3)_2$], 2.75 (m, 2H, H_e-1, H-10b), 3.25 (m, 1H, H-4a), 3.75 (m, 4H, H-4 and OCH_3), 3.95 [s, 3H, (OCH_3)], 5.85 (m, 1H, H-3), 5.96 (m, 1H, H-2), 6.50 (s, 1H, H-10), 6.90 (s, 1H, H-7), 7.30-7.60 (m, 3H, phenyl protons).

6-[(3,4-Dimethoxyphenyl)methyl]-1,4,4a,10b-tetrahydro-8,9-dimethoxy-*N*,*N*-dimethyl-4-phenanthridinamine (**3e**).

This compound had uv: λ max nm (ε) 226 (20,130), 278 (10,040), 298-306 plateau (6650); ^1H nmr (deuteriochloroform): δ 2.15 (m, 1H, H_a-1), 2.39 [s, 6H, $N(CH_3)_2$], 2.57 (m, 1H, H_e-1), 2.68 (m, 1H, H-10b), 3.07 (m, 1H, H-4a), 3.58 (m, 1H, H-4), 3.69 (OCH_3), 3.73, 3.75 [6H, $(OCH_3)_2$], 3.82 (OCH_3), 3.85-4.05 (m, 2H, two benzylic protons), 5.82 (m, 1H, H-3), 5.93 (m, 1H, H-2), 6.63-6.83 (m, 4H, aromatic), 6.92 (s, 1H, H-7); ms: m/z 436.

1,4,4a,12b-Tetrahydro-*N*,*N*-dimethyl-4-benzo[j]phenanthridinamine (**3f**).

This compound had uv: λ max nm (ε) 224 (43,710), 246 sh (19,740), 316-320 plateau (7050); ^1H nmr (deuteriochloroform): δ 2.20 (m, 1H, H_a-1), 2.45 [s, 6H, $N(CH_3)_2$], 2.76 (m, 2H, H_e-1, H-10b), 3.20 (m, 1H, H-4a), 3.85 (m, 1H, H-4), 5.75 (m, 1H, H-3), 5.88 (m, 1H, H-2), 7.10-8.10 (m, 11H, aromatic); ms: m/z 352.

N^6-Ethyl-1,4,4a,10b-tetrahydro-8,9-dimethoxy-N^4,N^4-dimethyl-4,6-phenanthridinediamine, Ethanolate, Dihydrochloride (**11a**).

A stirred suspension of 3.5 g (0.01 mole) of *N*-[6-(3,4-dimethoxyphenyl)-2-(dimethylamino)-3-cyclohexen-1-yl]-N^1-ethylurea (**10a**) and 15 ml of phosphorus oxychloride was heated to the boiling point and the resulting yellowish solution was refluxed for 30 minutes under nitrogen. After standing overnight at room temperature, the resulting white precipitate (3.6 g) was collected by filtration, mp 258-259°. Recrystallization from absolute ethanol gave 3.5 g of pure **11a** as a dihydrochloride containing one mole of ethanol, mp 260-261° dec; uv: λ max nm (ε) 229 (33,400), 277 (11,650), 313 (8800). The tlc (dioxane-methanol, 1:1) showed the product **11a** having slower mobility (R_f = 0.2) than the starting urea **10a** (R_f = 0.25); ms: m/z 329.

1,4,4a,10b-Tetrahydro-8,9-dimethoxy-N^4,N^4-dimethyl-N^6-(1-methylethyl)-4,6-phenanthridinediamine (**11b**).

This compound had uv: λ max nm (ε) 229 (29,320), 277 (10,800), 313 (7760); ir (chloroform): 3400 (NH), 1625, 1602 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.22 [d, J = 7.0 Hz, 6H, $CH(CH_3)_2$], 2.16 (m, 1H, H_a-1), 2.25 [s, 6H, $N(CH_3)_2$], 2.35 (m, 1H, H_e-1), 2.50-3.70 [m, 4H, H-10b, H-4, H-4a and $CH(CH_3)_2$], 3.80 (OCH_3), 3.86 (OCH_3), 5.55 (N*H*), 5.76 (m, 1H, H-3), 5.88 (m, 1H, H-2), 6.60 (1H, aromatic), 7.75 (1H, aromatic); ms: m/z 343.

N^6-Ethyl-1,4,4a,11b-tetrahydro-N^4,N^4-dimethyl[1,3]-dioxolo[4,5-j]phenanthridine-4,6-diamine (**11c**).

This compound had uv: λ max nm (ε) 229 (22,500), 274 (6400), 315 (6950); ir (chloroform): 3430 (NH), 1635, 1613 (C=N) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.33 (t, J = 6.9 Hz, 3H, CH_2CH_3), 2.12 (m, 1H, H_a-1), 2.30 [s, 6H, $N(CH_3)_2$], 2.73 (m, 1H, H_e-1), 2.88 (m, 1H, H-4a), 3.18 (m, 4H, CH_2CH_3, H-10b, H-4), 5.66 (1H, deuterium oxide-exchangeable, NH), 5.82 (d of m, $J_{2,3}$ = 10.1 Hz, H-3), 5.93 (m, 3H, H-2 and OCH_2O), 6.88 (s, 1H, H-10), 7.76 (s, 1H, H-7).

6-Aryl-1,4,4a,5,6,10b-hexahydro-*N,N*-dimethyl-4-phenanthridinamines (**4**).

Condensation of diamines **8** with aryl aldehydes under azeotropic conditions followed by cyclization of the resulting imines **12** will constitute method A.

1,4,4a,5,6,10b-Hexahydro-8,9-dimethoxy-*N,N*-dimethyl-6-phenyl-4-phenanthridinamine (**4a**). Method A.

A solution of 13.1 g (0.045 mole) of 6-(3,4-dimethoxyphenyl)-N^2,N^2-dimethyl-3-cyclohexene-1,2-diamine and 4.8 g (0.045 mole) of benzaldehyde in 200 ml of benzene was refluxed until the theoretical amount of water separated in a Dean-Stark trap. After the solvent was evaporated, the resulting imine **12a** was dissolved in 40 ml of trifluoroacetic acid and allowed to stand overnight at room temperature. The tlc (silica gel G, methanol-tetrahydrofuran, 2:1) showed complete reaction. The contents were poured onto crushed ice, made basic with 50% aqueous sodium hydroxide and extracted twice with 150 ml of dichloromethane. The combined extracts were washed, dried over sodium sulfate and evaporated. The residue was crystallized from 2-propanol to give 11.0 g of **4a** as white crystals, mp 184-185°; uv: λ max nm (ε) 232 (10,210), 280-286 plateau (4010), 290 (3650); ir (chloroform): 3300 (NH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.60 (NH), 2.02 (m, 1H, H-1 axial), 2.28 [s, 6H, $N(CH_3)_2$], 2.75 (m, 1H, H-1 equatorial), 2.86 (t, J = 10.1 Hz, 1H, H-4a), 3.05 (m, 1H, H-10b), 3.27 (m, 1H, H-4), 3.57 (s, 3H, 8-OCH_3), 3.87 (s, 3H, 9-OCH_3), 5.05 (s, 1H, H-6), 5.82 (d of m, $J_{2,3}$ = 10.3 Hz, H-3), 5.95 (m, 1H, H-2), 6.16 (s, 1H, H-7), 6.76 (s, 1H, H-10), 7.23-7.40 (m, 5H, phenyl protons); ms: m/z 364.

Following the above general procedure (A), most of 6-arylhexahydrophenanthridines **4** were prepared and are listed in Table V. In many instances it was necessary to reflux the intermediate imine **12** in excess trifluoroacetic acid in the same reaction pot (after the solvent was first removed) to complete the reaction. The method, temperature, time or reaction as well as solvents of crystallization are indicated in Table V. Whenever sensitive groups were present, aqueous ammonia or sodium carbonate (instead of sodium hydroxide), were used as neutralizing base. The potassium borohydride reduction of tetrahydrophenanthridines **3** in methanol to give **4** will represent method B. Compounds **4c** and **4m**, prepared by both methods, are identical.

1,4,4a,5,6,10b-Hexahydro-9,10-dimethoxy-*N,N*-dimethyl-6-phenyl-4-phenanthridinamine (**4b**). Method B.

A stirred solution of 5.2 g (0.012 mole) of 1,4,4a,10b-tetrahydro-9,10-dimethoxy-*N,N*-dimethyl-6-phenyl-4-phenanthridinamine hydrochloride (**3b**) in 100 ml of methanol was treated with 1.9 g (0.036 mole) of potassium borohydride portionwise at 10°. After additional stirring for two hours at 15-20°, acetic acid was added to *p*H 7.0 and the solution was evaporated *in vacuo*. The residue was extracted twice with 150 ml of dichloromethane. The combined extracts were washed, dried over sodium sulfate and evaporated. Crystallization of the residue from 2-propanol gave 3.4 g of **4b** as white crystals; uv: λ max nm (ε) 232 (10,220), 280-285 plateau (4000), 292 (3600); ir (chloroform): 3320 (NH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.75 (NH), 2.01 (m, 1H, H_a-1), 2.26 [s, 6H, $N(CH_3)_2$], 2.73 (m, 1H, H_e-1), 2.83 (t, J = 10.0 Hz, 1H, H-4a), 3.03 (m, 1H, H-10b), 3.27 (m, 1H, H-4), 3.75 (s, 3H, 10-OCH_3), 3.80 (s, 3H, 9-OCH_3), 5.06 (s, 1H, H-6), 5.79 (d of m, J = 10.0 Hz, 1H, H-3), 5.95 (m, 1H, H-2), 6.23 (d, J = 8.5 Hz, 1H, H-7), 6.57 (d, J = 8.5 Hz, 1H, H-8), 7.25-7.40 (m, 5H, phenyl protons).

1,4,4a,5,6,10b-Hexahydro-7,8,9-trimethoxy-*N,N*-dimethyl-6-phenyl-4-phenanthridinamine (**4c**). Method B.

This compound had uv: λ max nm (ε) 252-262 plateau (790), 272-280 plateau (1180); ir (chloroform): 3225 (NH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.97 (m, 1H, H_a-1), 2.25 [s, 6H, $N(CH_3)$], 2.55 (m, 1H, N*H*), 2.73 (m, 2H, H_e-1 and H-4a), 2.98 (s, 3H, OCH_3-7), 3.02 (m, 1H, H-10b), 3.12 (m, 1H, H-4), 3.73 (s, 3H, OCH_3-8), 3.85 (s, 3H, OCH_3-9), 5.15 (1H, H-6), 5.78 (d of m, J = 10.0 Hz, 1H, H-3), 5.90 (m, 1H, H-2), 6.80 (s, 1H, H-10), 7.22 (m, 5H, phenyl protons); ^1H nmr (deuteriomethanol): δ 1.93 (m, 1H, H_a-1), 2.30 [s, 6H, $N(CH_3)_2$], 2.73 (m, 1H, H-4a), 2.82-2.98 (m, 2H, H_e-1 and 10b), 3.02 (3H, OCH_3-7), 3.21 (m, 1H, H-4), 3.68 (s, 3H, OCH_3-8), 3.82 (s, 3H, OCH_3-9), 5.07 (1H, H-6), 5.78 (d of m, J = 10.0 Hz, H-3), 5.98 (m, 1H, H-2), 6.73 (s, 1H, H-10), 7.23 (m, 5H, phenyl protons).

Compound **4c** was also prepared by method A to give 80% of pure product, mp 126-127°, and was identical in all respects to the above obtained by method B.

By following the above procedure B, the tetrahydrophenanthridines **3e** and **3f** (Table IV) were converted into hexahydrophenanthridines **4j** and **4m**, respectively (Table V).

6-([3,4-Dimethoxyphenyl)methyl]-1,4,4a,5,6,10b-hexahydro-8,9-dimethoxy-*N,N*-dimethyl-4-phenanthridinamine Dihydrochloride (**4j**).

This compound had uv: λ max nm (ε) 230-232 (15,860), 280 (6650); ^1H nmr (deuteriochloroform, for the base): δ 1.88 (m, 1H, H_a-1), 2.15 [s, 6H, $N(CH_3)_2$], 2.62 (m, 2H), 2.78 (m, 1H), 2.90 (m, 1H), 3.13 (m, 1H, H-4), 3.54 (m, 1H), 3.80, 3.81, 3.83, 3.84 [12H, $(OCH_3)_4$], 4.20 (m, 1H), 5.76 (m, H-3), 5.92 (m, H-2), 6.84 (s, 1H, H-7), 6.88-6.99 (m, 4H, aromatic); ms: m/z 438.

4-(Dimethylamino)-1,4,4a,5,6,10b-hexahydro-9-methoxy-6-phenyl-8-phenanthridinol (**4k**).

This compound had uv: λ max nm (ε) 228 sh (8760), 282-290 (3500); ir (chloroform): 3595 (OH), 3350 (NH) cm^{-1}; ^1H nmr (deuteriomethanol): δ 1.96 (m, 1H, H_a-1), 3.00 [s, 6H, $N(CH_3)$], 2.82 (m, 1H, H_e-1), 2.87 (t, J = 9.5 Hz, 1H, H-4a), 3.01 (m, 1H, H-10b), 3.28 (m, 1H, H-4), 3.81 (3H, OCH_3), 4.97 (s, 1H, H-6), 5.82 (m, 1H, H-3), 5.98 (m, 1H, H-2), 6.06 (s, 1H, H-7), 6.81 (s, 1H, H-10), 7.35-7.40 (m, 5 phenyl protons).

N-[[4-(Dimethylamino)-1,4,4a,5,6,11b-hexahydro[1,3]dioxolo[4,5-j]phenanthridin-6-yl]phenyl]acetamide (**4l**).

This compound had uv: λ max nm (ε) 247 (23,000), 291 (2550); ir (chloroform): 3410, 3390 (NH), 1696 (C=O), 1523 (NHCO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.95 (m, 1H, H_a-1), 2.18 (s, 3H, CH_3CO), 2.25 [s, 6H, $N(CH_3)_2$], 2.55-2.83 (m, 3H, H_e-1, H-5, H-4a), 3.00 (m, H-10b), 3.25 (m, 1H, H-4), 4.97 (s, H-6), 5.78-5.83 (3H, H-3 and OCH_2O), 5.92 (m, 1H, H-2), 6.14 (s, 1H, H-7), 6.73 (s, 1H, H-10), 7.28 (m, 3H, H-2′, H-6′ and N*H*CO), 7.48 (d, J = 8.5 Hz, H-3′, H-5′).

The 6-unsubstituted hexahydrophenanthridines **4o-4s** (Table V) were prepared by refluxing a solution of diamines **8** dihydrochlorides and excess paraformaldehyde in proper alcohol (usually methanol or ethanol) at *p*H 1.5-2.5. In one case (preparation of **4q**) the reaction was rather sluggish, and it was necessary to use *n*-propanol to raise the refluxing temperature. The preparation of **4o** will represent method C.

1,4,4a,5,6,10b-Hexahydro-8,9-dimethoxy-*N,N*-dimethyl-4-phen-

anthridinamine (**4o**).

A solution of 5.53 g (0.02 mole) of 6-(3,4-dimethoxyphenyl)-N^2,N^2-dimethyl-3-cyclohexene-1,2-diamine (**8a**) and 1.0 g of paraformaldehyde in 75 ml of ethanol (adjusted to *p*H 2.0 with hydrochloric acid) was refluxed for two hours when the white crystals of dihydrochloride began to separate. After three hours at room temperature, 5.5 g (76% yield) of **4o** dihydrochloride was collected, mp 254-255° dec.

Anal. Calcd. for $C_{17}H_{24}N_2O_2 \cdot 2HCl$: C, 56.51; H, 7.25; N, 7.76. Found: C, 56.39; H, 7.33; N, 7.68.

The free base **4o** was regenerated by dissolving the dihydrochloride in water, treatment with potassium carbonate and extraction with ethyl acetate. Concentration of the extract (after washing and drying) to a low volume and cooling gave 4.1 g of pure **4o** as white crystals, mp 153-154°. The tlc (silica gel G, dioxane-methanol, 1:1) shows the new product **4o** to have faster mobility (R_f = 0.3) than the starting diamine **8a** (R_f = 0.23).

Alternate Procedure: Two-step, "One-pot Reaction" (from **7a**).

To a vigorously stirred solution of 12.2 g (0.04 mole) of nitroamine **7a** in 120 ml of glacial acetic acid was added 18.0 g of zinc dust portionwise over 30 minutes at 18-22° and allowed to stir for 16 hours. The tlc (dioxane-methanol, 1:1) showed complete reduction of the nitro group, the new diamine having considerably slower mobility (R_f = 0.23) than the starting **7a** (R_f = 0.55). The solvent was evaporated under rotary evaporator at 35°. The residue was taken up with 100 ml of ethanol, adjusted to *p*H 2.0 with hydrochloric acid and treated with 2.5 g of paraformaldehyde. After the solution was refluxed for two hours and allowed to stand overnight at room temperature, the product **4o**, as white crystalline dihydrochloride, was collected (12.1 g, 87% yield), mp 254-255° dec; uv (for free base): λ max nm (ε) 226 sh (7600), 282-286 plateau (3400); ir (chloroform): 3350, (NH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.90 (m, 1H, axial H of CH_2-1), 2.35 [s, 6H, N(CH_3)], 3.64 (NH, deuterium oxide-exchangeable), 2.55-2.95 (m, 4H, 1H equatorial of CH_2-1, H-10b, H-4a, H-4), 3.87 [6H, (OCH_3)$_2$], 4.08 (m, narrow, 2H, benzylic CH_2), 5.75 (m, 1H, H-3), 5.92 (m, 1H, H-2), 6.65 (s, 1H, H-7), 6.83 (s, 1H, H-10); ms: m/z 284.

1,4,4a,5,6,10b-Hexahydro-9,10-dimethoxy-*N*,*N*-dimethyl-4-phenanthridinamine, Acetate, Dihydrochloride (**4q**).

A solution of 5.7 g (0.02 mole) of **8d**, 1.5 g of paraformaldehyde and 5 ml of concentrated hydrochloric acid in 100 ml of ethanol was refluxed for two hours. The subsequent tlc (alumina;acetonitrile) showed only about 10% conversion, R_f = 0.5. The solution was concentrated to about 15 ml, 75 ml of 1-propanol and 0.5 g of paraformaldehyde were added and the solution was refluxed for seven hours after which time all starting **8d** was consumed (R_f = 0.35). On cooling to 25°, 5.6 g of **4q** dihydrochloride had separated, mp 214-215°, dec. Recrystallization from glacial acetic acid gave analytically pure **4q** dihydrochloride containing 1 mole of acetic acid as a solvent of crystallization, mp 206-207°, dec; uv: λ max nm (ε) 227 sh (8600), 277-284 plateau (1800); ir (nujol): 3420, 3290, 1707 (C=O) cm^{-1}; ^1H nmr (deuteriomethanol + sodium deuteroxide): δ 2.02 (m, 2H, CH_2-1), 2.32 [s, 6H, N(CH_3)$_2$], 2.63 (t, J = 9.6 Hz, 1H, H-4a), 2.98 (m, 1H, H-10b), 3.12 (m, 1H, H-4), 3.76 (s, 3H, 10-OCH_3), 3.85 (s, 3H, 9-OCH_3), 3.88, 3.97 (dd, J = 14.5 Hz, 2H, CH_2-6), 5.78 (m, 1H, H-3), 5.94 (m, 1H, H-2), 8.00, 8.40 (dd, $J_{7,8}$ = 8.5 Hz, 2H, H-7, H-8).

1,4,4a,5,6,10b-Hexahydro-*N*,*N*-dimethyl[1,3]dioxolo[4,5-j]phenanthridinamine (**4r**).

This compound had uv: λ max nm (ε) 232 sh (3400), 292 (4100); ir (chloroform): 3600 (NH), 1230, (OCH_2O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.87 (m, 1H, H_a-1), 2.23 [s, 6H, N(CH_3)$_2$], 2.46 (m, 1H, H_e-1), 2.52 (t, J = 9.8 Hz, H-4a), 2.62 (NH), 2.73 (m, 1H, H-10b), 3.11 (m, 1H, H-4), 3.88, 3.99 (dd, J = 14.7 Hz, 2H, CH_2-6), 5.72 (m, 1H, H-3), 5.82 (2H, OCH_2O), 5.88 (m, 1H, H-2), 6.44, 6.65 (ss, 2H, H-7, H-10).

1,4,4a,5,6,10b-Hexahydro-*N*,*N*-dimethyl-7,8,9-trimethoxy-4-phenanthridinamine, Methanolate, Dihydrochloride (**4s**).

Compound **4s** was isolated directly in a pure form from methanol as a reaction solvent; uv: λ max nm (ε) 226 sh (10,000), 278 (1200); ^1H nmr (deuteriochloroform + sodium deuteroxide): δ 1.97 (m, 1H, H_a-1), 2.24 [s, 6H, N(CH_3)$_2$], 2.57 (t, J = 9.5 Hz, 1H, H-4a), 2.62 (m, 1H, H_e-1), 2.81 (m, 1H, H-10b), 3.15 (m, 1H, H-4), 3.80 [broad, overlapping signals, 10H, (OCH_3)$_3$ and 1H of CH_2-6], 4.15 (d, J = 15.0 Hz, 1H, 1H of CH_2-6), 5.78 (d, J = 10.3 Hz, 1H, H-3), 5.92 (m, 1H, H-2), 6.68 (s, 1H, H-10).

5-Benzoyl-1,4,4a,5,6,10b-hexahydro-8,9-dimethoxy-*N*,*N*-dimethyl-4-phenanthridinamine (**4u**).

To a rapidly stirred mixture of 8.7 g (0.03 mole) of **4o**, 75 ml of chloroform and 60 ml of 10% aqueous sodium hydroxide was added 4.6 g (10% excess) of benzoyl chloride over a period of 15 minutes at 0° and continued to stir for additional 45 minutes. The chloroform phase was shaken up with 2 ml of methanol to destroy excess chloride, washed, dried over sodium sulfate and evaporated. Crystallization of the residue from ethyl acetate gave 9.1 g of pure **4u**; uv: λ max nm (ε) 229 sh (15,200), 280 (5050); ir (chloroform): 1628 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.15 (m, 1H, H_a-1), 2.38 [7H, N(CH_3)$_2$ and H_e-1], 2.55 (m, 2H, H-10b, H-4a), 3.15 (m, 1H, H-4), 3.75, 3.88 (6H, 8-OCH_3, 9-OCH_3), 3.95 (d, J = 12.0 Hz, 1H, 1H of CH_2-6), 4.25 (d, J = 12.0 Hz, 1H, 1H of CH_2-6), 5.75 (m, 1H, H-3), 5.92 (m, 1H, H-2), 6.65-6.83 (ss, H-7, H-10), 7.15 (m, 5H, phenyl protons).

1,4,4a,5,6,10b-Hexahydro-8,9-dimethoxy-*N*,*N*-dimethyl-5-(phenylmethyl)-4-phenanthridinamine (**4v**).

To a stirred suspension of 2.0 g of lithium aluminum hydride in 60 ml of anhydrous ether was added a solution of 5.9 g (0.015 mole) of **4u** in 20 ml of tetrahydrofuran at such a rate that the reaction temperature did not exceed 35°. After the mixture was stirred for three hours at 25°, the subsequent tlc (tetrahydrofuran-methanol, 1:2) showed complete reduction, the new product having a slower mobility (R_f = 0.25) than the startinf material (R_f = 0.35). Ethyl acetate (20 ml) was added at 0° to destroy excess lithium aluminum hydride, followed by the addition of aqueous sodium hydroxide. The suspension was filtered through the supercell, saturated with sodium chloride and extracted twice with 75 ml of ethyl acetate. The extracts were washed, dried and evaporated. Crystallization of the residue from 2-propanol gave 4.4 g of **4v** as white crystals, mp 100-101°; uv: λ max nm (ε) 227 (8800), 282-287 plateau (3800); ^1H nmr (deuteriochloroform): δ 2.03 (m, 1H, H_a-1), 2.46 [s, 6H, N(CH_3)$_2$], 2.78 (m, 1H, H_e-1), 2.98 (m, 1H, H-10b), 3.09 (dd, J = 11.4 Hz and 9.4 Hz, 1H, H-4a), 3.46, 3.90 (dd, J = 13.5 Hz, 2H, benzylic CH_2), 3.57 (m, 1H, H-4), 3.63, 3.95 (dd, J = 16.4 Hz, 2H, benzylic CH_2), 3.82, 3.89 [ss, 6H, (OCH_3)$_2$], 5.73 (d, J = 10.0 Hz, 1H, H-3), 5.93 (m, 1H, H-2), 6.46 (s, 1H, H-7), 6.79 (s, 1H, H-10), 7.30 (m, 5H, phenyl protons).

4-(Dimethylamino)-*N*-ethyl-1,4,4a,5,6,10b-hexahydro[1,3]dioxolo[4,5-j]phenanthridine-5(1*H*)-carboxamide (**4w**).

Ethyl isocyanate (1.55 g, 0.022 mole) was added to a solution of 5.44 g (0.02 mole) of **4r** in 50 ml of dichloromethane at 20° and it was allowed to stay overnight at room temperature. Methanol (0.5 ml) was added and the solution was evaporated. Crystallization of the residue from isopropyl ether gave 5.4 g of pure **4w** as white crystals, mp 138-139°; uv: λ max nm (ε) 233 (4000), 288 (4680); ir (chloroform): 3800, 3190 (NH), 1635 (C=O), 1560 (CONH); ^{1}H nmr (deuteriochloroform): δ 0.96 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.16 (m, 1H, H_a-1). 2.27 [s, 6H, $N(CH_3)_2$], 2.58 (m, 2H, H_e-1 and H-10b), 2.90 (m, 1H, H-4a), 3.08 (m, 2H, CH_2CH_3), 3.40 (m, 1H, H-4), 3.49 (d, J = 14.4 Hz, 1H of CH_2-6), 5.02 (d, J = 14.4 Hz, 1H of CH_2-6), 5.67 (m, 1H, H-3), 5.79, 5.84 (dd, J = 1.4 Hz, 2H, OCH_2O), 6.07 (m, 1H, H-2), 6.61 (s, 1H, H-7), 6.80 (s, 1H, H-10), 8.56 (1H, deuterium oxide-exchangeable, NH).

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[9] This series will be a subject of another paper.

[10] As the molecular models indicate, the dihedral angle between H-6 and H-1 (the latter in *pseudo*axial conformation) is smaller than between H-5 and H-6 which are in diaxial relationship.

[11] Two-Dimensional NMR Spectroscopy, W. R. Croasmun and R. M. K. Carlson, eds, VCH Publishers, Inc., New York, NY, 1987.

[12] The latter characteristics is easy to see, considering the mutual deshielding effect of the A-ring and the 6-substituent being nearly in-plane to each other. Note change in numbering.

[13] In the amide precursor, **9a**, the signals of protons H-1, H-2, and H-6 resonate at δ 4.25 (m), δ 3.51 (m) and δ 3.10 (m), respectively. On cyclodehydration to **3a**, those protons resonate at δ 3.28 (m), δ 3.82 (m) and δ 2.78 (m, together with one equatorial proton of CH_2-1). Note change in numbering.

[14] This lack of coupling between 6-H and the vicinal NH implies a dihedral angle of about 90° between these protons which could result from a deformation of a half-chair conformation.

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