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Studies on New β-Adrenergic Blocking Agents. I. Syntheses and Pharmacology of Coumarin Derivatives[1)]

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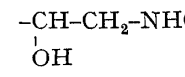
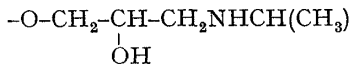
Several (2-hydroxy-3-aminopropoxy)coumarin derivatives were synthesized from 5-, 7- and 8-hydroxycoumarin derivatives by established methods and β-adrenergic blocking activity was examined. A systematic study of the positional isomers in the coumarin derivatives showed that 5-methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin ($XXIIa_2$) was most favorable as a β-adrenergic blocking agent. It was shown that the classical structure requirement prevailed, but 7-positional isomer was much less active. Resolution of $XXIIa_2$ revealed that the 1-isomer possessed the major activity.

During the last few years, many β-adrenergic blocking agents have been described in which the 1-hydroxy-2-isopropylaminoethyl (A) or 2-hydroxy-3-isopropylaminopropoxy (B) side chain or the minor variants are attached to an aromatic or heterocyclic nucleus.[3)] The relationship between the nucleus and the β-adrenergic blocking activity has been of interest in pharmacological and clinical studies.



A



B

We attempted to synthesize compounds in which the coumarin nucleus would be favorable in achieving some specificity of pharmacological action. In fact, 5-methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin ($XXIIa_2$) was found to possess significant β-adrenergic blocking activity and we are reporting here the syntheses and pharmacology of $XXIIa_2$ and related compounds.

Chemistry

Compound $XXIIa_2$ and related compounds were prepared generally by addition reaction of (2,3-epoxypropoxy)coumarin derivatives (method A) or condensation reaction of (2-hydroxy-3-chloropropoxy)coumarin derivatives (method B) with the appropriate amine.

According to method A, 7-(2-hydroxy-3-alkylaminopropoxy)coumarin derivatives (III) were prepared and the results of biological test, as shown in Table I, suggested that they were only weakly active, contrary to our expectation.

We then turned to the synthesis of coumarin derivatives in which 2-hydroxy-3-alkylaminopropoxy groups were substituted at peri positions. 5-(2-Hydroxy-3-alkylaminopropoxy)coumarin derivatives (VI) were prepared by method A. 8-(2-Hydroxy-3-alkylaminopropoxy)coumarin derivatives (X) were obtained by method A or B. The preparation of the quaternary analog (XI) was accomplished by heating 8-(2,3-epoxypropoxy)coumarin

1) Sankyo Co., Ltd., German Patent Application 2021958 (1970).
2) Location: *Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*
3) *a*) E.J. Ariens, *Ann. N.Y. Acad. Sci.*, **139**, 606 (1967); *b*) J.H. Biel and B.K.B. Lum, *Arzneimittel Forsch.*, **10**, 46 (1966).

(VIIIa) with diethylamine followed by treatment with methyl iodide. Reaction of VIIIa with succinimide afforded 8-(2-hydroxy-3-succinimidopropoxy)coumarin (XII), which was converted to 8-(2-hydroxy-3-aminopropoxy)coumarin (XIII) by acidic hydrolysis.

Reaction of 7-methallyl-8-(2,3-epoxypropoxy)coumarin (VIIIe) with *t*-butylamine afforded an oily addition product, to which addition of a solution of ethanolic hydrogen

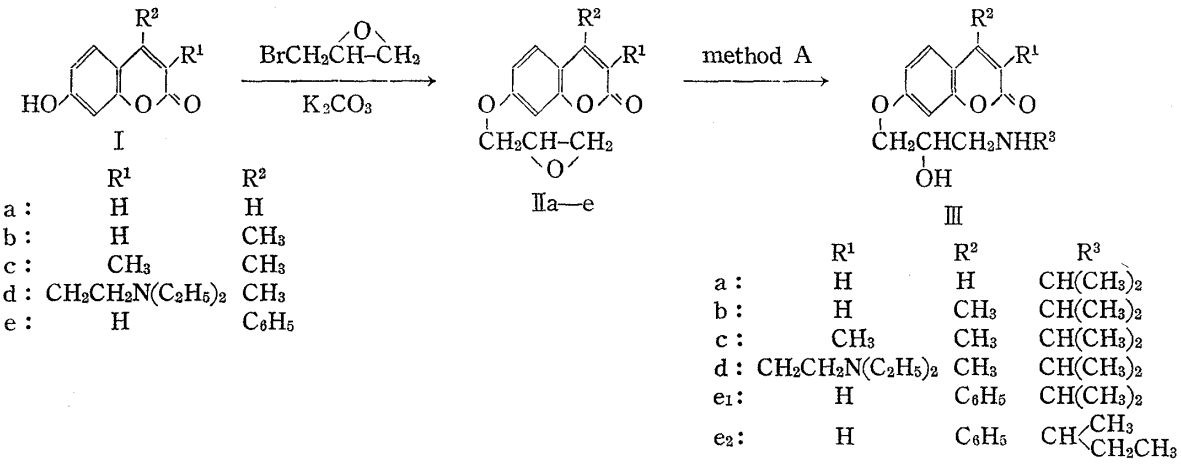


Chart 1

TABLE I. 7-(2-Hydroxy-3-alkylaminopropoxy)coumarin Derivatives (III) and Their β-Adrenergic Blocking Activities

Compd. No.	R^1	R^2	R^3	HX	mp (°C)	Formula
IIIa	H	H	$CH(CH_3)_2$		98.5—100	$C_{15}H_{19}O_4N$
IIIb	H	CH_3	$CH(CH_3)_2$		111 —112	$C_{16}H_{21}O_4N$
IIIc	CH_3	CH_3	$CH(CH_3)_2$		124 —125	$C_{17}H_{23}O_4N$
IIId	$CH_2CH_2N(C_2H_5)_2$	CH_3	$CH(CH_3)_2$	2HCl	225 —227	$C_{22}H_{36}O_4N_2Cl_2$
IIIe1	H	C_6H_5	$CH(CH_3)_2$		125 —127	$C_{21}H_{23}O_4N$
IIIe2	H	C_6H_5	$CH(CH_3)CH_2CH_3$		104 —106	$C_{22}H_{25}O_4N$

Compd. No.	Analysis (%) Calcd. C	H	N	Found C	H	N	Dose[a] (g/ml)	β-Blocking CF(%)	activity CR(%)
IIIa	64.96	6.91	5.05	65.19	6.91	4.82	10^{-5}	40	70
IIIb	65.95	7.27	4.81	66.29	7.21	4.87	10^{-5}	61	72
IIIc	66.86	7.59	4.59	67.24	7.44	4.52	10^{-5}	23	44
IIId	57.01	7.83	6.04	57.52	7.88	5.65	10^{-5}	−5	0
IIIe1	71.37	6.56	3.96	71.56	6.42	3.67	10^{-5}	50	63
IIIe2	71.91	6.86	3.81	72.00	6.87	3.95	10^{-5}	59	44

a) concentration of tested compound

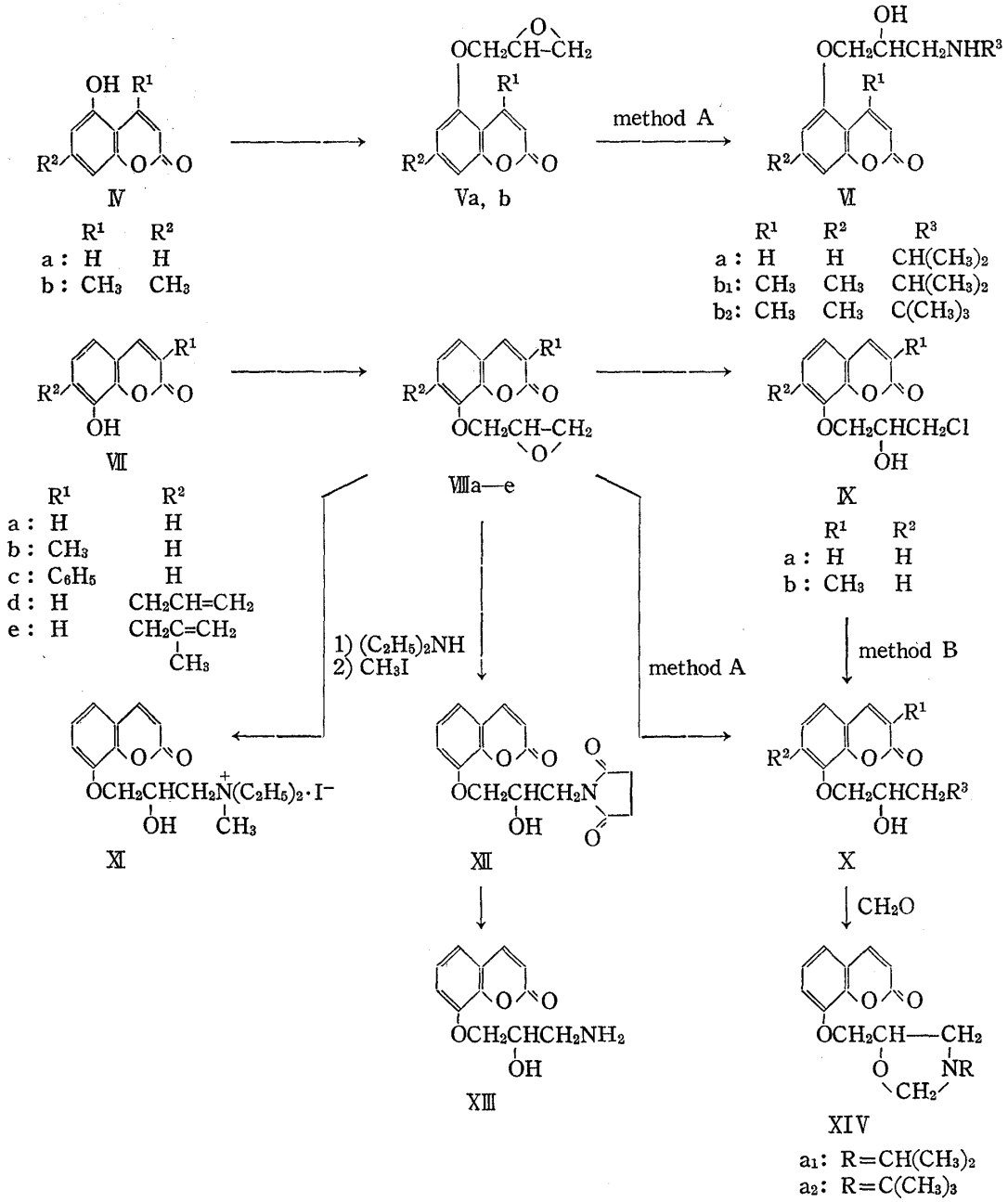


Chart 2

chloride gave 7-(2-chloroisobutyl)-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin hydrochloride (Xf), instead of 7-methallyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin hydrochloride. The structural assignment of Xf was based on the elemental analysis and the nuclear magnetic resonance (NMR) spectrum (in d_6-DMF) which showed six protons at 1.7 ppm ($-\underset{Cl}{C}-(CH_3)_2$) and disappearance of the terminal double bond absorption band in the infrared (IR) spectrum. They are listed in Table II and III.

Furthermore, 8-(2-hydroxy-3-isopropylaminopropoxy)-(XXIIa$_1$), 5-methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin (XXIIa$_2$), and 5-piperidinmoethyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin (XXVI) were prepared from 5-methyl-8-(2-hydroxy-3-chloropropoxy) coumarin (XXI) or 5-piperidinomethyl-8-(2,3-epoxypropoxy)coumarin (XXV). Compound XXI and XXV were obtained by following reactions.

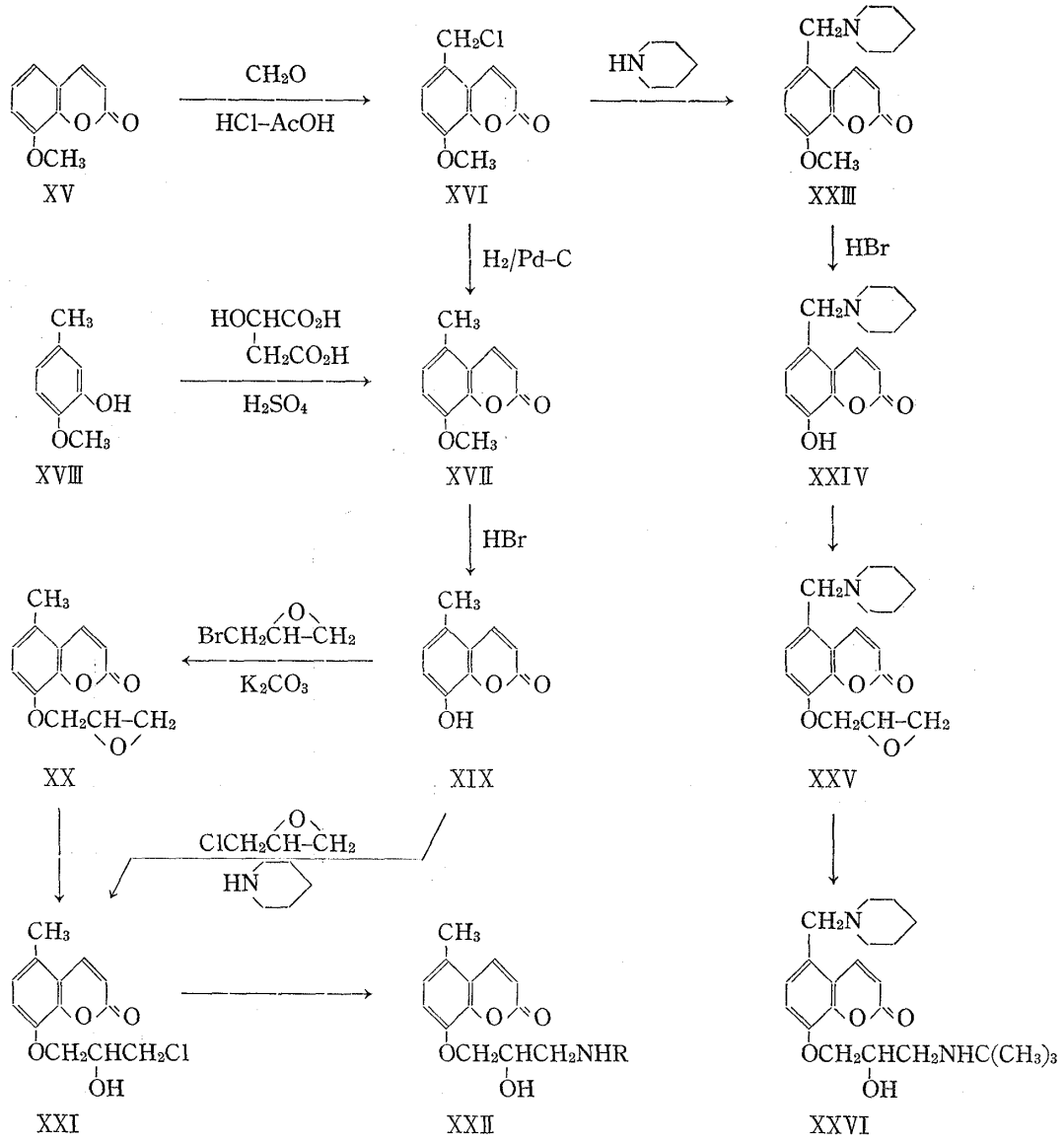
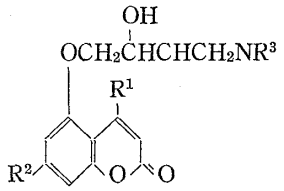


Chart 3

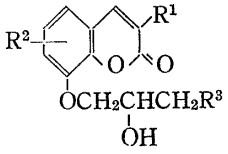
TABLE II. 5-(Hydroxy-3-alkylaminopropoxy)coumarin Derivatives (VI) and Their β-Adrenergic Blocking Activities



Compd. No.	R^1	R^2	R^3	mp (°C)	Formula
VIa	H	H	$CH(CH_3)_2$	103—104	$C_{15}H_{19}O_4N$
VIb$_1$	CH_3	CH_3	$CH(CH_3)_2$	131—133	$C_{17}H_{23}O_4N$
VIb$_2$	CH_3	CH_3	$C(CH_3)_3$	135—136	$C_{18}H_{25}O_4N$

Compd. No.	Analysis (%) Calcd. C	H	N	Found C	H	N	Dose (g/ml)	β-Blocking CF(%)	activity CR(%)
VIa	64.91	6.91	5.05	65.11	7.00	4.97	10^{-7}	80	73
							10^{-8}	48	64
VIb_1	66.86	7.59	4.59	66.84	7.69	4.58	10^{-6}	100	87
							10^{-7}	69	29
VIb_2	67.69	7.84	4.39	68.05	7.87	4.35	10^{-7}	78	88
							10^{-8}	42	33

TABLE III. 8-(2-Hydroxy-3-aminopropoxy)coumarin Derivatives (X) and Their β-Adrenergic Blocking Activities



Compd. No.	R^1	R^2	R^3	Acid Salt[a]	mp (°C)	Formula	Anaysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl	Dose (g/ml)	β-Blocking CF (%)	activity CR (%)
Xa_1	H	H	NHC_2H_5	H	194—196	$C_{14}H_{18}O_4NCl$	56.09	6.05	4.67	11.83	55.65	6.02	4.67	11.67	10^{-6}	83	83
															10^{-7}	−7	40
Xa_2	H	H	$NHCH(CH_3)_2$		106—107	$C_{15}H_{19}O_4N$	64.96	6.91	5.05		64.91	7.47	5.07		10^{-6}	100	100
															10^{-7}	69	73
Xa_3	H	H	$NHC(CH_2CH_3)(CH_3)H$	H	200—202	$C_{16}H_{22}O_4NCl$	58.62	6.77	4.27		58.40	6.83	4.26		10^{-6}	91	93
															10^{-7}	−17	50
Xa_4	H	H	$NHC(CH_3)_3$		100—101	$C_{16}H_{21}O_4N$	65.95	7.21	4.81		65.69	7.25	4.61		10^{-7}	86	83
															10^{-8}	30	50
Xa_5	H	H	NH-C6H5		102—103	$C_{18}H_{23}O_4N$	68.12	7.31	4.41		68.19	7.48	4.61		10^{-5}	75	50
Xa_6	H	H	N(NCH3)	2M	172—173	$C_{25}H_{30}O_{12}N_2$	54.54	5.49	5.09		54.36	5.60	5.67		10^{-5}	51	36
Xa_7	H	H	N(NCH2C6H5)	2M	172.5—174	$C_{31}H_{34}O_{12}N_2$	59.42	5.47	4.47		53.96	5.58	4.60		10^{-6}	36	50
Xa_8	H	H	N(NCH2CONH-C6H3(CH3)2)		175—176	$C_{26}H_{31}O_5N_3$	67.08	6.71	9.03		66.87	6.81	8.64		10^{-6}	−17	36
Xa_9	H	H	$N(CH_2C{\equiv}CH)(CH(CH_3)_2)$		106—107	$C_{15}H_{24}O_4N$	68.55	6.71	4.44		68.05	6.92	4.37		10^{-6}	−71	29
Xa_{10}	H	H	$N(CH_2C_6H_5)(CH(CH_3)_2)$	H	180—182	$C_{22}H_{26}O_4NCl$	65.42	6.49	3.47	8.78	65.04	6.56	3.78	8.59	10^{-6}	−47	25
Xb_1	CH_3	H	$NHCH(CH_3)_2$	H	193—195	$C_{16}H_{22}O_4NCl$	58.62	6.77	4.27	10.82	58.11	6.70	4.35	10.52	10^{-8}	50	56
															10^{-9}	27	38
Xb_2	CH_3	H	$NHC(CH_3)_3$	H	194.5—196	$C_{17}H_{24}O_4NCl$	59.73	7.08	4.10	10.37	59.48	7.24	3.91	10.14	10^{-8}	44	50
															10^{-9}	−17	17
Xc_1	C_6H_5	H	$NHCH(CH_3)_2$		101—102	$C_{21}H_{23}O_4N$	71.37	6.56	3.96		71.58	6.62	3.97		10^{-6}	−22	43
Xc_2	C_6H_5	H	$NHC(CH_3)_3$	H	195—197	$C_{22}H_{26}O_4NCl$	65.42	6.49	3.47	8.78	64.84	6.51	3.40	8.22	10^{-6}	22	31
Xd_1	H	7-$CH_2CH{=}CH_2$	$NHCH(CH_3)_2$	H	114—116	$C_{18}H_{24}O_4NCl$	61·09	6.84	3.96	10.02	60.69	6.96	4.06	10.01	10^{-6}	0	18
Xd_2	H	7-$CH_2CH{=}CH_2$	$NHC(CH_3)_3$		85 — 86	$C_{19}H_{25}O_4N$	68.86	7.60	4.23		69.04	7.55	4.13		10^{-6}	8	40
Xe	H	7-$CH_2C(CH_3)=CH_2$	$NHCH(CH_3)_2$		89 — 91	$C_{19}H_{25}O_4N$	68.86	7.60	4.23		68.92	7.67	4.03		10^{-6}	−23	25
Xf	H	7-$CH_2C(CH_3)(CH_3)Cl$	$NHC(CH)_3$	H	151—152	$C_{20}H_{29}O_4NCl_2$	57.42	6.99	3.35	16.95	57.72	7.24	3.62	16.36	10^{-6}	9	9
XI	H	H	$N^+(C_2H_5)_2CH_3 \cdot I^-$		142—144	$C_{17}H_{33}O_4NI \cdot 1/2H_2O$	46.16	5.70	3.16		46.26	5.69	3.21		10^{-6}	−45	18
XII	H	H	N(=O)(=O)		170—172	$C_{16}H_{15}O_6N$	60.56	4.77	4.44		60.67	4.85	4.45		10^{-6}	−43	11
XIII	H	H	NH_2	H	190—192	$C_{12}H_{14}O_4NCl$	53.04	5.19	5.16	13.05	52.99	5.38	5.01	12.55	10^{-6}	−50	17
$XXIIa_1$	H	5-CH_3	$NHCH(CH_3)_2$	H	189—191	$C_{16}H_{22}O_4NCl$	58.62	6.77	4.27	10.82	58.34	6.79	4.14	10.63	10^{-7}	88	80
															10^{-8}	32	64
$XXIIa_2$	H	5-CH_3	$NHC(CH_3)_3$	H	226—228	$C_{17}H_{24}O_4NCl$	59.73	7.08	4.10	10.37	59.78	7.36	4.16	10.26	10^{-7}	81	80
															10^{-8}	42	53
															10^{-9}	36	37
XXVI	H	5-CH_2-N(CH2)4	$NHC(CH_3)_3$	2H	199—201	$C_{22}H_{34}O_4N_2Cl_2 \cdot H_2O$	55.11	7.57	5.84	14.79	54.61	7.60	5.74	14.38	10^{-6}	−43	9

a) H: hydrochloric acid ; M: maleic acid

Chloromethylation of 8-methoxycoumarin (XV) afforded colorless crystals, mp 186—188°, whose NMR spectrum (in d_6-DMF) exhibited three protons at 4.00 (singlet, $-OCH_3$), two protons at 5.10 (singlet, $-CH_2Cl$), one proton at 6.63 (doublet, J=9.8 cps, 3-position proton), one proton at 7.29 (doublet, J=9 cps, 6- or 7-position proton), one proton at 7.49 (doublet, J=9 cps, 6- or 7-position proton) and one proton at 8.36 ppm (doublet, J=9.8 cps, 4-position proton). Therefore, the product was assumed as being 5-chloromethyl-8-methoxycoumarin (XVI) and further confirmation was carried out as follows. Catalytic reduction of XVI with palladium on carbon afforded a dechlorinated product, whose NMR spectrum (in d_6-DMF) showed AB-pattern absorption corresponding to the protons at 6 and 7 at 7.07 and 7.24 ppm with a coupling constant of 9 cps. Furthermore, in study of the Nuclear Overhauser Effect (in $CDCl_3$), irradiation of the methyl absorption at 2.48 ppm affected the absorption of 4-position proton with 11.2% increase in signal area and 19.04% increase in signal height. Consequently, the dechlorinated product was confirmed as being 5-methyl-8-methoxycoumarin (XVII) and was obtained also by an unambigous route, *i.e.* the condensation of 5-methylguaiacol (XVIII) with malic acid afforded XVII.

Heating XVII with 48% hydrobromic acid afforded 5-methyl-8-hydroxycoumarin (XIX). Reaction of XIX with epibromohydrin in the presence of potassium carbonate gave 5-methyl-8-(2,3-epoxypropoxy)coumarin (XX) which was cleaved by hydrochloric acid affording XXI. XXI was also obtained by reaction of XIX with epichlorohydrin in the presence of piperidine.

Compound (XXV) used as the starting material was obtained in a manner analogous to that for XX.

Confirmation that the epoxide opened in the manner indicated was obtained by NMR spectrum (in $CDCl_3$) and alternative syntheses, in the case of 8-(2-hydroxy-3-isopropylaminopropoxy)coumarin (Xa_2). Compound (Xa_2) showed the expected NMR spectrum, *i.e.* six protons at 1.10 (doublet, J=6 cps, $-CH(CH_3)_2$), three protons at 2.92 (multiplet, $-C\underline{H}_2-NH-C\underline{H}$), two protons at 3.08 (singlet, OH, NH) and three protons at 4.19 ppm (multiplet, $-OC\underline{H}_2-C\underline{H}(OH)-$). Reaction of 8-hydroxycoumarin (VIIa) with N-benzyl-N-isopropyl-2-hydroxy-3-chloropropylamine[4] afforded 8-[2-hydroxy-3-(N-benzyl-N-isopropylaminopropoxy)]coumarin (Xa_{10}). Catalytic hydrogenation of Xa_{10} with 5% palladium on carbon afforded the expected Xa_2. Furthermore, 8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin (Xa_4) was obtained through an alternate route involving the reaction of VIIa with 1,2-epoxy-3-butylaminopropane.[5]

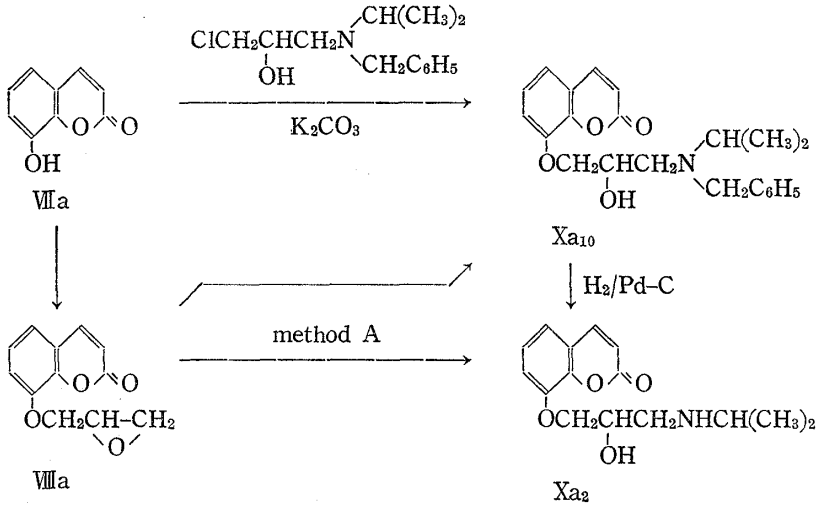
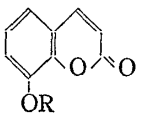


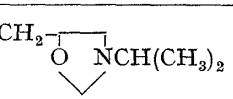
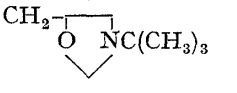
Chart 4

4) English Patent Application 62328 (1968) (Sandoz AG).
5) V.R. Gaertner, *Tetrahedron*, 23, 2123 (1967).

Furthermore, 8-[(3-alkyloxazolidine-5-yl)methoxy]coumarin derivatives ($XIVa_1$ and $XIVa_2$) were formed when Xa_2 or Xa_4 were treated with formaldehyde in hot ethanol. Both $XIVa_1$ and $XIVa_2$ were readily hydrolyzed to Xa_2 and Xa_4.

TABLE IV. 8-(3-Alkyloxazolidine-5-yl)methoxy Coumarin Derivatives (XIV) and Their β-Adrenergic Blocking Activities

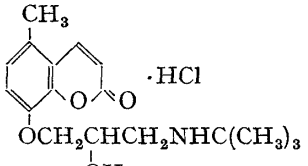


Compd. No.	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	Dose (g/ml)	β-Blocking activity CF(%)	CR(%)
XIVa1		92—93	$C_{16}H_{19}O_4N$	66.42	6.62	4.84	66.55	6.58	4.80	10^{-7}	89	100
										10^{-8}	61	78
XIVa1		95—96	$C_{17}H_{21}O_4N$	67.31	6.98	4.62	67.39	6.97	4.62	10^{-7}	87	100
										10^{-8}	23	30

As mentioned above, among the coumarin derivatives, $XXIIa_2$ was the most interesting compound. Therefore, it was desirdable to obtain the optical isomers of $XXIIa_2$ for the pharmacological studies.

Attempts using the (+)- and (−)-forms of tartaric acid as the resolving agent for $XXIIa_2$ were unsuccessful. However, $XXIIa_2$ was resolved using the (+)- and (−)-forms of O,O-di-*p*-toluoyltartaric acid. The O,O-di-*p*-toluoyltartarate salts were obtained and recrystallized to constant rotation and analytical purity before conversion to the optically active bases. The enantiomorphs were further purified as their crystalline hydrochlorides to constant rotation samples possessing equal, but opposite signs of rotation.

TABLE V

		Dose (g/ml)	β-Blocking activity CF(%)	CR(%)
	levo isomer	10^{-7}	94	100
		10^{-8}	56	76
		10^{-9}	40	28
	dextro isomer	10^{-5}	85	93
		10^{-6}	66	62
		10^{-7}	5	20
Propranolol		10^{-8}	82	77
		10^{-9}	9	18
Alprenolol (H 56/28)		10^{-7}	97	89
		10^{-8}	37	38

Pharmacology

Test for the β-adrenergic blocking activity.

Isolated right atrial preparations of guinea pigs were used for estimation of the β-adrenergic blocking activity. Hertley-strain guinea pigs of either sex, weighing 250 to 350 g were killed by a blow on the neck. The heart was immediately exposed and a narrow strip of atrium including the sino-atrial node was then excised. The muscle strip was attached to

a force displacement transducer (Nihon Kohden, SB-1T) and placed in a 40 ml organ-bath filled with Tyrode solution (g/liter: NaCl 8.0, KCl 0.2, $CaCl_2$ 0.2, $MgCl_2$ 0.1, NaH_2PO_4 0.05, $NaHCO_3$ 1.0, glucose 1.0) at 38°, which was bubbled with a mixture of 95% oxygen and 5% carbon dioxide. The resting muscle tension applied to the preparation was adjusted to 1 g throughout the course of experiment. A rate meter (Nihon Kohden, RT-2) was triggered by the output from the force transducer. Contractile force (CF) and contraction rate (CR) were simultaneously recorded on ink-writing oscillograph (Nihon Kohden, WI-200). The preparation was left for 5 to 10 min or until a steady contraction had been attained, Isoproterenol (10^{-8} g/ml) was added before and 20 min after administration of the compound to be tested. β-Adrenergic blocking activity was calculated from the tracing (Fig. 1) according to the following equation.

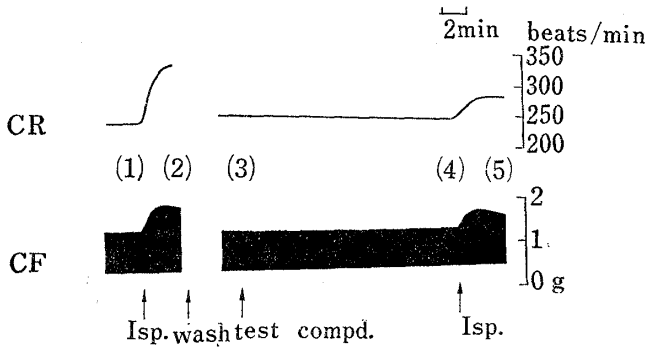


Fig. 1

Isp.: isoporoterenol 10^{-8} g/ml
Wash: washing out isoproterenol
Test compd.: test compound 10^{-5}—10^{-9} g/ml
(1): Amplitude or rate of control run.
(2): Maximum response in amplitude or rate to isoproterenol.
(3): Amplitude or rate after washing out isoproterenol.
(4): Amplitude or rate 20 min after test compound.
(5): Maximum response to isoproterenol after test compound.
β-Adrenergic blocking activity: $\frac{(2)-(5)}{(2)-(4)} \times 100(\%)$

Water soluble compounds were dissolved in saline. Bases were first dissolved in 1/100N hydrochloric acid, and then neutralized with 1/100N sodium hydroxide. Isoproterenol (sulfate) was purchased from Boehringer Sohn.

Structure and Activity Relationships

The initial study of coumarin derivatives as β-blocking agent involved a systematic evaluation of the positional isomers. Results indicate as shown in Table I, II, and III that when the side chain substitution was maintained as 2-hydroxy-3-isopropoylaminopropoxy, the 5- and 8-positional isomers exhibited significant β-adrenergic blocking activity, while 7-positional isomer was much less active. Therefore, most comparisons of the substitution effects on the amino function were made within the 8-substituted isomers. The observed potency order for the amino substituents was *t*-butyl>isopropyl>*sec*-butyl>ethyl>cyclohexyl and hydrogen for the 8-(2-hydroxy-3-substituted aminopropoxy)coumarin derivatives. Conversion into the tertiary-amine or quaternary ammonium salt led to only weakly active or inactive compounds. Furthermore, introduction of large groups such as phenyl, allyl, and methallyl groups into Xa_2 and Xa_4 which were found to possess significant β-adrenergic blocking activity was in general disappointing, and even if the substituent was smaller, introduction of two methyl groups led to some loss of β-adrenergic blocking activity.

However, the introduction of one methyl group was favorable, *i.e.* Xb_1, Xb_2, $XXIIa_1$ and $XXIIa_2$ were found to possess significant β-adrenergic blocking activity. This finding was observed in the case of $XXIIa_2$ and XXVI; *i.e.* XXVI did not show any notable β-adrenergic blocking activity. Alternation of the side chain structure such as by the formation of oxazolidine derivatives $XIVa_1$ and $XIVa_2$ resulted in maintenance of β-adrenergic blocking potency, which was probably due to the rapid hydrolysis of the oxazolidine ring in aqueous solution as shown in Table IV. However, the isomeric form of the side chain of Xa_4 led to total loss of the β-adrenergic blocking activity (see Experimental).

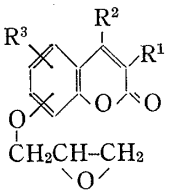
Among the coumarin derivatives, $XXIIa_2$ exhibited the most favorable characteristics from the pharmacological point of β-adrenergic blocking activity and antiarrhythmic activity in dog, *i.e.* $XXIIa_2$ was more potent than Propranolol. The details will be reported elsewhere.

As has been found in other series of compounds with similar β-adrenergic blocking action, the *l*-antipode of $XXIIa_2$ was more active and was about 100 times stronger than *d*-antipode.

Experimental[6]

(2,3-Epoxypropoxy)coumarin Derivatives (IIa—c, IIe, Va, b, VIIIa—e, XX, XXV)——A typical synthesis is described for 5-methyl-8-(2,3-epoxypropoxy)coumarin (XX). A mixture of 2 g of XIX 7.8 g of potassium carbonate, 7.7 g of epibromohydrin and 60 ml of methyl ethyl ketone was heated under reflux for 15 hr with stirring. The reaction mixture was filtered while hot and the filtrate was concentrated under reduced pressure. The residue was recrystallized from EtOH to give a colorless crystalline powder (XX), mp 113—114°. Yield, 1.3 g. The elemental analysis is shown in Table VI.

Table VI. (2,3-Epoxypropoxy)coumarin Derivatives



Compd. No.	Position of 2,3-epoxy propoxy group	R^1	R^2	R^3	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa	7	H	H	H	110	$C_{12}H_{10}O_4$	66.05	4.62		66.02	4.59	
IIb	7	H	CH_3	H	100—101	$C_{13}H_{12}O_4$	67.23	5.21		66.84	5.08	
IIc	7	CH_3	CH_3	H	101—103	$C_{14}H_{14}O_4$	68.28	5.73		68.35	5.70	
IIe	7	H	C_6H_5	H	125—126	$C_{18}H_{14}O_4$	73.46	4.80		73.46	4.79	
Va	5	H	H	H	120—122	$C_{12}H_{10}O_4$	66.05	4.62		65.52	4.89	
Vb	5	H	CH_3	7-CH_3	141—143	$C_{14}H_{14}O_4$	68.25	5.73		67.88	5.69	
VIIIa	8	H	H	H	94— 95	$C_{12}H_{10}O_4$	66.05	4.62		65.96	4.81	
VIIIb	8	CH_3	H	H	108—109	$C_{13}H_{12}O_4$	67.23	5.21		66.97	5.28	
VIIIc	8	C_6H_5	H	H	130—131	$C_{18}H_{14}O_4$	73.46	4.80		73.80	4.77	
VIIId	8	H	H	7-$CH_2CH{=}CH_2$	77— 79	$C_{15}H_{14}O_4$	69.75	5.46		69.72	5.50	
VIIIe	8	H	H	7-$CH_2C(CH_3){=}CH_2$	60— 61	$C_{16}H_{16}O_4$	70.57	5.92		70.33	5.91	
XX	8	H	H	5-CH_3	113—114	$C_{13}H_{12}O_4$	67.23	5.21		66.81	5.23	
XXV	8	H	H	5-CH_2N⟨⟩	113—115	$C_{18}H_{21}O_4N$	68.55	6.71	4.44	68.38	6.80	4.54

(2-Hydroxy-3-alkylaminopropoxy)coumarin Derivatives (IIIa—e_2, VIa—b_2, Xa_1—a_5, Xa_9, Xb_1, b_2, Xc_1, c_2, Xd_1, d_2, Xe, Xf, $XXIIa_1$, a_2, XXVI)——Method A: A typical synthesis is described for 4-methyl-7-(2-hydroxy-3-isopropylaminopropoxy)coumarin (IIIb).[7]

A mixture of 1 g of IIb, 1.6 g of isopropylamine and 50 ml of EtOH was heated at 100° for 7—10 hr in a sealed tube. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed over Al_2O_3 with $CHCl_3$ as eluent. The residue left after evaporation of $CHCl_3$ was recrystallized from benzene to give pale yellow prisms (IIIb) mp 111—112°. Yield 1 g. NMR (in $CDCl_3$) ppm: 2.66 (2H, OH and NH), 2.90 (3H, $-C\underline{H}_2-NH-C\underline{H}-$) and 4.08 (3H, $-OC\underline{H}_2-C\underline{H}-$).
OH

Method B: A typical synthesis is described for 5-methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin ($XXIIa_2$).

A mixture of 622.7 g XXI, 1.2 kg of *t*-butylamine and 5.7 liter of EtOH was heated under reflux for 32 hr with stirring. The reaction mixture was concentrated under reduced pressure and the residue was

6) All melting points are uncorrected. NMR spectra were taken using Varian A-60 spectrometer and the chemical shifts were expressed in ppm unit from the internal standard of tetramethylsilane.

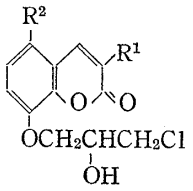
7) Recently, IIIb hydrochloride was reported by Soc. ANONYME LAB. DAUSSE, French Patent Application 1588855 (1970).

dissolved in a mixture of 800 ml of 10% hydrochloric acid and 800 ml of water. To the resulting solution was added active carbon and the mixture was filtered. The filtrate was made basic with a saturated potassium carbonate solution and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, the $CHCl_3$ was evaporated, and the residue was dissolved in 400 ml of EtOH. Into this solution was added dropwise a solution of methanolic hydrogen chloride and the precipitate thereby formed was recrystallized from EtOH to give colorless crystals (XXIIa$_2$), mp 226—228° (decomp.). Yield, 505.6 g. NMR (in d_6-DMF) ppm: 1.51 (9H, singlet, $-C(CH_3)_3$), 2.49 (3H, singlet, 5-position CH_3), 3.17—3.68 (4H, multiplet, $-CH(OH)-CH_2-NH-$), 4.18—4.64 (3H, multiplet, $-OCH_2-CH-$), 6.5 (1H, doublet, $J=9.8$ cps, 3-H), 7.12 (1H, doublet, $J=9$ cps, 6 or 7-H), 7.34 (1H, doublet, $J=9$ cps, 6 or 7-H), 8.19 (1H, doublet, $J=9.8$ cps, 4-H). This compound which was recrystallized from iso-PrOH gave colorless crystals of mp 217—219° (decomp.), but showed the same pattern absorption in the NMR spectra.

(2-Hydroxy-3-chloropropoxy)coumarin Derivatives (IXa, b, XXI)——A typical synthesis is described for 5-methyl-8-(2-hydroxy-3-chloropropoxy)coumarin (XXI). 1) A mixture of 0.2 g of XX and 30 ml of methyl ethyl ketone was saturated with dry hydrogen chloride under ice cooling and allowed to stand overnight at room temperature. The residue left after evaporation of the solvent was recrystallized from EtOH to give colorless crystals (XXI), mp 156—158°. Yield, 0.22 g.

2) A mixture of 344 g of XIX, 980 g of epichlorohydrin and 4 ml of piperidine was heated at 100° for 6.5 hr with stirring and allowed to stand overnight at room temperature. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 70 ml of conc. hydrochloric acid under cooling and allowed to stand overnight at room temperature. The crystals were collected by filtration and washed with water. After drying, the compound was recrystallized from EtOH to give colorless crystals (XXI), mp 156—158°. Yield, 491.6 g. This compound was identified by IR spectral comparison with XXI prepared by method 1).

Table VII. (2-Hydroxy-3-chloropropoxy)coumarin Derivatives



Compd. No.	R¹	R²	mp (°C)	Formula	Analysis (%) Calcd. C	H	Cl	Found C	H	Cl
IXa	H	H	138.5—139.5	$C_{12}H_{11}O_4Cl$	56.59	4.35	13.92	56.68	4.35	13.79
IXb	CH_3	H	165 —166	$C_{13}H_{13}O_4Cl$	58.11	4.88	13.20	57.94	4.86	12.86
XXI	H	CH_3	156 —158	$C_{13}H_{13}O_4Cl$	58.11	4.88	13.20	57.83	4.79	12.84

8-(2-Hydroxy-3-piperazinopropoxy)coumarin Derivatives (Xa$_6$—a$_8$)——A typical synthesis is described for 8-(2-hydroxy-3-N-methylpiperazinopropoxy)coumarin (Xa$_6$). A mixture of 1.2 g of IXa, 0.5 g of N-methylpiperazine, 1 g of triethylamine and 30 ml of dry toluene was heated under reflux for 12 hr with stirring. The reaction mixture was filtered while hot. The residue left after evaporation of the solvent was dissolved in benzene–*n*-hexane mixture and filtered. The filtrate was cooled and the precipitate thereby formed was collected by filtration. The crystals converted to maleic acid salt by the usual method. The crude salt was recrystallized from EtOH to give colorless needles (Xa$_6$), mp 172—173°. Yield, 0.5 g.

8-(2-Hydroxy-3-diethylaminopropoxy)coumarin Methiodide (XI)——A mixture of 0.55 g of VIIIa, 0.92 g of diethylamine and 30 ml of EtOH was heated at 105° for 7 hr in a sealed tube. The residue left after evaporation of the solvent was chromatographed over Al_2O_3 with $CHCl_3$ as eluent. The residual oil left after evaporation $CHCl_3$ was heated with excess of methyl iodide in 10 ml of EtOH for 5 hr. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized from iso-PrOH to give pale yellow needles, mp 142—144°. Yield, 0.3 g.

8-(2-Hydroxy-3-succinimidopropoxy)coumarin (XII)——A mixture of 5.4 g of VIIIa, 2.5 g of succinimide, three drops of pyridine and 70 ml of EtOH was refluxed for 24 hr. After cooling, the precipitate thereby formed was collected by filtration and recrystallized from 20% aq. EtOH to give pale yellow needles, mp 170—172°. Yield, 4.1 g.

8-(2-Hydroxy-3-aminopropoxy)coumarin (XIII)——A mixture of 1.58 g of XII and 40 ml of conc. hydrochloric acid was heated under reflux for 12 hr. The residue left after evaporation of the solvent was recrystallized from EtOH to give pale yellow crystals, mp 190—192°. Yield, 0.5 g.

8-[2-Hydroxy-3-(N-benzyl-N-isopropylamino)propoxy]coumarin Hydrochloride (Xa_{10})——1) A mixture of 1.5 g of VIIa, 6.7 g of N-benzyl-N-isopropyl-2-hydroxy-3-chloropropylamine,[4] 6.4 g of potassium carbonate and 30 ml of methyl ethyl ketone was heated at 100° for 120 hr in a seled tube. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure. The redidual oil was submitted to column chromatography over Al_2O_3. The column was eluted with $CHCl_3$–benzene (1:1) mixture and the residue left after evaporation of solvent was converted to crystalline hydrochloride which was recrystallized from EtOH to give colorless needles, mp 180—182. Yield, 1 g.

2) A mixture of 2 g of VIIIa, 4.12 g of N-benzylisopropylamine and 25 ml of EtOH was heated at 100° for 50 hr in a sealed tube. The residual oil left after evaporation of the solvent was dissolved in methyl ethyl ketone, and then saturated with dry hydrogen chloride and allowed to stand a few hours. The solution was concentrated under reduced pressure and the residue was recrystallized from EtOH to give 2.43 g of colorless needles, mp 180—182°, which were identified by mixed melting point determination and IR spectral comparison with Xa_{10} prepared by method 1).

Debenzylation of 8-[2-Hydroxy-3-(N-benzyl-N-isopropylamino)propoxy]coumarin Hydrochloride (Xa_{10})——A mixture of 0.62 g of Xa_{10}, 0.6 g of 5% palladium on carbon, 10 ml of EtOH and 10 ml of H_2O was hydrogenated unti l25 ml of hydrogen was absorbed. The catalyst was filtered off, the solvent was evaporated and the residual oil was made basic with 10% K_2CO_3 solution and extracted with $CHCl_3$. The $CHCl_3$ was evaporated to give 0.15 g of crystals, mp 106—107°, which were identified by IR spectral comparison with 8-(2-hydroxy-3-isopropylaminopropoxy)coumarin (Xa_2), prepared from VIIIa by method A.

Reaction of 8-Hydroxycoumarin (VIIa) with 1,2-Epoxy-3-*t*-butylaminopropane——A mixture of 1.5 g of VIIa, 2.6 g of 1,2-epoxy-3-*t*-butylaminopropane[5] and 30 ml of EtOH was heated at 100° for 5 hr in a sealed tube. Production of 8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin (Xa_4) in this reaction was observed by thin layer chromatography. The residual oil left after evaporation of the solvent was chromatographed over Al_2O_3 with $CHCl_3$–EtOH (95:5) mixture as eluent. The residue left after evaporation of the solvent was recrystallized from *n*-hexane–benzene mixture to give colorless crystals, mp 115—116°. Yield, 0.17 g. *Anal.* Calcd. for $C_{16}H_{21}O_4N$: C, 65.95; H, 7.27; N, 4.81. Found: C, 66.02; H, 7.34; N, 4.86. UV λ_{max}^{EtOH} mμ (log ε): 251.8 (3.91); 286.5 (4.06). NMR (in $CDCl_3$) ppm: 1.18 (9H, singlet, $-C(CH_3)_3$), 2.29 (2H), 3.37 (1H, multiplet), 3.71 (2H, doublet, J=5.3 cps), 4.12 (2H, doublet, J=6 cps), 6.48 (1H, doublet, J=9.8 cps, 3-H), 7.20 (3H, multiplet, 5,6 and 7-H) and 7.75 (1H, doublet, J=9.8 cps, 4-H). NMR (in $CDCl_3$) of Xa_4, ppm: 1.13 (9H, singlet, $-C(CH_3)_3$), 2.63 (2H, OH and NH), 2.88 (2H, multiplet, $-CH_2-NH-$), 4.12 (3H, multiplet, $-CH_2-\underset{\underset{OH}{|}}{CH}-$), 6.40 (1H, doublet, J=9.8 cps 3-H), 7.14 (3H, multiplet, 5,6- and 7-H), and 7.66 (1H, doublet J=9.8 cps, 4-H). From NMR spectral data, this compound was assumed to be a isomeric form of the side chain of Xa_4. In the biological test, CF was O and CR was 36% in concentration of 10^{-6} g/ml.

8-[(3-Alkyloxazolidine-5-yl)methoxy]coumarin Derivatives ($XIVa_1$, a_2)——A typical synthesis is described for 8-[(3-isopropyloxazolidine-5-yl)methoxy]coumarin ($XIVa_1$). A mixture of 1.3 g of Xa_2, 0.5 ml of 37% formaldehyde and 20 ml of EtOH was refluxed for 6 hr. The residue left after evaporation of the solvent was recrystallized from benzene–*n*-hexane mixture to give colorless needles, mp 92—93°. Yield, 0.35 g.

7-Methallyl-8-hydroxycoumarin (VIIe)——A mixture of 15 g of VIIa, 50 g of methally chloride, 60 g potassium carbonate and 200 ml of methyl ethyl ketone was heated under reflux for 15 hr with stirring. The reaction mixture was filtered while hot. The residual oil left after evaporation of the solvent was heated with 50 ml of diethylaniline at 210° for 2 hr. The reaction mixture was cooled in ice–water and the precipitate thereby formed was collected by filtration and recrystallized from 60% aq. MeOH to give needles, mp 140°. Yield, 7 g. *Anal.* Calcd. for $C_{12}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.12; H, 5.63.

5-Chloromethyl-8-methoxycoumarin (XVI)——A mixture of 400 g of XV, 1.93 liter of glacial acetic acid, 4.82 liter of conc. hydrochloric acid and 227 g of 37% aq. formaldehyde was stirred at 60—65° for 4 hr while introducing dry hydrogen chloride. The reaction mixture was then poured into 1000 ml of ice–water and the precipitate was collected by filtration and washed with water. The product was recrystallized from ethyl acetate to give colorless needles, mp 186—188°. Yield, 471.5 g. *Anal.* Calcd. for $C_{11}H_9O_3Cl$: C, 58.81; H, 4.04; Cl, 15.78. Found: C, 58.42; H, 4.12; Cl, 15.61.

5-Methyl-8-methoxycoumarin (XVII)——A mixture of 300 g of XVI, 20 g of 5% palladium on carbon and 1.4 liter of DMF was hydogenated until hydrogen uptake ceased. The catalyst was filtered off, the residue left after evaporation of the solvent was recrystallized from 60% aq. EtOH to give colorless needles, mp 152—153°. Yield, 243.9 g. *Anal.* Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.33; H, 5.39. UV λ_{max}^{EtOH} mμ (log ε): 255.2 (3.99); 295 (4.07).

5-Methyl-8-hydroxycoumarin (XIX)——A mixture of 437.6 g of XVII and 1.8 liter of 48% aq. hydrobromic acid was heated under reflux for 6 hr with stirring. The reaction mixture was heated with 400 ml of H_2O and cooled gradually. The precipitate thereby formed was collected by filtration and washed with H_2O. After drying, the product was recrystallized from ethyl acetate to give pale yellow needles, mp 175—

177°. Yield, 381.8 g. *Anal.* Calcd. for $C_{10}H_8O_3$: C, 68.17; H, 4.58. Found: C, 68.37; H, 4.37. UV λ_{max}^{EtOH} mμ (log ε); 257.6 (4.01); 300.0 (4.05).

Reaction of 5-Methylguaiacol (XVIII) with Malic Acid——A mixture of 3.76 g of XVIII, 2.46 g of malic acid and 6.1 ml of sulfuric acid was stirred at room temperature and then was heated at 110—115° for 1.5 hr in an oil-bath. After cooling, the reaction mixture was poured into ice-water and the separated oil was extracted with $CHCl_3$. The residue left after evaporation of the solvent was washed with 50% aq. EtOH, and then was chromatographed over Al_2O_3 with $CHCl_3$ as eluent. The residue left after evaporation of $CHCl_3$ was recrystallized from 60% aq. EtOH to give 5-methyl-8-methoxycoumarin (XVII), mp 152—153°. Yield, 0.5 g. This compound was identified by IR spectral comparison with XVII prepared by hydrogenation of XVI.

The previous filtrate (50% aq. EtOH) was concentrated under reduced pressure and the residue was recrystallized from ethyl acetate to give colorless crystals, mp 174—177°. Yield, 1.4 g. This compound was identified by IR spectral comparison with 5-methyl-8-hydroxycoumarin (XIX) prepared by XVII with 48% aq. hydrobromic acid.

5-Piperidinomethyl-8-methoxycoumarin (XXIII)——A suspension of 5 g of XVI, 4.7 g of piperidine and 120 ml of EtOH was heated under reflux for 7 hr with stirring. The reaction mixture was concentrated under reduced pressure and the residue was recrystallized from EtOH to give colorless needles, mp 172—174°. Yield, 5.8 g. *Anal.* Calcd. for $C_{16}H_{19}O_3N$: C, 70.31; H, 7.01; N, 5.13. Found: C, 70.31; H, 7.09; N, 5.28.

5-Piperidinomethyl-8-hydroxycoumarin (XXIV)——A mixture of 0.4 g of XXIII and 25 ml of 48% aq. hydrobromic acid was heated under reflux for 3 hr with stirring. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in water and treated with 10% $NaHCO_3$ solution until basic. The precipitate thereby formed was collected by filtration. After drying, the product was recrystallized from aq. EtOH to give yellowish green needles, mp 162—164°. Yield, 0.37 g. *Anal.* Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found C, 69.62; H, 6.57; N, 5.45.

Optical Resolution of (±)-5-Methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin (XXIIa$_2$)——1) Into a solution of 25.3 g of O,O-di-*p*-toluoyl-*l*-tartaric acid[8] in 100 ml of acetone was added a solution of 20 g of XXIIa$_2$ in 100 ml of acetone. The solution was allowed to stand for 20 min at room temperature. A crystalline precipitate thereby formed was collected by filtration. The salt was recrystallized several times from MeOH to give a white crystalline salt possessing constant melting point and rotation values mp 183° (decomp.). Yield, 9.42 g. $[\alpha]_D^{25}$ +70.6° (c=0.5 in MeOH). *Anal.* Calcd. for $C_{37}H_{41}O_{12}N$: C, 64.24; H, 5.97; N, 20.2. Found: C, 63.99; H, 6.13; N, 2.00.

A suspension of 9.43 g of the crystalline salt in 70 ml of benzene and 100 ml of 3N K_2CO_3 solution was stirring for 3 hr at room temperature. The benzene layer, upon drying with Na_2SO_4, gave the free base as an oil. This material was converted into (−)-5-methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy) coumarin hydrochloride by the usual method and was recrystallized from EtOH until the melting point and rotation became constant, mp 230—222° (decomp.). Yield, 1.3 g. $[\alpha]_D^{25}$ −18.6° (c=0.5 in MeOH). *Anal.* Calcd. for $C_{17}H_{24}O_4NCl$: C, 59.73; H, 7.08; N, 4.10; Cl 10.37. Found: C, 59.29; H, 6.95; N, 4.04; Cl, 10.19.

The mother liquor containing the remaining O,O-di-*p*-toluoyl-*l*-tartarate of *d*-antipode was concentrated and the residue was partitioned between 70 ml of benzene and 100 ml of 3N K_2CO_3 solution. The benzene layer gave 3.1 g of the free base as an oil. Into a solution of 3.9 g of O,O-di-*p*-toluoyl-*d*-tartaric acid[8] in 15.5 ml of acetone was added a solution of 3.1 g of free base in 15.5 ml of acetone. The solution was allowed to stand for 14.5 hr at room temperature. A crystalline precipitate thereby formed was collected by filtration. The salt was recrystallized several times from MeOH to give a white crystalline salt possessing constant melting point and rotation values, mp 183° (decomp.). Yield, 6.3 g. $[\alpha]_D^{25}$ −69.4° (c=0.51 in MeOH). *Anal.* Calcd. for $C_{37}H_{41}O_{12}N$: C, 64.24; H, 5.97; N, 2.02. Found: C, 64.16; H, 5.94; N, 1.92.

A suspension of 5 g of the crystalline salt in 50 ml of benzene and 50 ml of 3N K_2CO_3 solution was stirred for 3 hr at room temperature. The benzene layer, upon drying with Na_2SO_4, gave the free base as an oil. This material was converted into (+)-5-methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin hydrochloride by the usual method. The product was recrystallized from EtOH until the melting point and rotation became constant, mp 231—232° (decomp.). Yield, 1 g. $[\alpha]_D^{25}$ +18.38° (c=0.49 in MeOH).

2) Into a solution of 6.54 g of O,O-di-*p*-toluoyl-*d*-tartaric acid in 25 ml of EtOH was added a solution of 5.17 g of XXIIa$_2$ in 25 ml of EtOH at 50°. The solution was allowed to stand for 22.5 hr at room temperature. The crystalline precipitate thereby formed was collected by filtration. The salt was recrystallized several times from MeOH to give a white crystalline salt possessing constant melting point and rotation values, mp 187.5°. (decomp.). Yield, 1.43 g. $[\alpha]_D^{25}$ −69.46° (c=0.56 in MeOH). *Anal.* Calcd. for $C_{37}H_{41}O_{12}N$: C, 64.24; H, 5.97; N, 2.02. Found: C, 63.96; H, 6.20; N, 2.12.

A suspension of 1.43 g of crystalline salt in 30 ml of benzene and 30 ml 3N K_2CO_3 solution was stirred for 3 hr at room temperature. The benzene layer, upon drying with Na_2SO_4, gave the free base as an oil. This material was converted into (+)-5-methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin hydrochloride by the usual method. The product was recrystallized from EtOH until the melting point and rota-

8) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922 (1943).

tion became constant, mp 231—232° (decomp.). Yield, 0.573 g. $[\alpha]_D^{25}$ +18.5° (c=0.535 in MeOH). *Anal.* Calcd. for $C_{17}H_{24}O_4NCl$: C, 59.73; H, 7.08; N, 4.10; Cl, 10.37. Found: C, 59.16; H, 7.16; N, 3.90; Cl, 10.28.

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