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Syntheses and β-Adrenergic Blocking Activities of Carbostyril Derivatives

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Many 5-(3-amino-2-hydroxypropoxy)-8-alkoxy and acyloxy-3,4-dihydrocarbostyrils and 5-(3-amino-2-hydroxypropoxy)-8-alkoxycarbostyrils were synthesized from 5,8-dihydroxy-3,4-dihydrocarbostyril, and their β-adrenergic blocking activities were examined. Among them, 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril hydrochloride hydrate (IVh) was found to have potent β_1-selective adrenergic blocking activity.

Keywords——5-(3-amino-2-hydroxypropoxy)-8-alkoxy-3,4-dihydrocarbostyrils; 5-(3-amino-2-hydroxypropoxy-8-acyloxy-3,4-dihydrocarbostyrils; 5-(3-amino-2-hydroxypropoxy)-8-alkoxycarbostyrils; β-adrenergic blocking; 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril, β_1-selective; 5-(2,3-epoxypropoxy)-8-alkoxy-3,4-dihydrocarbostyrils; 8-benzyloxy-5-hydroxy-3,4-dihydrocarbostyril; 8-benzyloxy-5-(2,3-epoxypropoxy)-1-alkyl-3,4-dihydrocarbostyril; 3,4-dimethoxyphenethylamine

Since propranolol[1] was introduced, the study of β-adrenergic blocking agents has made remarkable progress. Recently, many compounds have been synthesized as candidates for the medical treatment of angina pectoris, arrythmia and hypertension, and research has centered on the synthesis of more potent,[2] more β_1-selective[3] or more potent anti-hypertensive[4] compounds. 5-(3-*tert*-Butylamino-2-hydroxypropoxy)-3,4-dihydrocarbostyril hydrochloride[5] (carteolol hydrochloride) was shown to have excellent β-adrenergic blocking activity by the present authors. In the present paper, 5-(3-amino-2-hydroxypropoxy)-8-alkoxy and acyloxy-

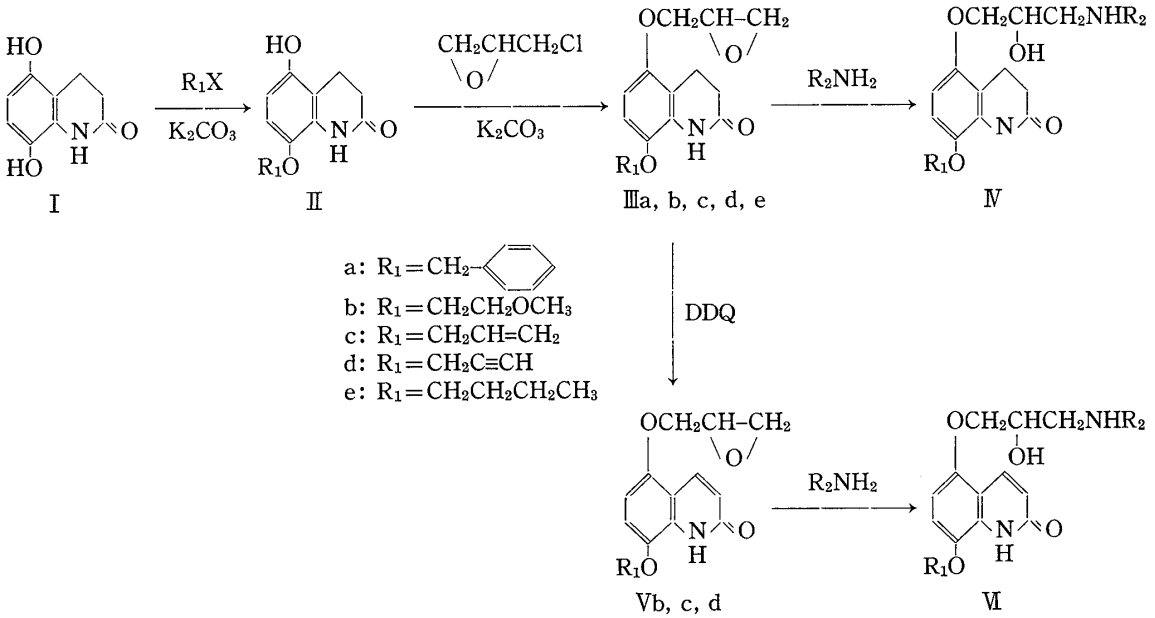


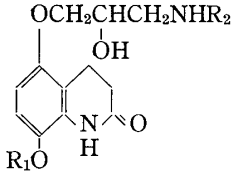
Chart 1

3,4-dihydrocarbostyrils and 5-(3-amino-2-hydroxypropoxy)-8-alkoxycarbostyrils were prepared as analogs of carteolol, and their β-adrenergic blocking activities were examined.

Chemistry

5-(3-Amino-2-hydroxypropoxy)-8-alkoxy-3,4-dihydrocarbostyrils (IVa—e) and 5-(3-amino-2-hydroxypropoxy)-8-alkoxycarbostyrils (IV) were synthesized from 5,8-dihydroxy-3,4-dihydrocarbostyril according to the method reported previously[6] as shown in Chart 1. Alkylation of 5,8-dihydroxy-3,4-dihydrocarbostyril (I) with alkyl halide gave the 8-alkoxy derivatives (IIa—e) as major products. Reaction of II, epichlorhydrin and K_2CO_3 gave the 5-(2,3-

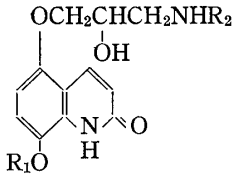
TABLE I. 5-(3-Amino-2-hydroxypropoxy)-8-alkoxy-3,4-dihydrocarbostyril Derivatives



Compd. No.	R_1	R_2	Acid salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
IVa$_1$	CH_2–Ph	iso-Pr	HCl	29	201—203	$C_{22}H_{28}N_2O_4\cdot HCl$	62.78 (62.83	6.94 7.17	6.65 6.50)
IVa$_2$	CH_2–Ph	*tert*-Bu	—	44	124—125	$C_{23}H_{30}N_2O_4$	69.32 (69.01	7.59 7.77	7.03 6.93)
IVa$_3$	CH_2–Ph	3,4-Di-MeO-phenethyl	—	44	108—109.5	$C_{29}H_{34}N_2O_6$	68.75 (68.83	6.77 6.94	5.53 5.41)
IVa$_4$	CH_2–Ph	CH_2CH_2–Ph	HCl	33	116—118	$C_{27}H_{30}N_2O_4\cdot HCl$	67.14 (67.09	6.47 6.62	5.80 5.60)
IVa$_5$	CH_2–Ph	$C(CH_3)_2CH_2$–Ph	—	40	80—82	$C_{20}H_{34}N_2O_4$	73.39 (73.05	7.22 7.26	5.90 5.75)
IVa$_6$	CH_2–Ph	4-MeO-Phenoxyethyl	—	34	67—69	$C_{28}H_{32}N_2O_6$	61.85 (61.70	5.88 6.54	4.81 4.75)
IVa$_7$	CH_2–Ph	3,4-Di-MeO-phenyl-α-Me-ethyl	—	31	133—135	$C_{30}H_{36}N_2O_6$	69.21 (69.42	6.97 7.12	5.38 5.36)
IVb$_1$	$CH_2CH_2OCH_3$	iso-Pr	HCl	62	168—169	$C_{18}H_{28}N_2O_5\cdot HCl$	55.59 (55.59	7.52 7.65	7.20 7.13)
IVb$_2$	$CH_2CH_2OCH_3$	*tert*-Bu	HCl H_2O	56	195—196	$C_{19}H_{30}N_2O_5\cdot HCl\cdot H_2O$	54.22 (54.06	7.90 7.99	6.65 6.61)
IVb$_3$	$CH_2CH_2OCH_3$	3,4-Di-MeO-phenethyl	HCl H_2O	11	101—103	$C_{25}H_{34}N_2O_7\cdot HCl\cdot H_2O$	60.96 (61.03	7.37 7.18	5.69 5.47)
IVb$_4$	$CH_2CH_2OCH_3$	CH_2CH_2–Ph	HCl	17	149.5—150.5	$C_{23}H_{30}N_2O_5\cdot HCl$	61.26 (60.86	6.93 6.84	6.21 6.27)
IVb$_5$	$CH_2CH_2OCH_3$	$C(CH_3)_2CH_2$–Ph	HCl	58	181—183	$C_{25}H_{34}N_2O_5\cdot HCl$	62.82 (62.71	7.17 7.47	5.86 5.86)
IVb$_6$	$CH_2CH_2OCH_3$	4-MeO-Phenoxyethyl	HCl H_2O	20	78—80	$C_{24}H_{32}N_2O_7\cdot HCl\cdot H_2O$	55.97 (56.08	6.85 6.79	5.44 5.41)
IVb$_7$	$CH_2CH_2OCH_3$	3,4-Di-MeO-phenyl-α-Me-ethyl	—	25	100—101.5	$C_{26}H_{36}N_2O_7$	63.91 (63.77	7.43 7.69	5.73 5.96)
IVb$_8$	$CH_2CH_2OCH_3$	3,4-OCH_2O-Phenethyl	HCl	17	115—117	$C_{24}H_{30}N_2O_7\cdot HCl$	58.24 (58.00	6.31 6.37	5.66 5.77)
IVc$_1$	$CH_2CH{=}CH_2$	*tert*-Bu	HCl	50	177—178	$C_{19}H_{28}N_2O_4\cdot HCl$	59.29 (59.24	7.59 7.86	7.28 7.20)
IVc$_2$	$CH_2CH{=}CH_2$	3,4-Di-MeO-phenethyl	HCl	65	154—156	$C_{25}H_{32}N_2O_6\cdot HCl$	60.91 (60.60	6.75 6.91	5.68 5.64)
IVc$_3$	$CH_2CH{=}CH_2$	$C(CH_3)_2CH_2$–Ph	HCl	21	180—182	$C_{25}H_{32}N_2O_4\cdot HCl$	65.13 (64.79	7.22 6.99	6.08 6.06)
IVc$_4$	$CH_2CH{=}CH_2$	3,4-Di-MeO-phenyl-α-Me-ethyl	—	18	163—165	$C_{26}H_{33}N_2O_6$	66.51 (66.37	7.08 6.99	5.97 6.05)
IVd$_1$	$CH_2C{\equiv}CH$	iso-Pr	HCl	63	205—206	$C_{18}H_{24}N_2O_4\cdot HCl$	58.61 (58.45	6.83 6.67	7.60 7.72)

Compd. No.	R_1	R_2	Acid salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
IVd$_2$	$CH_2C{\equiv}CH$	*tert*-Bu	HCl	84	182—183	$C_{19}H_{26}N_2O_4\cdot HCl$	59.60 (59.36	7.10 7.34	7.31 7.33)
IVd$_3$	$CH_2C{\equiv}CH$	3,4-Di-MeO-phenethyl	HCl	45	160—162	$C_{25}H_{30}N_2O_6\cdot HCl$	61.16 (60.93	6.36 6.49	5.70 5.79)
IVd$_4$	$CH_2C{\equiv}CH$	iso-Pr	HCl	49	201—202	$C_{19}H_{24}N_2O_4\cdot HCl$	59.60 (59.51	7.10 7.07	7.31 7.23)
IVd$_5$	$CH_2C{\equiv}CH$	$C(CH_3)_2CH_2$–Ph	HCl	13	190—192	$C_{25}H_{30}N_2O_3\cdot HCl$	65.42 (65.26	6.81 7.05	6.10 6.10)
IVd$_6$	$CH_2C{\equiv}CH$	4-H_2NOC-Phenoxyethyl	HCl	17	163—165	$C_{24}H_{27}N_3O_6\cdot HCl$	56.75 (57.21	5.95 5.81	8.27 8.13)
IVd$_7$	$CH_2C{\equiv}CH$	3,5-Di-MeO-phenoxy-ethyl	HCl	12	187—189	$C_{25}H_{30}N_2O_7\cdot HCl$	59.23 (58.97	6.16 6.45	5.52 5.49)
IVd$_8$	$CH_2C{\equiv}CH$	Cyclohexyl	HCl	55	201—202	$C_{21}H_{28}N_2O_4\cdot HCl$	61.68 (61.61	7.15 7.37	6.85 6.78)
IVd$_9$	$CH_2C{\equiv}CH$	$CH_2CH_2CH_2CH_3$	HCl	56	184—185	$C_{19}H_{26}N_2O_4\cdot HCl$	59.61 (59.74	7.11 7.41	7.31 7.08)
IVd$_{10}$	$CH_2C{\equiv}CH$	$CH_2CH{=}CH_2$	HCl	43	176—177.5	$C_{18}H_{22}N_2O_4\cdot HCl$	58.93 (59.03	6.32 6.28	7.64 7.53)
IVe	$CH_2CH_2CH_2CH_3$	3,4-Di-MeO-phenethyl	HCl	52	74—76	$C_{26}H_{36}N_2O_6\cdot HCl$	61.35 (61.27	7.33 7.14	5.50 5.63)
IVf	$CH_2CO(CH_2)_3CH_3$	3,4-Di-MeO-phenethyl	HCl 1/2H_2O	20	108—110	$C_{28}H_{38}N_2O_7\cdot HCl\cdot 1/2H_2O$	60.05 (59.74	7.20 7.55	5.00 5.00)
IVg	$CH_2COCH(CH_3)_2$	3,4-Di-MeO-phenethyl	HCl 1/2H_2O	42	118—120	$C_{27}H_{36}N_2O_7\cdot HCl\cdot 1/2H_2O$	59.39 (59.64	7.01 7.29	5.13 5.23)
IVh	CH_2COCH_3	3,4-Di-MeO-phenethyl	HCl H_2O	25	135—136	$C_{25}H_{32}N_2O_7\cdot HCl\cdot H_2O$	56.98 (57.05	6.69 6.77	5.32 5.24)
IVi	$CH_2COOC_2H_5$	3,4-Di-MeO-phenethyl	HCl H_2O	47	93—95	$C_{26}H_{34}N_2O_8\cdot HCl\cdot H_2O$	56.06 (56.39	6.70 6.83	5.03 5.05)
IVj	CH_2COOH	3,4-Di-MeO-phenethyl	—	33	241.5—242.5	$C_{24}H_{30}N_2O_8$	60.75 (60.55	6.39 6.50	5.90 5.79)
IVk	CH_2CONH_2	3,4-Di-MeO-phenethyl	HCl H_2O	24	207—209	$C_{24}H_{30}N_3O_7\cdot HCl$	54.59 (54.49	6.49 6.56	7.96 7.89)

TABLE II. 5-(3-Amino-2-hydroxypropoxy)-8-alkoxycarbostyril Derivatives



Compd. No.	R_1	R_2	Acid salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
VIb	$CH_2CH_2OCH_3$	3,4-Di-MeO-phenethyl	$C_2H_2O_4$ H_2O	47	158—162	$C_{25}H_{32}N_2O_7\cdot (COOH)_2\cdot H_2O$	55.86 (55.88	6.25 6.30	4.82 4.65)
VIc$_1$	$CH_2CH{=}CH_2$	iso-Pr	—	43	161—163	$C_{18}H_{24}N_2O_4$	65.04 (64.71	7.28 7.42	8.43 8.22)
VIc$_2$	$CH_2CH{=}CH_2$	3,4-Di-MeO-phenethyl	HCl 1/2H_2O	54	62—63	$C_{25}H_{30}N_2O_6\cdot HCl\cdot 1/2H_2O$	60.12 (60.18	6.46 6.73	5.61 5.52)
VId	$CH_2C{\equiv}CH$	3,4-Di-MeO-phenethyl	HCl	52	148—150	$C_{25}H_{28}N_2O_6\cdot HCl$	61.41 (61.10	5.98 5.92	5.73 5.68)
VIe	$CH_2CH_2CH_2CH_3$	3,4-Di-MeO-phenethyl	HCl H_2O	46	75—78	$C_{26}H_{34}N_2O_6\cdot HCl\cdot H_2O$	59.48 (59.05	7.10 6.99	5.33 5.20)

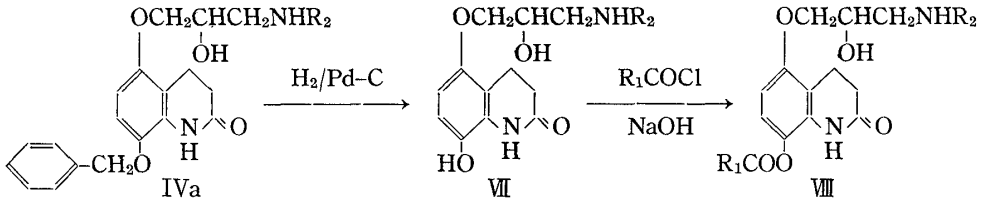
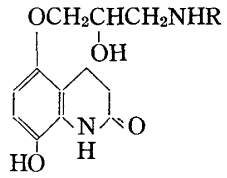


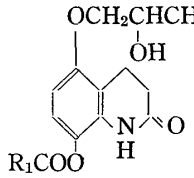
Chart 2

TABLE III. 5-(3-Amino-2-hydroxypropoxy)-8-hydroxy-3,4-dihydrocarbostyril Derivatives



Compd. No.	R	Acid salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
VIIa	iso-Pr	HCl	81	226—227.5	$C_{15}H_{22}N_2O_4\cdot HCl$	54.46 (54.47	7.01 7.16	8.47 8.31)
VIIb	*tert*-Bu	HCl $1/2H_2O$	76	208—210	$C_{16}H_{24}N_2O_4\cdot HCl\cdot 1/2H_2O$	54.31 (54.43	7.40 7.31	7.91 7.69)
VIIc	3,4-Di-MeO-phenethyl	HCl	77	171—173	$C_{22}H_{28}N_2O_4\cdot HCl$	62.77 (62.71	6.94 7.04	6.66 6.45)
VIId	CH_2CH_2–Ph	$1/2C_2H_2O_4$	65	185(dec.)	$C_{20}H_{24}N_2O_4\cdot 1/2C_2H_2O_4$	62.97 (62.66	6.51 6.61	6.96 6.54)
VIIe	$C(CH_3)_2CH_2Ph$	$C_2H_2O_4$	83	128(dec.)	$C_{22}H_{28}N_2O_4\cdot C_2H_2O_4$	60.75 (60.66	6.37 6.41	5.90 6.15)
VIIf	4-MeO-Phenoxyethyl	HCl	77	193—194	$C_{21}H_{26}N_2O_5\cdot HCl$	59.64 (59.37	6.44 6.31	6.62 6.43)

TABLE IV. 5-(3-Amino-2-hydroxypropoxy)-8-acyloxy-3,4-dihydrocarbostyril Derivatives



Compd. No.	R_1	R_2	Acid salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
VIIIa	CH_3	iso-Pr	HCl	37	240 (dec.)	$C_{17}H_{24}N_2O_5\cdot HCl$	54.76 (54.90	6.76 6.95	7.51 7.61)
VIIIb	CH_3	*tert*-Bu	HCl	13	248 (dec.)	$C_{18}H_{26}N_2O_5\cdot HCl$	55.88 (55.65	7.04 7.15	7.23 7.19)
VIIIc	CH_3	$C(CH_3)_2CH_2$–Ph	HCl	25	245 (dec.)	$C_{24}H_{30}N_2O_5\cdot HCl$	62.26 (62.04	6.75 6.53	6.05 5.97)
VIIId	Cyclohexyl	iso-Pr	HCl	34	227—228	$C_{22}H_{32}N_2O_5\cdot HCl$	60.06 (59.66	7.33 7.67	6.37 6.32)
VIIIe	Cyclohexyl	CH_2CH_2–Ph	HCl	41	199.5—203	$C_{27}H_{34}N_2O_5\cdot HCl$	64.47 (64.23	7.01 6.95	5.57 5.71)
VIIIf	CH_3	3,4-Di-MeO-phenethyl	HCl	24	208—210	$C_{24}H_{30}N_2O_7\cdot HCl$	58.24 (58.11	6.31 6.07	5.66 5.78)

epoxypropoxy) derivatives (IIIa—e). Treatment of III with the appropriate amine gave IVa—e (Table I). Treatment of IIIb—d with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in dioxane gave the 5-(2,3-epoxypropoxy) derivatives (V). Treatment of V with the appropriate amine gave VI (Table II).

The 8-acyloxy derivatives (VIIIa—e) were synthesized from 5-(3-amino-2-hydroxypropoxy)-8-hydroxy-3,4-dihydrocarbostyrils (VII) as shown in Chart 2. Compound IVa was hydrogenated over 10% palladium on charcoal to give VII (Table III). Compound VII was acylated with acetyl chloride and cyclohexanecarbonyl chloride to give VIIIa—e (Chart 2) (Table IV).

1-Alkyl-8-benzyloxy-5-(3-amino-2-hydroxypropoxy)-3,4-dihydrocarbostyrils (XIII) and 1-alkyl-8-hydroxy-5-(3-amino-2-hydroxypropoxy)-3,4-dihydrocarbostyril (XIV) were synthesized from 8-benzyloxy-5-hydroxy-3,4-dihydrocarbostyril (IIa) as a starting material by the procedures shown in Chart 3.

Reaction of IIa with dihydropyran using *p*-toluenesulfonic acid as a catalyst in tetrahydrofuran (THF) gave 8-benzyloxy-5-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (IX) in a yield of 72%. Treatment of IX with alkyl halide in dimethylformamide (DMF) gave 1-alkyl-8-benzyloxy-5-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyrils (X), which were hydrolyzed with conc. HCl to give 1-alkyl-8-benzyloxy-5-hydroxy-3,4-dihydrocarbostyrils (XI). Reaction of XI, epichlorhydrin and piperidine gave 1-alkyl-8-benzyloxy-5-(2,3-epoxypropoxy)-3,4-dihydrocarbostyrils (XII). Reaction of XII with the appropriate amine gave III (Table V). In the same manner as described for the preparation of VII, XIV was obtained from XIII (Table VI).

The synthesis of 8-acetoxy-VIIIf and 8-alkylcarbonylalkoxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyrils (IVf—k) from 5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-8-hydroxy-3,4-dihydrocarbostyril (VIIc) was achieved, with the use of benzyloxycarbonyl as a protecting group, according to the route shown in

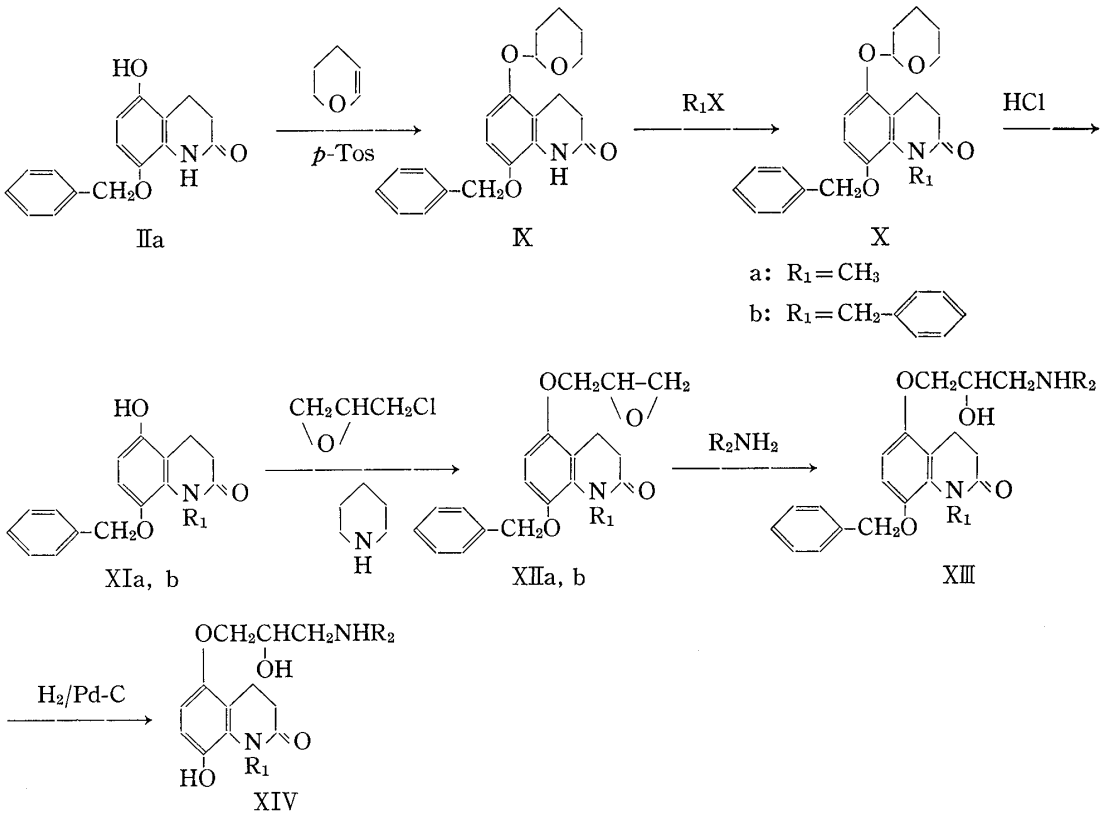
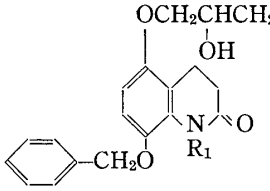


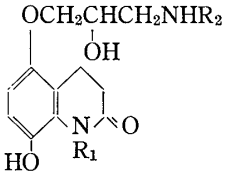
Chart 3

Table V. 5-(3-Amino-2-hydroxypropoxy)-8-benzyloxy-1-alkyl-3,4-dihydrocarbostyril Derivatives



Compd. No.	R_1	R_2	Acid salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XIIIa	CH_3	iso-Pr	CHCOOH ‖ CHCOOH	71	151—154	$C_{27}H_{30}N_2O_4 \cdot C_4H_4O_4$	63.03 (62.88	6.66 6.57	5.45 5.51)
XIIIb	CH_3	*tert*-Bu	—	62	72—74	$C_{24}H_{32}N_2O_4$	69.88 (69.56	7.82 7.78	6.79 6.78)
XIIIc	CH_3	CH_2–Ph	HCl	58	155—157	$C_{27}H_{30}N_2O_4 \cdot HCl$	67.14 (66.68	6.46 6.48	5.79 5.89)
XIIId	CH_3	3,4-Di-MeO-phenethyl	—	51	93—95	$C_{30}H_{36}N_2O_6$	69.21 (68.82	6.97 6.93	5.38 5.29)
XIIIe	CH_2–Ph	*tert*-Bu	HCl	88	200—201	$C_{30}H_{36}N_2O_4 \cdot HCl$	68.62 (68.53	7.10 7.11	5.33 5.42)

Table VI. 5-(3-Amino-2-hydroxypropoxy)-8-hydroxy-1-alkyl-3,4-dihydrocarbostyril Derivatives



Compd. No.	R_1	R_2	Acid salt	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
XIVa	CH_3	H	HCl	70	230—231	$C_{13}H_{18}N_2O_4 \cdot HCl$	51.57 (51.53	6.32 6.42	9.25 9.27)
XIVb	CH_3	*tert*-Bu	HCl	43	230—231	$C_{17}H_{26}N_2O_4 \cdot HCl$	56.90 (56.88	7.58 7.76	7.80 7.74)
XIVc	CH_3	3,4-Di-MeO-phenethyl	HCl	85	174—176	$C_{23}H_{30}N_2O_6 \cdot HCl$	59.16 (59.45	6.69 6.78	6.00 5.75)
XIVd	CH_2–Ph	*tert*-Bu	HCl	80	257—258	$C_{23}H_{30}N_2O_4 \cdot HCl$	63.51 (63.45	7.18 7.35	6.44 6.44)

Chart 4 and Chart 5. Reaction of XVI with acetyl chloride or alkylcarbonylalkyl chloride[7] gave 8-acetoxy or 8-alkylcarbonylalkyloxy-5-[3-(N-benzyloxycarbonyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyrils (XVIIa—e). Compounds XVIIa—e were hydrogenated over 10% palladium on charcoal to give VIIIf, IVf—i (Tables I and IV).

Compound XVIIe was hydrolyzed to give XVIIIa in a yield of 80%. In the same manner as for the preparation of VIIIf, IVj was obtained from XVIIIa in a yield of 83%. Treatment of XVIIe with 28% NH_4OH gave XVIIIb in a yield of 65%. In the same manner as for XVIIIa, IVk was obtained in a poor yield of 24%.

In order to establish a reasonable route for the industrial synthesis of 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril hydrochloride

(IVb) which was the most desirable compound among these derivatives, we carried out the following reactions.

Partial hydrolysis of 5,8-diacetoxy-3,4-dihydrocarbostyril (XIX)[8] with AcONa in MeOH gave 5-acetoxy-8-hydroxy-3,4-dihydrocarbostyril (XX) (80%). Reaction of XX with dihydropyran using conc. H_2SO_4 as a catalyst gave 5-acetoxy-8-tetrahydropyranyloxy-3,4-dihydrocarbostyril (XXI) in more than 90% yield. Reaction of XXI, epichlorhydrin and K_2CO_3 in MeOH gave 5-(2,3-epoxypropoxy)-8-tetrahydropyranyloxy-3,4-dihydrocarbostyril (XXII) (84%). Reaction of XXII with N-benzyl-3,4-dimethoxyphenethylamine in MeOH and

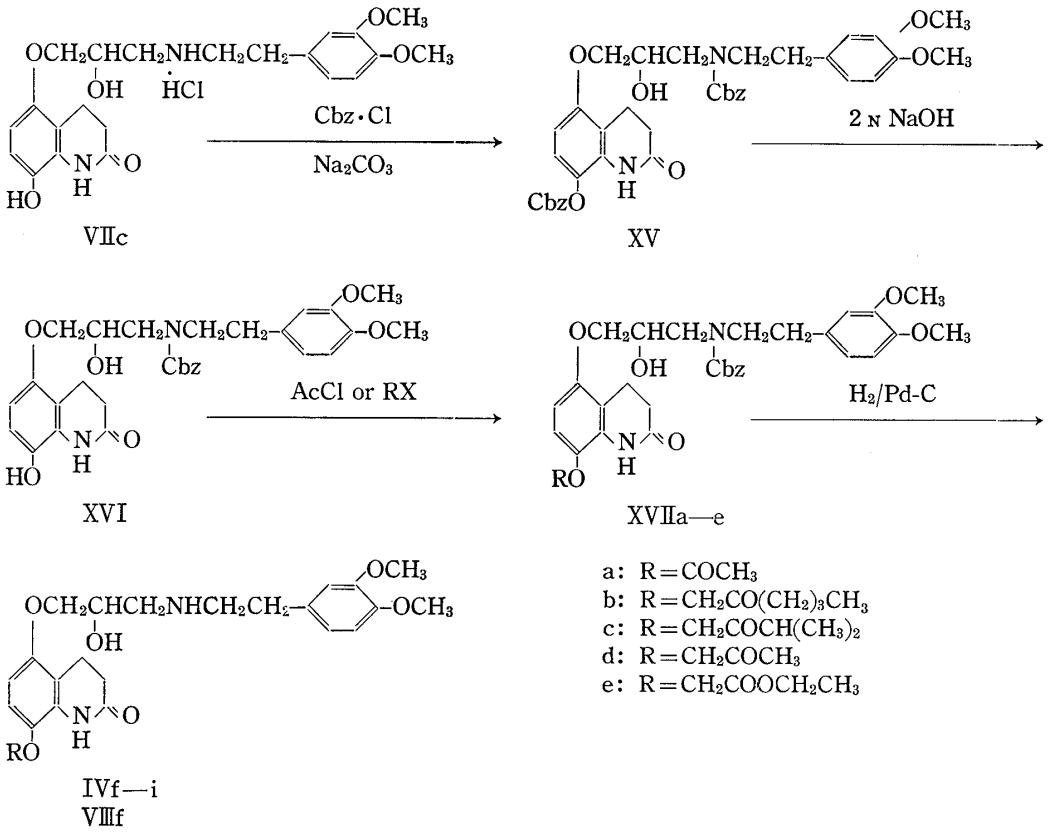


Chart 4

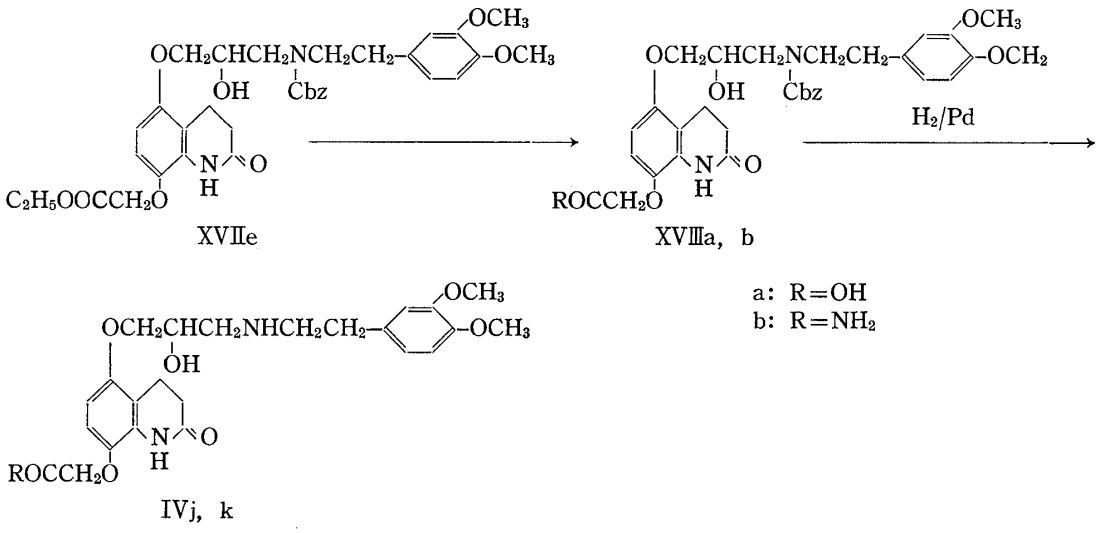


Chart 5

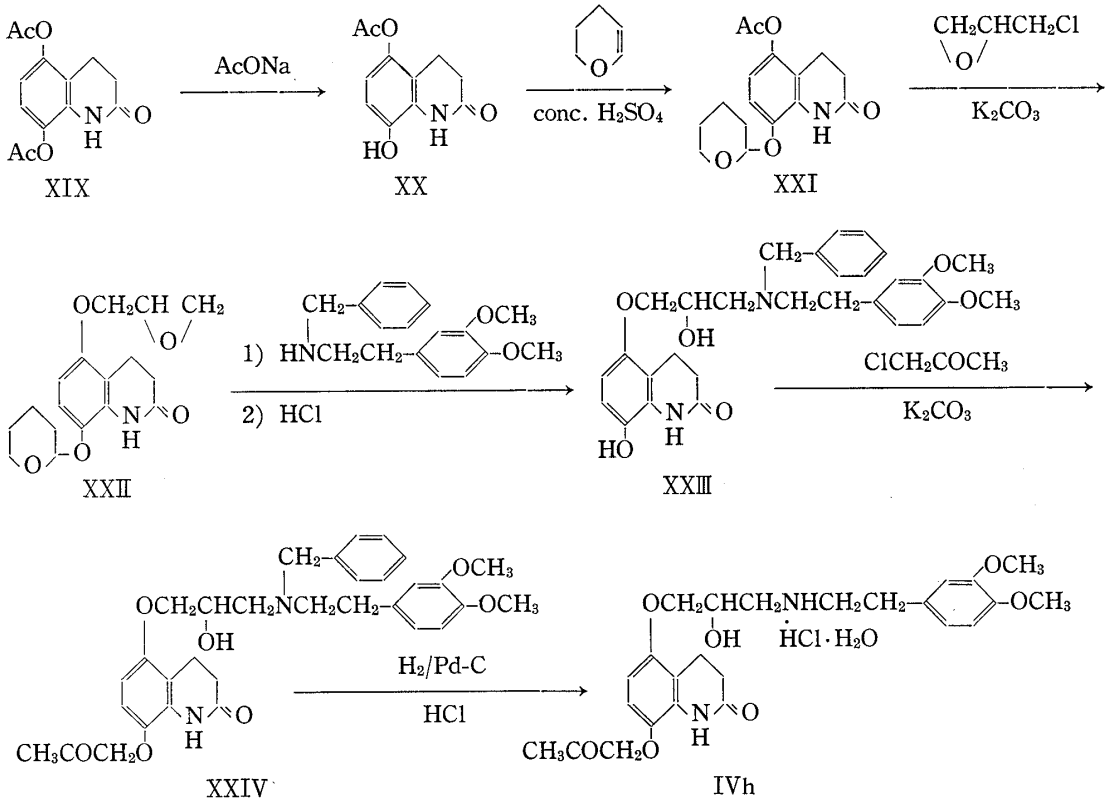


Chart 6

treatment with HCl gave 5-[3-(N-benzyl-3,4-dimethoxyphenethylamino-2-hydroxypropoxy]-8-hydroxy-3,4-dihydrocarbostyril (XXIII) (81%). Reaction of XXIII with $ClCH_2COCH_3$ in acetone–H_2O gave 8-acetonyloxy-5-[3-(N-benzyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (XXIV) as a colorless oil in quantitative yield. Compound XXIV was debenzylated over 10% Pd-C to give 8-acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril hydrochloride hydrate (IVh) (64%) (Chart 6).

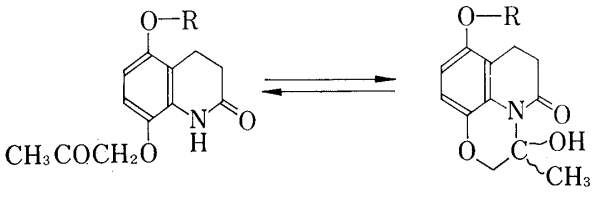


Chart 7

In the nuclear magnetic resonance (NMR, 90 MHz) spectrum of IVh in dimethylsulfoxide-d_6 (DMSO-d_6), two signals for methyl protons of acetonyl groups were observed at 1.75 ppm (1.7H, s) and 2.21 ppm (1.3H, s). It is suggested that the acetonyl groups exist as two tautomers of extended type and linkage type in a 2:3 ratio on the basis of the methyl signal intensities.

Anti-isoproterenol Activity

The antagonistic activities against isoproterenol of the compounds with 3,4-dimethoxyphenethylamino substituent groups were less potent than those of the compounds with isopropylamino, *tert*-butylamino or ethylamino substituent groups, but the selectivity for β_1-receptors was excellent in the anesthetized dog. The antagonistic activities of the compounds with 3,4-dimethoxyphenethylamino substituent groups against isoproterenol in the anesthetized dog are shown in Table X, and those on isolated guinea-pig atrial and tracheal preparations are shown in Table XI. Compounds IVb_3, IVc_2, IVd_3, IVe, IVh and VId showed excellent β_1-selective blocking activities.

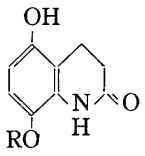
In particular, compound IVh was as potent as atenolol and about 10 times more potent than practolol on atria, and about 4 to 6 times more selective for β_1-receptor than atenolol and practolol.

Experimental

All melting points are uncorrected. NMR spectra were recorded on a Varian EM-390NMR spectrometer using 3-(trimethylsilyl)propanesulfonic acid sodium salt (DSS) or tetramethylsilane as an internal standard.

8-Allyloxy-5-hydroxy-3,4-dihydrocarbostyril (IIc)——A mixture of 50 g of I, 50.6 g of allylbromide and K_2CO_3 in 600 ml of acetone and 120 ml of H_2O was heated under reflux with stirring for 4 h. After the reaction mixture had been acidified with conc. HCl, it was evaporated to dryness under reduced pressure. The residue was dissolved in 200 ml of 10% NaOH and the solution was washed with $CHCl_3$ three times. The water layer was acidified with conc. HCl. The precipitated crystals were collected by filtration and washed with water. Recrystallization from iso-PrOH–H_2O gave IIc (35.0 g, 57.2%) as a colorless powder, mp 127.5—129°C. NMR (DMSO-d_6) δ: 4.47 (2H, dt, $J_1=6$ Hz, $J_2=2$ Hz, H_2C=CHC$\underline{H}_2$O–), 5.23 [(dt, $J_1=18$ Hz, $J_2=2$ Hz) +5.40 (dt, $J_1=18$ Hz, $J_2=2$ Hz), total 2H, $\underline{H}_2$C=CHCH$_2$O–], 5.82—6.33 (1H, m, H_2C=C$\underline{H}$CH$_2$O–), 6.43, 6.72 (each 1H, d, $J=9$ Hz, aromatic H), 8.72 (1H, s), 9.12 (1H, s). The elemental analysis data are shown in Table VII.

Table VII. 5-Hydroxy-8-alkoxy-3,4-dihydrocarbostyril Derivatives



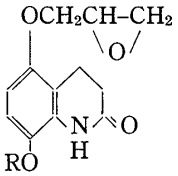
Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
IIa	CH_2–Ph	48	159.5—160.5	$C_{16}H_{15}NO_3$	71.36	5.61	5.20
					(71.25	5.34	5.22)
IIb	$CH_2CH_2OCH_3$	40	86—89	$C_{12}H_{15}NO_4\cdot 1/2H_2O$	58.53	6.55	5.69
					(58.83	6.60	6.12)
IIc	CH_2CH=CH_2	57	127.5—129	$C_{12}H_{13}NO_3$	65.74	5.98	6.39
					(65.69	5.96	6.38)
IId	$CH_2C\equiv CH$	45	143—144	$C_{12}H_{11}NO_3$	66.35	5.10	6.45
					(66.29	5.12	6.25)
IIe	$CH_2CH_2CH_2CH_3$	55	123—124	$C_{13}H_{17}NO_3$	66.36	7.28	5.95
					(66.39	7.17	5.90)

The $CHCl_3$ washings were collected, washed with H_2O and dried over Na_2SO_4. After removal of $CHCl_3$, the residue was recrystallized from iso-PrOH to give 5,8-diallyloxy-3,4-dihydrocarbostyril (8.6 g, 11.9%) as yellow needles, mp 104—105°C. NMR ($CDCl_3$) δ: 4.48 (4H, dt, $J_1=6$ Hz, $J_2=2$ Hz, 2×H_2C=CHC$\underline{H}_2$O–), 5.12—5.56 (4H, m, 2×$\underline{H}_2$C=CHCH$_2$O–), 5.75—6.29 (2H, m, 2×H_2C=C$\underline{H}$CH$_2$O–), 6.42, 6.65 (each 1H, d, $J=9$ Hz, aromatic H), 7.78 (1H, s, –N$\underline{H}$CO–). *Anal.* Calcd for $C_{15}H_{17}NO_3$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.39; H, 6.56; N, 5.44.

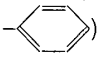
8-Allyloxy-5-(2,3-epoxypropoxy)-3,4-dihydrocarbostyril (IIIc)——A mixture of 35 g of IIc, 75 ml of epichlorhydrin and 26.5 g of K_2CO_3 in 300 ml of iso-PrOH was stirred at 70—80°C for 5 h. Removal of the solvent under reduced pressure left a residue, which was dissolved in H_2O and $CHCl_3$. The $CHCl_3$ layer was separated, washed with 5% NaOH and saturated NaCl solution, and dried over Na_2SO_4. After removal of the $CHCl_3$ by evaporation, the residue was recrystallized from iso-PrOH to give IIIc (22 g, 50.0%) as a colorless powder, mp 118.5—120°C. NMR ($CDCl_3$) δ: 2.36—3.16 (6H, m, –C$\underline{H}_2$C$\underline{H}_2$–, –OCH$_2$C$\underset{\diagup\,\mathrm{O}\,\diagdown}{\mathrm{H}}$–C$\underline{H}_2$), 3.16—3.53 (1H, m, –OCH$_2$C$\underset{\diagup\,\mathrm{O}\,\diagdown}{\underline{\mathrm{H}}}$–CH$_2$), 3.69—4.32 (2H, m, –OC$\underline{H}_2C\underset{\diagup\,\mathrm{O}\,\diagdown}{\mathrm{H}}$–CH$_2$), 4.50 (2H, dt, $J_1=6$ Hz, $J_2=2$ Hz, H_2C=CHC$\underline{H}_2$O–), 5.12—5.56 (2H, m, $\underline{H}_2$C=CHCH$_2$O–), 5.74—6.31 (1H, m, H_2C=C$\underline{H}$CH$_2$O–), 6.46, 6.67 (each 1H, d, $J=9$ Hz, aromatic H), 7.80 (1H, br.s, –N$\underline{H}$CO–). The elemental analysis data are shown in Table VIII.

8-Benzyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (IVa)——3,4-Dimethoxyphenethylamine (10 g) was added to a solution of 5.0 g of IIIa in 50 ml of MeOH, and the

Table VIII. 5-(2,3-Epoxypropoxy)-8-alkoxy-3,4-dihydrocarbostyril Derivatives



Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
IIIa	CH_2–Ph	56	106.5—107	$C_{19}H_{19}NO_4$	70.14 (70.16	5.89 5.75	4.31 4.51)
IIIb	$CH_2CH_2OCH_3$	47	109.5—110.5	$C_{15}H_{19}NO_5$	61.42 (61.43	6.53 6.48	4.78 4.71)
IIIc	$CH_2CH{=}CH_2$	50	118.5—120	$C_{15}H_{17}NO_4$	65.44 (65.49	6.22 6.18	5.09 4.93)
IIId	$CH_2C{\equiv}CH$	65	143—144	$C_{15}H_{15}NO_4$	65.92 (65.81	5.53 5.57	5.13 5.06)
IIIe	$CH_2CH_2CH_2CH_3$	49	107—109	$C_{16}H_{21}NO_4$	65.95 (65.73	7.27 7.18	4.81 4.74)

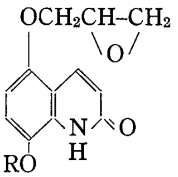
mixture was stirred at room temperature for 20 h. After removal of the solvent, the residue was washed with ether and crystallized from iso-PrOH. Recrystallization from acetone gave IVa$_3$ (3.4 g, 43.6%) as a colorless powder, mp 108—109.5°C. NMR ($CDCl_3$) δ: 2.30—3.10 (10H, m, $-C\underline{H}_2C\underline{H}_2-$, $-OCH_2\overset{OH}{\overset{|}{C}}HC\underline{H}_2-$, $-NHC\underline{H}_2C\underline{H}_2-$), 3.58—4.25 [9H, m, $-OC\underline{H}_2\overset{OH}{\overset{|}{C}}\underline{H}CH_2-$, 3.81 (3H, s, $-OC\underline{H}_3$), 3.83 (3H, s, $-OC\underline{H}_3$)], 4.98 (2H, s, $-OC\underline{H}_2-$ ), 6.42 (1H, d, $J=9$ Hz, aromatic H), 6.52—6.93 (4H, m, aromatic H), 7.35 (5H, s, aromatic H). The elemental analysis data are shown in Table I.

8-Allyloxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril Hydrochloride (IVc$_2$)——A solution of 2.5 g of IIIc in 30 ml of MeOH was treated with 6.5 g of 3,4-dimethoxyphenethylamine and the whole was stirred at 40—50°C for 8 h. After removal of the solvent, the residue was washed with ether and dissolved in MeOH containing HCl. The solution was evaporated to dryness and the residue was recrystallized from MeOH–ether to give IVc$_2$ (2.9 g, 64.8%) as colorless needles, mp 154—156°C. NMR ($CDCl_3$) δ: 3.88 (6H, s, $2\times-OC\underline{H}_3$), 4.52 (2H, d, $J=5$ Hz, $CH_2{=}CHC\underline{H}_2O-$), 5.17—5.59 (3H, m, $C\underline{H}_2{=}C\underline{H}-CH_2O-$), 6.47, 6.73 (each 1H, d, $J=9$ Hz, aromatic H), 6.57—6.95 (4H, m, aromatic H), 7.96 (1H, s, $-N\underline{H}CO-$). The elemental analysis data are shown in Table I.

8-Allyloxy-5-(2,3-epoxypropoxy)carbostyril (Vc)——A mixture of 5 g of IIIc and 6.0 g of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 60 ml of dioxane was stirred under reflux for 1.5 h. After removal of the solvent, the residue was dissolved in 5% K_2CO_3 solution and $CHCl_3$. The $CHCl_3$ layer was separated, washed with water and dried over Na_2SO_4. Removal of the $CHCl_3$ by evaporation left a residue which was recrystallized from iso-PrOH to give Vc (3.5 g, 70.5%) as a colorless powder, mp 171—173°C. NMR ($CDCl_3$) δ: 2.65—3.02 (2H, m, $-OCH_2\overset{O}{\overset{/\backslash}{C}}H-C\underline{H}_2$), 3.22—3.55 (1H, m, $-OCH_2C\underline{H}\overset{O}{\overset{/\backslash}{}}-CH_2$), 3.78—4.47 (2H, m, $-OC\underline{H}_2\overset{O}{\overset{/\backslash}{C}}H-CH_2$), 4.60 (2H, dt, $J_1=6$ Hz, $J_2=2$ Hz, $H_2C{=}CHC\underline{H}_2-$), 5.20—5.62 (2H, m, $\underline{H}_2C{=}CHCH_2-$), 5.81—6.33 (1H, m, $H_2C{=}C\underline{H}CH_2-$), 6.49, 6.85 (each 1H, d, $J=9$ Hz, aromatic H), 6.57, 8.13 (each 1H, d, $J=10$ Hz, C_3- and C_4–H), 9.24 (1H, br.s, $-N\underline{H}CO-$). The elemental analysis data are shown in Table IX.

5-[3-(3,4-Dimethoxyphenethylamino)-2-hydroxypropoxy]-8-propargyloxycarbostyril Hydrochloride (VId)——A mixture of 1.5 g of Vd and 5 g of 3,4-dimethoxyphenethylamine in 20 ml of MeOH was left to stand at room temperature for 7 h. Then, in the same manner as for IVc$_2$, VId (1.4 g, 51.8%) was obtained as a colorless powder, mp 148—150°C (from EtOH). NMR (DMSO-d_6) δ: 2.72—4.62 [15H, m, 3.72, 3.76 (each 3H, s, $2\times-OC\underline{H}_3$), $-OC\underline{H}_2\overset{OH}{\overset{|}{C}}\underline{H}CH_2-$, $-NHC\underline{H}_2C\underline{H}_2-$], 4.65—5.15 (2H, m, $HC{\equiv}CC\underline{H}_2O-$), 5.76—6.20 (1H, m, $-O\underline{H}$), 6.27—7.40 [6H, m, 6.48 (1H, d, $J=10$ Hz, C_3–H), 7.19 (1H, d, $J=9$ Hz, aromatic H), aromatic H], 8.13 (1H, d, $J=10$ Hz, C_4–H), 9.15 (1H, br. s), 10.75 (1H, br. s). The elemental analysis data are shown in Table II.

Table IX. 5-(2,3-Epoxypropoxy)-8-alkoxycarbostyril Derivatives



Compd. No.	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found) C	H	N
Vb	$CH_2CH_2OCH_3$	67	142.5—143.5	$C_{15}H_{17}NO_5$	61.85 (61.89)	5.88 (5.80)	4.81 (4.71)
Vc	$CH_2CH{=}CH_2$	71	171—173	$C_{15}H_{15}NO_4$	65.92 (65.67)	5.53 (5.49)	5.13 (5.01)
Vd	$CH_2C{\equiv}CH$	76	173—175	$C_{15}H_{13}NO_4$	66.41 (66.26)	4.83 (4.91)	5.16 (5.12)
Ve	$CH_2CH_2CH_2CH_3$	77	145.5—146.5	$C_{16}H_{19}NO_4$	66.42 (66.53)	6.62 (6.59)	4.84 (4.78)

5-[3-(3,4-Dimethoxyphenethylamino)-2-hydroxypropoxy]-8-hydroxy-3,4-dihydrocarbostyril Hydrochloride (VIIc)——A mixture of 5.2 g of IVa$_3$ and 4 g of 10% Pd-C in 70 ml MeOH and a small amount of H_2O was stirred at room temperature for 8 h under atmospheric pressure of hydrogen. The catalyst was removed by filtration, the filtrate was evaporated to dryness under reduced pressure, and the residual oil was crystallized from MeOH containing HCl with warming. The precipitated crystals were collected by filtration and washed with EtOH and acetone. Recrystallization from MeOH–ether gave VIIc (3.6 g, 77.2%) as colorless needles, mp 171—173°C. NMR (DMSO-d_6) δ: 3.75 (3H, s, $-OC\underline{H}_3$), 3.77 (3H, s, $-OC\underline{H}_3$), 3.77—4.53 (3H, m, $-OC\underline{H}_2C(OH)\underline{H}CH_2-$), 5.89 (1H, br. s), 6.52 (1H, d, $J=9$ Hz, aromatic H), 6.62—7.06 (4H, m, aromatic H), 8.76 (1H, s, $-N\underline{H}CO-$), 8.85—9.83 (2H, br., $-\overset{+}{N}\underline{H}_2CH_2-$). The elemental analysis data are shown in Table III.

8-Acetoxy-5-(3-*tert*-butylamino-2-hydroxypropoxy)-3,4-dihydrocarbostyril Hydrochloride (VIIIb)——A solution of 0.19 g of CH_3COCl in a small amount of acetone was added dropwise to a solution of 0.71 g of VIIb in 4.4 ml of 1 N NaOH and 10 ml of acetone, under ice-water cooling. The reaction mixture was left to stand at the same temperature, then 2 ml of 1 N HCl was added and the whole was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel; eluent, $CHCl_3$–MeOH=8: 1). Recrystallization from MeOH–ether gave VIIIb (0.1 g, 13%) as colorless leaflets, mp 247—248°. NMR (DMSO-d_6) δ: 1.37 (9H, s, $-NHC(C\underline{H}_3)_3$), 2.32 (3H, s, $-OCOC\underline{H}_3$), 5.96 (1H, br. s, $-O\underline{H}$), 6.72, 7.02 (each 1H, d, $J=9$ Hz, aromatic H), 10.03 (1H, s, $-N\underline{H}CO-$). The elemental analysis data are shown in Table IV.

8-Benzyloxy-5-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (IX)——A mixture of 10 g of IIa, 10 g of dihydropyran and 100 mg of *p*-toluenesulfonic acid in 100 ml of anhydrous THF was stirred overnight, then poured into saturated NaCl solution and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with 5% NaOH, H_2O and dried over K_2CO_3. After removal of the solvent, the residue was crystallized from petroleum ether. The precipitated powder was collected by filtration and recrystallized from EtOH–H_2O to give IX (9.5 g, 72.4%) as colorless crystals, mp 113.5—114°C. NMR ($CDCl_3$) δ: 1.30—2.25 (6H, m, $-OCH_2(C\underline{H}_2)_3C\underline{H}\langle$), 2.32—3.27 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 3.27—4.20 (2H, m, $-OC\underline{H}_2(CH_2)_3CH\langle$), 5.03 (2H, s, $-OC\underline{H}_2-C_6H_5$), 5.34 (1H, br. t, $J=4$ Hz, $-OCH_2(CH_2)_3C\underline{H}\langle$), 6.78 (2H, s, $C_{6,7}$–H), 7.44 (5H, s, $-OCH_2C_6\underline{H}_5$), 7.85 (1H, br. s, $-N\underline{H}CO-$). *Anal.* Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.23; H, 6.53; N, 4.03.

8-Benzyloxy-1-methyl-5-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (Xa)——To a solution of 5 g of IX in 150 ml of anhydrous DMF, 810 mg of 50% NaH was added slowly. The reaction mixture was stirred at room temperature for 1 h, then a solution of 1.05 ml of CH_3I in 10 ml of anhydrous DMF was added dropwise. After the addition, the reaction mixture was stirred at room temperature for 2 h then extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over K_2CO_3. The solvent was evaporated off, and the residue was crystallized from ether. The precipitated crystals were collected by filtration and recrystallized from ligroin to give Xa (3.4 g, 65.4%) as pale yellow needles, mp 110.5—111.5°C. NMR ($CDCl_3$) δ: 1.35—2.20 (6H, m, $-OCH_2(C\underline{H}_2)_3C\underline{H}\langle$), 2.30—3.05 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 3.15—4.15 [5H, m, $-OC\underline{H}_2(CH_2)_3CH\rangle$, 3.37 (3H, s, $\rangle N-C\underline{H}_3$)], 5.00 (2H, s, $-OC\underline{H}_2C_6H_5$), 5.28 (1H, br. t, $J=4$ Hz, $-OCH_2-$

$(CH_2)_3C\underline{H}\langle$), 6.84 (2H, s, $C_{6,7}$-H), 7.36 (5H, s, $-OCH_2C_6\underline{H}_5$). *Anal.* Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 71.95; H, 6.83; N, 3.96.

8-Benzyloxy-5-hydroxy-1-methyl-3,4-dihydrocarbostyril (XIa)——A solution of 4 g of Xa in 5 ml of conc. HCl and 60 ml of MeOH was stirred at room temperature for 30 min. The reaction solution was neutralized with dil. NaOH, then evaporated to dryness under reduced pressure. The residue was extracted with $CHCl_3$ and the extract was washed with water, and dried over $MgSO_4$. The solvent was evaporated off to leave a residue, which was recrystallized from EtOH to give XIa (2.7 g, 87.5%) as colorless needles, mp 196—197°C. NMR ($CDCl_3$) δ: 2.27—3.05 (4H, m, $-C\underline{H}_2C\underline{H}_2-$), 3.38 (3H, s, $>N-C\underline{H}_3$), 4.97 (2H, s, $-OC\underline{H}_2C_6\underline{H}_5$), 6.00 (1H, br. s), 6.56, 7.75 (each 1H, d, $J=9$ Hz, aromatic H), 7.35 (5H, s, $-OCH_2C_6\underline{H}_5$). *Anal.* Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 71.98; H, 6.03; N, 4.91.

8-Benzyloxy-5-(2,3-epoxypropoxy)-1-methyl-3,4-dihydrocarbostyril (XIIa)——A mixture of 5.5 g of XIa, 15 g of epichlorhydrin and 1 ml of piperidine was stirred at 90—100°C for 3 h. After removal of the excess epichlorhydrin by evaporation, the residue was dissolved in $CHCl_3$. The $CHCl_3$ extract was washed with water and dried over K_2CO_3. After removal of the solvent, the residue was purified by column chromatography (silica gel; eluent, $CHCl_3$–MeOH=8: 1) to give XIIa (3.7 g, 55.8%) as colorless needles, mp 111—112.5°C. NMR ($CDCl_3$) δ: 2.27—3.05 (6H, m, $-C\underline{H}_2C\underline{H}_2$, $-OCH_2\underset{\diagdown O \diagup}{C}H-C\underline{H}_2$), 3.15—3.50 [4H, m, $-OCH_2C\underline{H}-CH_2$, $\underset{\diagdown O \diagup}{}$; 3.37 (3H, s, $>N-C\underline{H}_3$)], 3.66—4.32 (2H, m, $-OC\underline{H}_2CH-CH_2$), 4.97 (2H, s, $-OC\underline{H}_2C_6H_5$), 6.58, 6.83 (each 1H, d, $J=9$ Hz, aromatic H), 7.34 (5H, s, $-OCH_2C_6\underline{H}_5$). *Anal.* Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.61; H, 6.27; N, 4.36.

5-(3-Benzylamino-2-hydroxypropoxy)-8-benzyloxy-1-methyl-3,4-dihydrocarbostyril Hydrochloride (XIIIc)——A solution of 1.7 g of XIIa and 1.6 ml of benzylamine in 20 ml of MeOH was stirred under reflux for 3 h. The reaction mixture was evaporated to dryness under reduced pressure. The residue was purified by column chromatography (silica gel; eluent, $CHCl_3$–MeOH=8: 1) and dissolved in EtOH containing HCl. The solution was evaporated to dryness, and the residue was precipitated from acetone–petroleum ether. The product was collected by filtration to give XIIIc (1.4 g, 57.8%) as a colorless powder, mp 155—157°C. NMR (DMSO-d_6) δ: 3.25 (3H, s, $>N-C\underline{H}_3$), 3.65—4.60 (5H, m, $-OC\underline{H}_2\underset{OH}{C}\underline{H}CH_2-$, $-NHC\underline{H}_2C_6H_5$), 5.07 (2H, s, $-OC\underline{H}_2-C_6H_5$), 5.72—6.22 (1H, br.), 6.75, 7.05 (each 1H, d, $J=9$ Hz, aromatic H), 7.23—7.83 (10H, m, $2\times-CH_2C_6\underline{H}_5$), 9.20—9.90 (1H, br.). The elemental analysis data are shown in Table V.

5-(3-Amino-2-hydroxypropoxy)-8-hydroxy-1-methyl-3,4-dihydrocarbostyril Hydrochloride (XIVa)——A mixture of 0.5 g of XIIIc, and 50 mg of 10% Pd-C in 5 ml of EtOH was stirred at room temperature under atmospheric pressure of hydrogen. Then, in the same manner as for VIIc, XIVa (220 mg, 70.2%) was obtained as colorless needles, mp 230—231°C (from EtOH–ligroin). The elemental analysis data are shown in Table VI.

8-Benzyloxycarbonyloxy-5-[3-(N-benzyloxycarbonyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (XV)——A solution of 10.0 g of carbobenzoxy chloride in 30 ml of acetone and 6.12 ml of 10% Na_2CO_3 were added dropwise to a solution of 10.8 g of VIIc in 26.4 ml of 2 N NaOH over a period of 1 h with stirring under cooling in ice-water, then stirring was continued at room temperature for 1.5 h. The precipitated material was collected by filtration and washed successively with water, ether and hot iso-PrOH to give crude XV (15.8 g, 96%) as a colorless powder, mp 132.5—134°C. NMR (DMSO-d_6) δ: 3.71 (6H, s, $2\times-OC\underline{H}_3$), 5.04 (2H, s, $>N-COOC\underline{H}_2-$), 5.23 (2H, s, $-OCOOC\underline{H}_2-$), 7.36, 7.47 (each 5H, s, $-CH_2C_6\underline{H}_5$), 9.98 (1H, s, $-N\underline{H}CO-$).

5-[3-(N-Benzyloxycarbonyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-8-hydroxy-3,4-dihydrocarbostyril (XVI)——A suspension of 3.5 g of crude XV in 5.0 ml of 2 N NaOH and 100 ml of MeOH was stirred until it became a clear solution at room temperature. The reaction solution was acidified with 1 N HCl under cooling in ice-water and evaporated to dryness under reduced pressure. The residual oil was extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated off to leave crude XVI (2.7 g, 100%) as a colorless oil. NMR (DMSO-d_6) δ: 3.70 (6H, s, $2\times-OCH_3$), 5.04 (2H, s, $>NCOOC\underline{H}_2-$), 7.35 (5H, s, $-CH_2C_6\underline{H}_5$), 8.63 (1H, s), 9.15 (1H, s).

8-Acetoxy-5-[3-(3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril Hydrochloride (VIIIf)——A solution of 0.28 ml of acetyl chloride in 8 ml of acetone and 4.1 ml of 10% Na_2CO_3 were added separately in 4 portions to a solution of crude XVI obtained from 1.5 g of VIIc in 1.8 ml of 2 N NaOH with stirring at room temperature, and stirring was continued at room temperature for 2 h. After removal of the solvent *in vacuo*, the residue was extracted with $CHCl_3$. The extract was washed with water and dried over Na_2SO_4. The solvent was evaporated off, and the residue was purified by column chromatography (silica gel; eluent, $CHCl_3$–MeOH=8: 1) to give 8-acetoxy-5-[3-(N-benzyloxycarbonyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (XVIIa) (1.0 g, 50.0%) as a colorless oil. NMR (DMSO-d_6) δ: 2.29 (3H, s, $-OCOC\underline{H}_3$), 3.70 (6H, s, $2\times-OC\underline{H}_3$), 5.03 (2H, s, $-COOC\underline{H}_2-$), 5.18 (1H, d, $J=5$ Hz, $-O\underline{H}$), 6.65—6.83 (3H, m, aromatic H), 6.53, 6.87 (each 1H, d, $J=9$ Hz, aromatic H), 7.35 (5H, s, $-COOCH_2C_6\underline{H}_5$), 9.81 (1H, s, $-N\underline{H}CO-$). A mixture of 1.0 g of crude XVIIa and 0.4 g of Pd black in 3 ml of 1 N HCl and 100 ml of MeOH was stirred at room temperature under stmospheric pressure of hydrogen for 1 h. Then in the

same manner as for VIIc, VIIIf (28.4% from VIIe) was obtained as colorless needles, mp 208—210°C (from MeOH–ether). NMR (DMSO-d_6) δ: 2.28 (3H, s, $-OCOCH_3$), 3.69, 3.73 (each 3H, s, $2\times-OCH_3$), 5.83 (1H, d, $J=5$ Hz, $-OH$), 6.56, 6.83 (each 1H, d, $J=9$ Hz, aromatic H), 6.78 (3H, m, aromatic H), 8.97 (2H, br. s, $-\overset{+}{N}H_2CH_2CH_2-$), 9.70 (1H, s, $-NHCO-$). The elemental analysis data are shown in Table IV.

8-Carboethoxymethoxy-5-[3-(N-benzyloxycarbonyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (XVIIe)——A mixture of 10 g of XVI, 7.3 g of $BrCH_2COOC_2H_5$ and 3.3 g of K_2CO_3 in 120 ml of acetone and 24 ml of H_2O was stirred at room temperature for 9 h. Then, in the same manner as for VIIIf, XVIIe (8.5 g, 73.8%) was obtained as a colorless oil. NMR (DMSO-d_6) δ: 1.23 (3H, t, $J=7$ Hz, $-OCH_2CH_3$), 3.69 (6H, s, $2\times-OCH_3$), 4.15 (2H, q, $J=7$ Hz, $-OCH_2CH_3$), 4.68 (2H, s, $-OCH_2COO-$), 5.02 (2H, s, $-OCH_2C_6H_5$), 5.17 (1H, d, $J=5$ Hz, $-OH$), 6.42, 6.82 (each 1H, d, $J=9$ Hz, aromatic H), 6.62—6.85 (3H, m, aromatic H), 7.32 (5H, s, $-OCH_2C_6H_5$), 8.78 (1H, s, $-NHCO-$).

5-[3-(N-Benzyloxycarbonyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-8-carboxymethoxy-3,4-dihydrocarbostyril (XVIIIa)——A solution of 5.5 g of XVIIe in 10 ml of 2 N NaOH and 150 ml of MeOH was stirred at room temperature for 15 min. Then, in the same manner as for XVI, XVIIIa (4.2 g, 79.9%) was obtained as colorless needles, mp 141—143°C (from MeOH). NMR (DMSO-d_6) δ: 3.70 (6H, s, $2\times-OCH_3$), 4.62 (2H, s, $-OCH_2COOH$), 6.40 (2H, s, $-OCH_2C_6H_5$), 6.67—6.83 (3H, m, aromatic H), 6.47, 6.86 (each 1H, d, $J=9$ Hz, aromatic H), 7.35 (5H, s, $-CH_2C_6H_5$), 8.97 (1H, s, $-NHCO-$). *Anal.* Calcd for $C_{32}H_{36}N_2O_{10}$: C, 63.15; H, 5.96; N, 4.60. Found: C, 62.79; H, 5.92; N, 4.81.

8-Carboxymethoxy-5-[3-(3,4-dimethoxyphenethylamino-2-hydroxypropoxy]-3,4-dihydrocarbostyril (IVj)—— A mixture of 2.0 g of XVIIIa, 0.5 g of Pd black and 3 drops of CH_3COOH in 50 ml of MeOH was stirred at room temperature under atmospheric pressure of hydrogen for 2 h. Then, in the same manner as for VIIc, IVj (1.3 g, 83.4%) was obtained as a colorless powder, mp 241.5—242.5°C (from H_2O–MeOH). NMR (DMSO-d_6) δ: 3.71 (6H, s, $2\times-OCH_3$), 4.22 (2H, s, $-OCH_2COOH$), 4.90 (2H, $\overset{+}{\text{br.}}$ s, $-NH_2-$), 6.42, 6.85 (each 1H, d, $J=9$ Hz, aromatic H), 6.60—6.80 (3H, m, aromatic H), 10.28 (1H, s, $-NHCO-$). The elemental analysis data are shown in Table I.

5-Acetoxy-8-hydroxy-3,4-dihydrocarbostyril (XX)——A mixture of 100 g of 5,8-diacetoxy-3,4-dihydrocarbostyril (XIX) 26 g of $AcONa\cdot3H_2O$ and 10 g of active carbon in 1 l of MeOH was stirred under reflux for 50 min. The active carbon was removed by filtration while hot and the filtrate was concentrated to about 600 ml. The precipitated crystals were collected by filtration and recrystallized from EtOH to give XX (57 g, 67.8%) as colorless crystals, mp 191—194°C (dec.). NMR (DMSO-d_6) δ: 2.22 (3H, s, $-OCOCH_3$), 6.46, 6.60 (each 1H, d, $J=9$ Hz, aromatic H), 8.76 (1H, br. s, $-NHCO-$). *Anal.* Calcd for $C_{11}H_{11}NO_4$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.61; H, 5.10; N, 6.42.

5-Acetoxy-8-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (XXI)——To a suspension of 92 g of XX in 1 l of CH_2Cl_2, 90 ml of dihydropyran and 0.1 ml of H_2SO_4 were added. The mixture was stirred at room temperature for 30 min. After addition of 0.5 ml of triethylamine, the solution was evaporated to dryness under reduced pressure. The residue was washed with acetone and recrystallized from MeOH–$CHCl_3$ to give XXI (99 g, 78.0%) as colorless granular crystals, mp 178—181°C. NMR ($CDCl_3$) δ: 1.31, 2.00 (6H, m, $-CH_2(CH_2)_3CH<$), 2.28 (3H, s, $-OCOCH_3$), 2.35—2.90 (4H, m, $-CH_2CH_2-$), 3.30—4.10 (2H, m, $-OCH_2(CH_2)_3CH<$), 5.32 (1H, br. t, $J=4$ Hz, $-OCH_2(CH_2)_3CH<$), 6.65, 7.05 (each 1H, d, $J=9$ Hz, aromatic H), 7.90 (1H, br. s, $-NHCO-$). *Anal.* Calcd for $C_{16}H_{19}NO_5$: C, 62.94; H, 6.27; N, 4.59. Found: C, 62.79; H, 6.20; N, 4.61.

5-(2,3-Epoxypropoxy)-8-(2-tetrahydropyranyloxy)-3,4-dihydrocarbostyril (XXII)——A mixture of 50 g of XXI, 56 g of K_2CO_3, 450 ml of epichlorhydrin and 300 ml of MeOH was stirred under reflux for 1 h. The precipitated KCl was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$ and H_2O. The $CHCl_3$ layer was separated, washed with water and dried over Na_2SO_4. After removal of the solvent by evaporation, the residue was recrystallized from iso-PrOH to give XXII (43.8 g, 83.8%) as colorless granular crystals, mp 117—119°C. NMR ($CDCl_3$) δ: 1.35—2.22 (6H, m, $-OCH_2(CH_2)_3CH<$), 2.42—4.39 (11H, m, $-OCH_2(CH_2)_3CH<$, $-CH_2CH_2-$, $-OCH_2\underset{\diagup O \diagdown}{CH}-CH_2$), 5.24 (1H, br. t, $J=4$ Hz, $-OCH_2(CH_2)_3CH<$), 6.46, 6.96 (each 1H, d, $J=9$ Hz, aromatic H), 7.87 (1H, br. s, $-NHCO-$). *Anal.* Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39. Found: C, 63.8; H, 6.59; N, 4.45.

5-[3-(N-Benzyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-8-hydroxy-3,4-dihydrocarbostyril Hydrochloride (XXIII)——A solution of 48 g of XXII and N-benzyl-3,4-dimethoxyphenethylamine in 300 ml of MeOH was stirred under reflux for 4 h. After removal of the solvent, the residue was dissolved in 500 ml of acetone, then 20 ml of conc. HCl was added with stirring under cooling in ice-water. The precipitated crystals were collected by filtration and washed with acetone. Recrystallization from MeOH gave XXIII (65.8 g, 80.6%), mp 122—124°C. NMR (DMSO-d_6) δ: 3.62—4.26 [8H, m, $-OCH_2\overset{OH}{\overset{|}{C}}HCH_2-$, 3.74, 3.76 (each 3H, s, $-OCH_3$)], 4.26—4.87 (3H, m, $-OCH_2\overset{OH}{\overset{|}{C}}HCH_2-$, $>N-CH_2C_6H_5$), 5.40—6.40 (1H, $-OCH_2\overset{OH}{\overset{|}{C}}HCH_2-$), 6.46 (1H, d, $J=9$ Hz, aromatic H), 6.57—7.09 (4H, m, aromatic H), 7.29—7.97 (5H, m, $>NCH_2-$

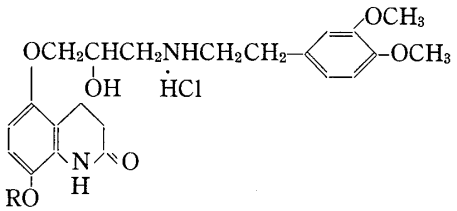
$C_6\underline{H}_5$), 8.75, 9.40 (each 1H, br. s). *Anal.* Calcd for $C_{29}H_{34}N_2O_6 \cdot HCl$: C, 64.14; H, 6.50; N, 5.16. Found: C, 63.86; H, 6.61; N, 5.11.

8-Acetonyloxy-5-[3-(N-benzyl-3,4-dimethoxyphenethylamino)-2-hydroxypropoxy]-3,4-dihydrocarbostyril (XXIV)——A solution of 35 ml of $ClCH_2COCH_3$ in 700 ml of acetone was added to a solution of 100 g of XXIII and 64 g of K_2CO_3 in 170 ml of H_2O. The reaction mixture was stirred under reflux for 4 h. The mixture was filtered while hot, and the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with $CHCl_3$, then the extract was washed with water and dried over Na_2SO_4. Removal of solvent by evaporation gave XXIV (103 g, 99.4%) as a colorless oil. NMR (CCl_4) δ: 1.69 (2.6H, s, $-OCH_2COC\underline{H}_3$), 2.13 (0.4H, s, $-OCH_2COC\underline{H}_3$), 2.25—3.05 (10H, m, $-C\underset{OH}{\underset{|}{H}}C\underline{H}_2N<$, $>NC\underline{H}_2C\underline{H}_2$, $-C\underline{H}_2C\underline{H}_2-$), 3.20—4.05 [13H, m, $-OC\underline{H}_2COCH_3$, $-OC\underline{H}_2C\underset{OH}{\underset{|}{H}}-$, $>NC\underline{H}_2C_6H_5$, 3.68, 3.71 (each 3H, s, $-OC\underline{H}_3$)], 4.38 (0.2H, br. s, $-OC\underline{H}_2COCH_3$), 6.18 (1H, br. s, $-O\underline{H}$), 6.32 (1H, d, $J=9$ H, aromatic H), 6.43—6.77 (4H, m, aromatic H), 7.16 (5H, s, $>NCH_2C_6\underline{H}_5$).

8-Acetonyloxy-5-[3-(3,4-dimethoxyphenethylamino-2-hydroxypropoxy]-3,4-dihydrocarbostyril Hydrochloride Hydrate (IVh)——A mixture of 50 g of XXIV, 5 g of 10% Pd-C and 2.6 ml of conc. HCl in 400 ml of EtOH and 100 ml of H_2O was stirred at 50°C under atmospheric pressure of hydrogen. The catalyst was removed by filtration, and 7 g of $NaHCO_3$ was added to the filtrate with stirring. The precipitated NaCl was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with water and dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in 100 ml of $CHCl_3$, 100 ml of H_2O and 8 ml of conc. HCl. The solution was stirred vigorously and cooled in ice-water. The precipitated crystals were collected by filtration and recrystallized from H_2O–acetone to give IVh (32.0 g 68.3%) as colorless crystals, mp 135—136°C. NMR (DMSO-d_6) δ: 1.75 (1.7H, s, $-OCH_2COC\underline{H}_3$), 2.21 (1.3H, s, $-OCH_2COC\underline{H}_3$), 3.57—4.83 [11H, m, 3.73, 3.77 (each 3H, s, $-OC\underline{H}_3$), 4.76 (0.7H, s, $OC\underline{H}_2COCH_3$), $OC\underline{H}_2COCH_3$, $-OC\underline{H}_2C\underset{OH}{\underset{|}{H}}CH_2-$], 5.93 (1H, br. d, $J=6$ Hz, $-O\underline{H}$), 6.42—7.05 [m, 5H, 6.60 (1H, d, $J=9$ Hz, aromatic H), aromatic H]. The elemental analysis data are shown in Table I.

Anti-isoproterenol Activity——1) *In Vivo*:[9] Adult male mongrel dogs, weighing 10—16 kg, were anesthetized by intravenous administration of sodium pentobarbital (30 mg/kg). The blood pressure (BP) was measured at the right caroid artery with a pressure transducer (Nippon Koden, MPU-0.5) and the heart rate (HR) was determined with a heart rate tachometer (San-ei Sokki, type 2130) triggered by the blood pressure pulse. The right femoral vein was cannulated for intravenous (*i.v.*) administration of drugs. The

Table X. Antagonistic Activity of 5-[3-(3,4-Dimethoxyphenethylamino)-2-hydroxypropoxy]-8-alkoxy-3,4-dihydrocarbostyril Derivatives against Isoproterenol in Anesthetized Dog (% Inhibition of Changes in HR[a], BP[b] and AR[c])



Compound	R	Dose (μg/kg)	n[d]	Inhibition per cent		
				HR	BP	AR
IVb$_3$	$CH_2CH_2OCH_3$	3000	6	83.5±2.1[e]	19.7±10.4	29.6± 6.2
IVc$_2$	$CH_2CH{=}CH_2$	1000	4	90.6±1.0	49.2± 6.4	48.2± 9.0
IVd$_3$	$CH_2C{\equiv}CH$	1000	4	86.7±1.2	73.3± 2.9	42.5±13.4
IVe	$CH_2CH_2CH_2CH_3$	1000	4	77.6±2.8	34.9± 8.2	20.5± 2.0
IVi	CH_2COCH_3	1000	5	78.9±5.5	41.7± 5.7	11.3± 6.9
VIIc	H	100	5	83.0±3.7	60.8± 9.0	49.2±13.1
Practolol		3000	6	84.7±1.3	30.1±13.4	33.0± 9.3
Atenolol		1000	5	77.4±1.4	40.0± 9.4	29.4± 5.4

a) Heart rate.
b) Blood pressure.
c) Air-way resistance.
d) Number of experiments.
e) Mean±standard error.

air-way resistance (AR) was measured by the method of Konzett–Rössler.[10] The trachea was cannulated and animals were respirated by means of a respirator (Harvard Apparatus, model 607) at a rate of 18 to 20 times per min with an air volume of 20 to 25 ml/kg, under a positive inflow pressure of about 11 cm H_2O. Histamine at a dose of 5 μg/kg was given as a bronchoconstrictor 45 s after administration of isoproterenol through the femoral vein. Each parameter was recorded on a polygraph (San-ei Sokki, type 8S28). The β-adrenergic blocking activity of a test compound was assessed in terms of antagonism of the BP, HR and AR effects of isoproterenol as follows. First, 1 μg/kg of isoproterenol, a dose causing a submaximal decrease in BP, an increase in HR and inhibition of the increase in AR induced by histamine, was given *i.v.* Then, the test compound was injected *i.v.* and isoproterenol (1μg/kg) was given 10 min after the test compound. The activity of the test compound was expressed as the per cent inhibition of the effects of isoproterenol.

2) *In Vitro*: i) Guinea Pig Atrial Test:[11] The atria were excised from male Hartley strain guinea pigs, weighing 350—550 g, and suspended in a 30 ml tissue bath containing Krebs–Henseleit solution maintained at 36°C and aerated with 95% O_2 and 5% CO_2. Atrial beats were measured through a digital tachometer (DATA GRAPH Co., Ltd., model T149) and the contractile force was determined by means of isometric recording using a force-displacement transducer (San-ei Sokki, Type 45072). The resting tension was maintained at 1.0 g for each atrium. Isoproterenol was added cumulatively to the bath fluid and the concentration–response curves were obtained. The test compound was added to the bath fluid before isoproterenol.

The activity of the test compound was expressed as pA_2 from its response curve by the method of Bristow *et al.*[12]

ii) Guinea Pig Tracheal Test: The trachea were excised from male Hartley strain guinea pigs, weighing 350—550 g. A spiral section of the trachea was prepared according to the method of Constantine[13] and suspended in a 30 ml tissue bath containing Krebs–Henseleit solution maintained at 36°C and aerated with 95% O_2 and 5% CO_2. The resting tension was maintained at 2 g during experiments. The tension of the preparation was measured isometrically using a force-displacement transducer (San-ei Sokki, type 45072). Phentolamine (10^{-5} M) was added to the bath fluid 5 min before induction of contraction with carbachol (10^{-6} M) to block α-adrenergic receptors. Isoproterenol was added cumulatively to the bath fluid and the concentration–response curve was obtained. The test compound was added to the bath fluid at the same time as phentolamine. The activity of the test compound was expressed as pA_2 from its response curve by the method of Van Rossum.[14]

Table XI. Antagonistic Activity against Isoproterenol on isolated Guinea-Pig Atrial and Tracheal Preparations

Compound	PA_2 (mean±S.E.)		Ratio of K_B[a] (T/A)
	Atrium(n)[b]	Trachea(n)	
IVd_3	7.75±0.10(9)	6.87±0.06(5)	7.6
IVe	7.65±0.11(8)	6.64±0.17(5)	1.0×10
IVi	7.49±0.10(12)	5.03±0.08(5)	2.9×10^2
VId	8.22±0.04(10)	6.26±0.17(4)	9.1×10
Practolol	6.49±0.07(8)	4.64±0.12(5)	7.1×10
Atenolol	7.14±0.13(15)	5.43±0.04(10)	5.2×10

a) $-\log K_B = pA_2$.
b) Number of experiments.
S.E.: standard error.

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References and Notes

1) J.W. Black, A.F. Crowther, R.G. Shanks, L.H. Smith, and A.C. Dornhorst, *Lancet*, **1**, 1080 (1964).
2) J.F. Giudicelli, H. Schmidt, and J.R. Boissier, *J. Pharmacol. and Exptl. Therap.*, **168**, 116 (1969).
3) M.L. Hoeffe, S.G. Hastings, R.F. Meyer, R.M. Corey, A. Holmes, and C.D. Stratton, *J. Med. Chem.*, **18**, 148 (1975); B. Basil, J.R. Clark, E.C.J. Caffe, R. Jordar, A.H. Loveless, D.L. Pain, and K.R.H. Wooldridge, *J. Med. Chem.*, **19**, 399 (1976); L.H. Smith and H. Tucher, *J. Med. Chem.*, **20**, 1653 (1977); W.J. Rzeszotarski, R.E. Gibson, W.C. Eckelman, and R.C. Reba, *J. Med. Chem.*, **22**, 735 (1979).
4) J.J. Baldwin, E.L. Engelhardt, R. Hirschmann, G.F. Lundell, and G.S. Ponticello, *J. Med. Chem.*, **22**, 687 (1979); J.J. Baldwin, W.C. Lumna, G.F. Lundell, G.F. Ponticello, A.W. Raab, E.L. Engelhardt, and R. Hirschmann, *J. Med. Chem.*, **22**, 1284 (1979); I.J. Baldwin, E.J. Engelhardt, R.H. Hirschmann,

and G.S. Ponticello, *J. Med. Chem.*, **23**, 65 (1980).
5) K. Nakagawa, N. Murakami, S. Yoshizaki, M. Tominaga, H. Mori, Y. Yabuuchi, and S. Shintani, *J. Med. Chem.*, **17**, 529 (1974).
6) M. Uchida, M. Tominaga, K. Oka, H. Tone, T. Uno, T. Ishihara, and K. Nakagawa, *Yakugaku Zasshi*, **96**, 571 (1976).
7) W.D. McPhee and E. Klengsberg, "Organic Syntheses," Coll. Vol. III, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 119.
8) M. Tominaga, E. Yo, M. Osaki, Y. Manabe, and K. Nakagawa, *Chem. Pharm. Bull.*, **29**, 2161 (1981).
9) R.D. Robson and H.R. Kaplan, *J. Pharmacol. Exp. Ther.*, **175**, 157 (1970).
10) H. Konzett and R. Rössler, *Naunyn-Schmiededebergs. Arch. Pharmakol. Exp. Pathol.*, **195**, 71 (1940).
11) J.R.C. Baird and J. Linnell, *J. Pharm. Pharmacol.*, **24**, 880 (1972).
12) M. Bristow, T.R. Sherrod, and R.D. Green, *J. Pharmacy, Exp. Ther.*, **171**, 52 (1970).
13) J.W. Constantine, *J. Pharm. Pharmacol.*, **17**, 384 (1965).
14) J.M. Van Rossum, *Arch. Int. Pharmacodyn. Ther.*, **143**, 299 (1963).