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Studies on New β-Adrenergic Blocking Agents. II.[1] Syntheses and Pharmacology of 2-Anilinotropone Derivatives[2]

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2-[*p*-(Aminoalkoxy)anilino]tropone derivatives were prepared from 2-(*p*-hydroxyanilino)tropone derivatives by established synthetic procedures and were tested for β-adrenergic blocking, coronary vasodilating, and anti-hypertensive activities. Some members of the series exhibited significant activities in one or more of the pharmacological tests, and introduction of a halogen atom into the 5-position of the tropone nucleus caused generally an increase in the pharmacological activities.

In part I syntheses and a β-adrenergic blocking activity of 5-methyl-8-(2-hydroxy-3-*t*-butylaminopropoxy)coumarin and its related compounds have been reported.[1] This compound is at present undergoing preclinical evaluation after further studies as a β-adrenergic blocking agent.

Recently, 4-(2-hydroxy-3-isopropylaminopropoxy)acetanilide (practolol) has been shown to be a cardioselective β-adrenergic blocking agent.[4] Sianesi[5] reported that N,N-disubstituted 2-glycinamidotropones exhibited a significant coronary vasodilating activity. In the course of an extension of our work, we considered that 2-[*p*-(2-hydroxy-3-aminopropoxy)-anilino]tropone derivatives might possess a β-adrenergic blocking activity with some specificity of pharmacological action.

The present paper deals with the syntheses and pharmacological activities of such compounds.

Chemistry

The synthetic routes used for obtaining 2-[*p*-(2-hydroxy-3-aminopropoxy)anilino]tropone derivatives are shown in Chart 1.

Reaction of tropolone tosylate (I)[6] with *p*-aminophenol in ethanol gave 2-(*p*-hydroxyanilino)tropone·*p*-toluenesulfonate (II). Compound (II) was passed through a column of silica gel to give 2-(*p*-hydroxyanilino)tropone (III), which was also prepared by the reaction of 2-methoxytropone (IV)[7] with *p*-aminophenol. Substituted 2-(*p*-hydroxyanilino)tropone derivatives were synthesized from substituted methoxytropones[7] and *p*-aminophenol. Then, the desired 2-[*p*-(2-hydroxy-3-aminopropoxy)anilino]tropone derivatives were synthesized in a manner analogous to that for (2-hydroxy-3-aminopropoxy)coumarin derivatives[1] by reaction of III with epibromohydrin followed by treatment with the appropriate amine.

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[1] Part I: Y. Sato, Y. Kobayashi, T. Nagasaki, T. Oshima, S. Kumakura, K. Nakayama, H. Koike, and H. Takagi, *Chem. Pharm. Bull.* (Tokyo), **20**, 905 (1972).

[2] Sankyo Co., Ltd., German Patent Application 2164153 (1972).

[3] Location: *2-58, 1-chome, Hiromachi, Shinagawa-ku, Tokyo.*

[4] *a*) A.M. Barrett, A.F. Crowther, D. Dunlop, R.G. Shanks, and L.H. Smith, *Arch. Pharmakol. Exp. Pathol.*, **259**, 152 (1968); *b*) A.F. Crowther, R. Howe, and L.H. Smith, *J. Med. Chem.*, **14**, 511 (1971).

[5] E. Sianesi, M.J. Magistretti, and I. Setnikar, *J. Med, Chem.*, **10**, 1144 (1967).

[6] T. Nozoe, "Dai Yukikagaku," Vol. 13, Asakura Shoten, Tokyo, 1960.

[7] *a*) T. Nozoe, S. Seto, T. Ikemi, and T. Arai, *Proc. Japan Acad,*. **27**, 102 (1951); *b*) T. Sato, *Nippon Kagaku Zasshi*, **80**, 1171, 1342; *c*) T. Nozoe and S. Seto, *Proc. Japan Acad.*, **27**, 188 (1951); *d*) J.W. Cook, J.D. Loudon, and D.K.V. Steel, *J. Chem. Soc.*, **1954**, 530.

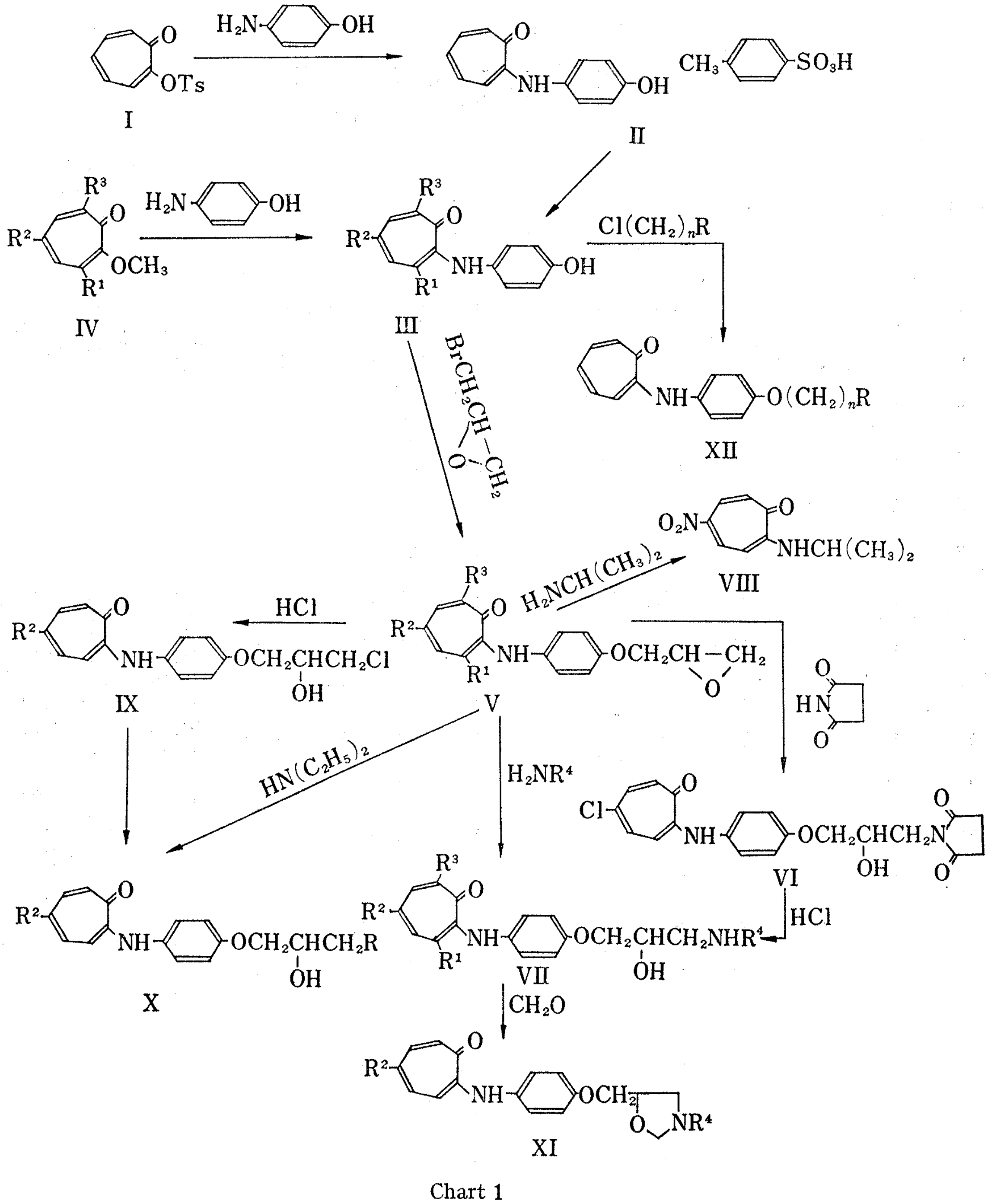


Chart 1

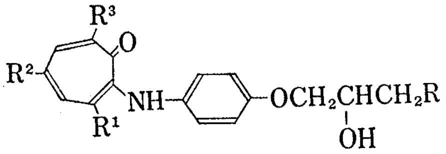
Reaction of 2-[*p*-(2,3-epoxypropoxy)anilino]-5-nitrotropone (V, R^1=R^3=H, R^2=NO_2) with isopropylamine gave 2-isopropylamino-5-nitrotropone (VIII), contrary to our expectation.

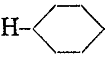
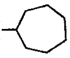
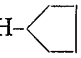
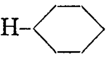
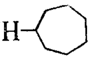
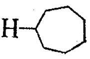
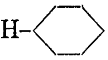
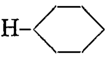
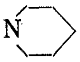
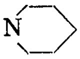
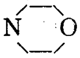
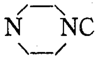
The 2-[*p*-(2-hydroxy-3-alicyclicaminopropoxy)anilino]tropone derivatives (X) were prepared by treating 2-[*p*-(2-hydroxy-3-chloropropoxy)anilino]tropone with the appropriate alicyclic amine.

Subsequently, 3-alkyl-5-[*p*-(2-troponylamino)phenoxymethyl]oxazolidine derivatives (XI) were formed when VII was treated with formaldehyde in hot ethanol.

Furthermore, 2-[*p*-(aminoalkoxy)anilino]tropone derivatives (XII) were synthesized from III and an aminoalkyl chloride. These are listed in Table I, II, and III.

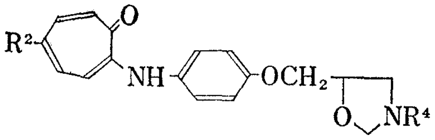
TABLE I. 2-[*p*-(2-Hydroxy-3-aminopropoxy)anilino]tropone Derivatives



Compd. No.	R¹	R²	R³	R	Acid salt[a]	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	Cl (Br)
1	H	H	H	NHCH(CH$_3$)$_2$		135.5—136.5	$C_{19}H_{24}O_3N_2$	69.49 (70.12	7.37 7.38	8.53 8.49)	
2	H	H	H	NHC(CH$_3$)$_3$		135—136	$C_{20}H_{26}O_3N_2$	70.15 (69.94	7.65 7.48	8.18 8.30)	
3	H	H	H	NH-		111—112.5	$C_{22}H_{28}O_3N_2$	71.71 (71.58	7.66 7.68	7.60 7.84)	
4	H	H	H	NH-	2H	252 (decomp.)	$C_{23}H_{32}O_3N_2Cl_2$	60.65 (60.77	7.08 7.18	6.15 6.13	15.57 15.49)
5	H	Cl	H	NH$_2$	H	252—254	$C_{16}H_{18}O_3N_2Cl_2$	53.79 (53.83	5.08 5.15	7.84 7.89	19.85 19.87)
6	H	Cl	H	NHCH(CH$_3$)$_2$		120—121	$C_{19}H_{23}O_3N_2Cl$	62.89 (62.76	6.39 6.32	7.72 7.57	9.77 9.51)
7	H	Cl	H	NHC(CH$_3$)$_3$		132—133	$C_{20}H_{25}O_3N_2Cl$	63.73 (63.55	6.69 6.60	7.43 7.38	9.41 9.13)
8	H	Cl	H	NH-		103—105	$C_{21}H_{25}O_3N_2Cl$	64.85 (64.82	6.48 6.47	7.20 7.12	9.12 9.16)
9	H	Cl	H	NH-		122—124	$C_{22}H_{27}O_3N_2Cl$	65.58 (66.06	6.75 6.77	6.95 6.86	8.80 8.33)
10	H	Cl	H	NH-		124—126	$C_{23}H_{29}O_3N_2Cl$	66.25 (66.40	7.01 6.87	6.72 6.79	8.51 8.58)
11	H	Cl	H	NH-		84.5—86	$C_{24}H_{31}O_3N_2Cl$	66.88 (66.95	7.25 7.32	6.50 6.23	8.23 8.62)
12	H	Br	H	NHCH(CH$_3$)$_2$		131—133	$C_{19}H_{23}O_3N_2Br$	56.02 (56.22	5.69 5.80	6.88 6.64	(19.62) (19.12))
13	H	Br	H	NHC(CH$_3$)$_3$		127.5—128	$C_{20}H_{25}O_3N_2Br$	57.01 (57.04	5.98 6.09	6.65 7.04	(18.97) (18.86))
14	H	Br	H	NH-		122—124	$C_{22}H_{27}O_3N_2Br$	59.06 (59.51	6.08 6.19	6.26 6.26)	
15	H	NHCOCH$_3$	H	NHCH(CH$_3$)$_2$	2H	146—149 (decomp.)	$C_{21}H_{29}O_4N_3Cl_2$	55.02 (55.41	6.38 6.60	9.17 8.87)	
16	H	NH$_2$	H	NHC(CH$_3$)$_3$	2H	258—260 (decomp.)	$C_{20}H_{29}O_3N_3Cl_2$	55.81 (55.37	6.79 6.84	9.76 9.64	16.48 16.25)
17	H	CH$_3$	H	NHCH(CH$_3$)$_2$		104—105	$C_{20}H_{26}O_3N_2$	70.15 (70.07	7.65 7.68	8.18 8.25)	
18	H	CH$_3$	H	NHC(CH$_3$)$_3$		109.5—110	$C_{21}H_{28}O_3N_2$	70.76 (70.60	7.92 7.77	7.86 7.84)	
19	H	CH$_3$	H	NH-		100—102	$C_{23}H_{30}O_3N_2$	72.22 (71.93	7.91 7.83	7.32 7.38)	
20	CH$_3$	CH$_3$	CH$_3$	NHCH(CH$_3$)$_2$		108—109.5	$C_{22}H_{30}O_3N_2$	71.32 (71.05	8.16 8.26	7.56 7.34)	
21	CH$_3$	CH$_3$	CH$_3$	NHC(CH$_3$)$_3$		95—96	$C_{23}H_{32}O_3N_2$	71.85 (71.85	8.39 8.50	7.29 7.39)	
22	H	H	H	 N		112—113	$C_{21}H_{26}O_3N_2$	71.16 (71.40	7.39 7.24	7.90 7.68)	
23	H	Cl	H	N(C$_2$H$_5$)$_2$		53—54	$C_{20}H_{25}O_3N_2Cl$	63.73 (63.50	6.69 6.57	7.43 7.03	9.41 9.48)
24	H	Cl	H	 N		101—101.5	$C_{21}H_{25}O_3N_2Cl$	64.85 (64.82	6.48 6.58	7.20 6.99	9.12 8.95)
25	H	Cl	H	 N O		109—110	$C_{20}H_{23}O_4N_2Cl$	61.45 (61.47	5.93 6.06	7.17 7.18	9.07 9.00)
26	H	Cl	H	 N NCH$_2$C$_6$H$_5$		118.5—119.5	$C_{27}H_{30}O_3N_3Cl$	67.56 (67.28	6.30 6.34	8.76 9.03	7.39 7.04)

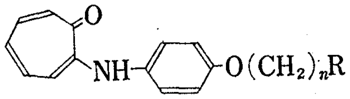
[a] H: hydrochloride

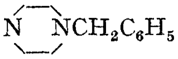
TABLE II. 3-Alkyl-5-[*p*-(2-troponylamino)phenoxymethyl]oxazolidine Derivatives



Compd. No.	R^2	R^4	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Cl	Found C	H	N	Cl
27	H	$CH(CH_3)_2$	92—93	$C_{20}H_{24}O_3N_2$	70.56	7.11	8.23		70.33	7.12	8.26	
28	H		106—107	$C_{23}H_{28}O_3N_2$	72.60	7.42	7.36		72.37	7.48	7.32	
29	Cl		92—94	$C_{23}H_{27}O_3N_2Cl$	66.57	6.56	6.75	8.55	66.98	6.35	6.98	8.62

TABLE III. 2-[*p*-(Aminoalkoxy) anilino]tropone Derivatives



Compd. No.	*n*	R	mp (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
30	2	$N(C_2H_5)_2 \cdot 2HCl$	148—150	$C_{19}H_{26}O_2N_2Cl_2 \cdot {}^1/_2H_2O$	57.87	6.90	7.10	57.46	6.80	7.22
31	3	$N(CH_3)_2$	65—66	$C_{18}H_{22}O_2N_2 \cdot {}^1/_2H_2O$	70.33	7.54	9.11	70.66	7.74	9.17
32	3		110—112	$C_{20}H_{24}O_2N_2$	74.04	7.46	8.64	73.64	7.56	8.76
33	3		108—110	$C_{27}H_{31}O_2N_3$	75.49	7.27	9.78	75.67	7.35	9.67

Pharmacology

Materials——Water soluble compounds were dissolved in physiological saline solution. Bases were dissolved in 1/10N hydrochloric acid.

1) β-Adrenergic Blocking Activity: The β-adrenergic blocking activity of 2-anilinotropone derivatives was estimated by the inhibition of positive inotropic and chronotropic responses of the isolated atrium of the guinea pig to isoproterenol at a concentration of 1×10^{-8} g/ml.[1] The results are shown in Table IV.

TABLE IV. β-Adrenergic Blocking Activity of 2-Anilinotropone Derivatives (Percent Inhibition)

Compd. No.	Dose (g/ml)	Contractile force (%)	Heart rate (%)
1	10^{-6}	58	73
	10^{-5}	98	94
2	10^{-6}	14	57
3	10^{-6}	9	27
6	10^{-7}	19	36
	10^{-6}	79	82
7	10^{-7}	26	33
	10^{-6}	75	70

Compd. No.	Dose (g/ml)	Contractile force (%)	Heart rate (%)
9	10^{-6}	27	27
12	10^{-6}	60	56
13	10^{-7}	47	62
	10^{-6}	83	88
14	10^{-6}	9	53
15	10^{-6}	21	22
16	10^{-6}	43	25
17	10^{-7}	30	22
	10^{-6}	50	63
18	10^{-6}	10	47
19	10^{-6}	6	21
20	10^{-7}	55	44
	10^{-6}	72	69
21	10^{-7}	0	27
	10^{-6}	77	71
27	10^{-6}	50	50
28	10^{-6}	0	38
Practolol	10^{-6}	50	46
	10^{-5}	80	69

TABLE V. Coronary Vasodilating Activity of 2-Anilinotropone Derivatives

Compd. No.	Dose (μg)	Relative potency[a]	Duration (min)
Nitroglycerin	10	1	1
1	100	1.5	2
2	100	2.3	3
3	100	2.5	5
5	100	0	0
6	30	1.6	3.7
	100	9.9	10
7	30	4.2	7
	100	8.7	10
9	30	8.7	13
	100	9	13
11	100	8.5	8
12	100	2.5	3
13	30	2.7	5.5
	100	9.4	10
14	100	4	4
15	100	0	0
16	100	0	0
17	100	2	2
18	100	1.5	1.5
19	100	2.5	2.5
20	100	2	1.5
21	100	2	2
23	100	2.4	2
24	100	2	2
25	100	1	1
26	100	1	5
27	100	3.4	4
28	100	5.3	8
29	30	2.2	3.5
Isoptin	30	14	16

a) see text

2) Coronary Vasodilating Activity: The chest of pentobarbital (30 mg/kg, *i.v.*) anesthetized dogs was opened by a midsternal incision under artificial respiration. The pericardium of the heart was opened to make a cradle for support of the heart. The right coronary artery was exposed to a length of about 1 cm as close to the orifice as possible and cannulated. The artery was then perfused with heparinized (1000 units/kg body weight) blood from one of the femoral arteries of the same dog by a peristaltic pump (Sigma motor pump) under a constant perfusion pressure set at 100 mmHg. The response of the coronary artery to each test compound injected intraarterially in a volume of 0.1 ml in 10 seconds was recorded with an electromagnetic flow meter (Nihon Kohden, MF-2). Vasoactive potency of the test compound was expressed in terms of total change in the flow reflected by the area under the tracing. The response produced by 10 μg of nitroglycerin was taken as unity in each preparation for calculation of relative potency among the test compounds. The results are shown in Table V.

3) Anti-hypertensive Activity: Blood pressure was measured by the tail-plethysmographic method. Animals used were male and female spontaneously hypertensive rats with higher than 180 mmHg systolic blood pressure levels. Each dose was given to 2 or 6 animals, weighing 200 to 300 g. Blood pressure was measured 2, 4, and 6 hr after oral administration of test compound. The area under the curve was calculated from the time-response curve and termed as the "hypotensive index".

hypotensive index $= 5X-(2a+2b+c)$

X: blood pressure before administration
a: blood pressure after 2 hr
b: blood pressure after 4 hr
c: blood pressure after 6 hr

The results are shown in Table VI.

TABLE VI. Anti-hypertensive Activity and Acute Toxicity of 2-Anilinotropone Derivatives

Compd. No.	Dose (mg/kg, *p.o.*)	Hypotensive index (hr × mmHg)	Toxicity in mice (LD_{50}mg/kg, *p.o.*)
1	30	0	—
3	30	40	1415
5	30	15	—
6	10	200	1024
	30	205	—
7	30	300	596
8	30	135	—
9	10	158	691
	30	205	—
10	30	260	—
11	30	190	—
12	30	135	—
13	30	215	—
14	30	155	—
15	30	25	647
16	30	0	—
17	30	5	—
18	30	130	—
19	30	95	—
20	30	31	—
21	30	0	—
24	30	125	—
25	30	135	—
26	30	35	—
27	30	5	—

Compd. No.	Dose (mg/kg, *p.o.*)	Hypotensive index (hr × mmHg)	Toxicity in mice (LD$_{50}$mg/kg, *p.o.*)
28	50	5	—
29	30	100	—
31	30	5	—
32	30	−10	—
33	30	15	—
Tolazoline	30	93	350
Mecamylamine	30	110	140

4) Acute Toxicity: Acute toxicity was determined by oral route in mice. Animals used were male mice of the ddy-strain, weighing 20 to 25 g. Each dose was given to five animals. Mortality was recorded one week later. LD$_{50}$ was calculated by the method of Litchfield and Wilcoxon.[8] The results are shown in Table VI.

Structure and Activity Relationships

In the pharmacological activities of the 2-anilinotropone derivatives, compounds 6, 7, 13, 20, and 21 showed a more potent β-adrenergic blocking activity than that of practolol. Compounds 6, 7, 9, 11, and 13 possessed a significant coronary vasodilating activity, and compounds 6, 7, 9, 10, and 13 exhibited a stronger anti-hypertensive activity than that of tolazoline or mecamylamine. The oral acute toxicity of these compounds was generally low.

The structure and activity relationships of the 2-anilinotropone derivatives could be summarized as follows: (1) introduction of a halogen atom into the 5-position in the tropone nucleus caused generally an increase in the pharmacological activities, (2) a β-adrenergic blocking activity of the 2-anilinotropone derivatives indicated that the effect of substitution on the aminopropanoloxy side chain paralleled that found for known β-adrenergic blocking agents. In general the highest activity was observed in 2-anilinotropone derivatives in which R^4 was isopropylamino or *t*-butylamino group, and much lower for cyclohexylamino group.

Experimental

2-(*p*-Hydroxyanilino)tropone•*p*-toluenesulfonate (II)——A mixture of 50 g of I, 21.6 g of *p*-aminophenol and 400 ml of EtOH was refluxed with stirring for 26 hr. The residue left after evaporation of the solvent was washed with acetone. The crude product was recrystallized from EtOH–AcOEt to give orange scales, mp 227—228°. Yield 40 g. *Anal.* Calcd. for $C_{20}H_{10}O_5NS$: C, 62.32; H, 4.97; N, 3.63; S, 8.32. Found: C, 62.23; H, 4.61; N, 3.08; S, 8.37. UV λ_{max}^{EtOH} nm (log ε): 223.5 (4.42), 228 (4.42), 244.5 (4.39), 344 (4.02), 404 (4.19).

2-(*p*-Hydroxyanilino)tropone Derivatives (III)——a) From II: Compound II (1 g) was submitted to column chromatography over silica gel. The column was eluted with $CHCl_3$–EtOH (95: 5) and the residue left after evaporation of the solvent was recrystallized from aq. EtOH to give orange yellow prisms, mp 183—184°. Yield 300 mg. UV λ_{max}^{EtOH} nm (log ε): 244 (4.40), 343 (4.02), 404 (4.19). IR (Nujol cm^{-1}): 3280, 3185, 1600.

b) From 2-Methoxytropone Derivatives (IV): A typical synthesis is described for 2-(*p*-hydroxyanilino)-tropone. A mixture of 1.5 g of IV ($R^1=R^2=R^3=H$), 1.3 g of *p*-aminophenol and 200 ml of EtOH was refluxed for 50 hr. The reaction mixture was filtered while hot. The residue left after evaporation of the solvent was chromatographed over silica gel. The eluate was concentrated and the crystals separated were recrystallized from aq. EtOH to give orange yellow prisms, mp 183—184°, which were identified by infrared (IR) spectral comparison with III ($R^1=R^2=R^3=H$) prepared by method a). The elemental analysis is shown in Table VII.

2-[*p*-(2,3-Epoxypropoxy)anilino]tropone Derivatives (V)——A typical synthesis is described for 2-[*p*-(2,3-epoxypropoxy)anilino]-5-chlorotropone. A mixture of 14.1 g of III ($R^1=R^3=H$, $R^2=Cl$), 23.5 g of epibromohydrin, 24 g of anhyd. K_2CO_3 and 200 ml of MeCOEt was refluxed with stirring for 11 hr. The reaction mixture was filtered while hot, and the filtrate was concentrated under reduced pressure. The residue

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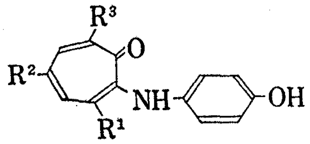
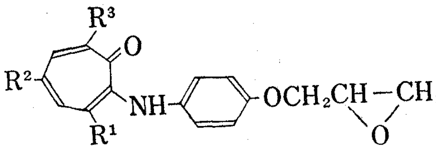
[8] J.T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.* 96, 99 (1949).

Table VII. 2-(*p*-Hydroxyanilino)tropone Derivatives



R¹	R²	R³	Reaction time (hr)	Yield (%)	mp (°C)	Formula	Analysis (%)							
							Calcd.				Found			
							C	H	N	Cl (Br)	C	H	N	Cl (Br)
H	H	H	50	70	183—184	$C_{13}H_{11}O_2N$	73.22	5.20	6.57		72.92	5.36	6.82	
H	Cl	H	20	68	203—204	$C_{13}H_{10}O_2NCl$	63.04	4.07	5.66	14.32	62.54	4.13	5.76	14.55
H	Br	H	16.5	60.3	215—217	$C_{13}H_{10}O_2NBr$	53.44	3.45	4.80	(27.36)	53.68	3.43	4.97	(26.94)
H	CH_3CONH	H	35	59.5	227—229	$C_{15}H_{14}O_3N_2$	66.65	5.22	10.37		66.39	5.44	10.25	
H	CH_3	H	165	68.8	186.5—188.5	$C_{14}H_{13}O_2N$	73.99	5.77	6.16		73.80	5.75	6.20	
CH_3	CH_3	CH_3	17	36.6	179—180	$C_{16}H_{17}O_2N$	75.27	6.71	5.49		74.91	6.60	5.44	
H	NO_2	H	6	95.3	236—237	$C_{13}H_{10}O_4N_2$	60.46	3.90	10.85		60.28	3.98	11.08	

Table VIII. 2-[*p*-(2,3-Epoxypropoxy)anilino]tropone Derivatives



R¹	R²	R³	mp (°C)	Formula	Analysis (%)							
					Calcd.				Found			
					C	H	N	Cl	C	H	N	Cl
H	Cl	H	138—139	$C_{16}H_{14}O_3NCl$	63.27	4.65	4.61	11.67	63.27	4.85	4.55	11.43
H	Br	H	145—146	$C_{16}H_{14}O_3NBr$	55.19	4.05	4.02		54.92	4.42	4.04	
H	CH_3CONH	H	125—126	$C_{18}H_{18}O_4N_2$	66.24	5.56	8.58		65.60	5.89	8.10	
H	CH_3	H	89—90	$C_{17}H_{17}O_3N$	72.06	6.05	4.94		71.74	6.16	5.16	
H	NO_2	H	184—186	$C_{16}H_{14}O_5N_2$	61.14	4.49	8.91		60.95	4.62	9.31	

was recrystallized from benzene to give orange yellow needles, mp 138—139°. Yield 15 g. IR (Nujol cm^{-1}): 3250, 1600.

2-[*p*-2,3-Epoxypropoxy)anilino]- and 2-[*p*-(2,3-epoxypropoxy)anilino]-3,5,7-trimethyltropone obtained in this way were used without purification.

2-[*p*-(2-Hydroxy-3-succinimidopropoxy)anilino]-5-chlorotropone (VI)——A mixture of 6 g of V (R^1=R^3=H, R^2=Cl), 2.2 g of succinimide, 3 drops of pyridine and 70 ml of EtOH was refluxed for 24 hr. After cooling, the crystals separated were collected by filtration and recrystallized from EtOH to give orange needles, mp 159—160°. Yield 6 g. *Anal.* Calcd. for $C_{20}H_{19}O_5N_2Cl$: C, 59.63; H, 4.75; N, 6.95; Cl, 8.80. Found: C, 59.70; H, 4.85; N, 6.89; Cl, 8.78. IR (Nujol cm^{-1}): 3450, 3210, 1685, 1590.

2-[*p*-(2-Hydroxy-3-aminopropoxy)anilino]-5-chlorotropone·hydrochloride (5)——A mixture of 2 g of VI and 40 ml of 37% HCl was refluxed with stirring for 10 hr. The reaction mixture was concentrated under reduced pressure. The crystals separated were collected by filtration and recrystallized from MeOH–EtOH (3: 1) to give yellow scales, mp 252—254° (decomp.).

2-[*p*-(2-Hydroxy-3-aminopropoxy)anilino]tropone Derivatives (VII)——a) From 2-[*p*-(2,3-Epoxypropoxy)anilino]-tropone Derivatives: A typical synthesis is described for 2-[*p*-(2-hydroxy-3-isopropylamino-propoxy)anilino]-5-chlorotropone (6). A mixture of 15 g of V (R^1=R^3=H, R^2=Cl), 30 ml of isopropylamine and 200 ml of iso-PrOH was refluxed with stirring for 40 hr. The reaction mixture was concentrated under reduced pressure and the residue was chromatographed over Al_2O_3 with $CHCl_3$–EtOH (95: 5) as eluent. The residue left after evaporation of the solvent was recrystallized from MeOH–isopropyl ether (1: 4) to give orange crystals, mp 120—121°. Yield 9.5 g. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (log ε): 248.5 (4.37), 290 (shoulder) (3.80), 355 (4.14), 423 (4.19). IR (Nujol cm^{-1}): 3260, 3180, 3100, 1600. NMR ($CDCl_3$) ppm: 1.10 (6H, $\mathrm{NCH(C\underline{H}_3)_2}$, d., J=6 Hz), 2.87 (5H, $\mathrm{C\underline{H}_2{-}\underset{|}{N}{-}C\underline{H}\langle}$, OH, NH, m.), 4.04 (3H, $\mathrm{-OC\underline{H}_2{-}\underset{\underset{O}{|}}{C}\underline{H}\langle}$, m).

b) From 2-[*p*-(2-Hydroxy-3-chloropropoxy)anilino]tropone Derivatives: A typical synthesis is described for 2-[*p*-(2-hydroxy-3-piperidinopropoxy)anilino]tropone (22). A mixture of 1 g of IX (R^2=H), 1 g of piperidine and 40 ml of dry toluene was refluxed for 19 hr. The reaction mixture was extracted with 1 N HCl. The acidic aq. layer was separated and then neutralized with Na_2CO_3 solution. The resulting mixture was extracted with $CHCl_3$, and $CHCl_3$ solution was concentrated under reduced pressure. The residue was recrystallized from AcOEt–*n*-hexane to give yellow needles, mp 112—113°. Yield 0.8 g. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (log ε): 239.5 (4.41), 344 (4.05), 403 (4.23). IR (Nujol cm^{-1}): 3350, 3175, 1600.

Reaction of 2-[*p*-(2,3-Epoxypropoxy)anilino]-5-nitrotropone (V, R^1=R^3=H, R^2=NO_2) with Isopropylamine——A mixture of 1.7 g of V (R^1=R^3=H, R^2=NO_2), 5 g of isopropylamine and 50 ml of iso-PrOH was refluxed for 3 hr. The reaction mixture was concentrated under reduced pressure. The residue was recrystallized to give orange plates, mp 132—133°. Yield 0.61 g. The product was 2-isopropylamino-5-nitrotropone (VIII). *Anal.* Calcd. for $C_{10}H_{12}O_3N_2$: C, 57.68; H, 5.81; N, 13.46. Found: C, 57.79; H, 5.89; N, 13.60. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (log ε): 247.5 (4.37), 410 (4.44). NMR ($CDCl_3$) ppm: 1.38 (6H, $\mathrm{CH(C\underline{H}_3)_2}$, d, J=6 Hz), 4.00 (1H, $\mathrm{-NC\underline{H}\langle}$, m.), IR (Nujol cm^{-1}): 3240, 1605. Compound (VIII) was also obtained by the reaction of V (R^1=R^3=H, R^2=NO_2) with isopropylamine at room temperature.

2-[*p*-(2-Hydroxy-3-chloropropoxy)anilino]tropone (IX, R^2=H)——To a mixture of 4.6 g of V (R^1=R^2=R^3=H) and 100 ml of MeCOEt, dry HCl gas was introduced for 1 hr. The reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$. The residue left after evaporation of the solvent was chromatographed over Al_2O_3 with $CHCl_3$–EtOH (95: 5) as eluent. The eluate was evaporated and the residue was recrystallized from aq. EtOH to give yellow needles, mp 140—141°. Yield 2.5 g. *Anal.* Calcd. for $C_{16}H_{16}O_3NCl$: C, 62.85; H, 5.27; N, 4.58. Found: C, 63.21; H, 5.42; N, 4.72.

2-[*p*-(2-Hydroxy-3-chloropropoxy)anilino]-5-chlorotropone (IX, R^2=Cl)——To a mixture of 26.2 g of V (R^1=R^3=H, R^2=Cl) and 400 ml of MeCOEt, dry HCl gas was introduced for 1 hr. After cooling, the crystals separated were collected by filtration and recrystallized from aq. EtOH to give orange yellow scales, mp 92—94°. Yield 15.4 g. *Anal.* Calcd. for $C_{16}H_{15}O_3NCl_2$: C, 56.48; H, 4.44; N, 4.12; Cl, 20.84. Found: C, 56.12; H, 4.68; N, 4.02; Cl, 20.47. IR (Nujol cm^{-1}): 3330, 3220, 1600.

3-Alkyl-5-[*p*-(2-troponylamino)phenoxymethyl]oxazolidine Derivatives (XI)——A typical synthesis is described for 3-isopropyl-5-[*p*-(2-troponylamino)phenoxymethyl]oxazolidine (27). A mixture of 1.6 g of VII (R^1=R^2=R^3=H, R^4=$CH(CH_3)_2$), 5 ml of 37% formalin and 5 ml of EtOH was refluxed for 6 hr. The residue left after evaporation of the solvent was recrystallized from benzene–*n*-hexane to give yellow prisms, mp 92—93°. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (log ε): 239 (4.39), 344 (4.05), 403.5 (4.22). IR (Nujol cm^{-1}): 3260, 1600.

2-[*p*-(Aminoalkoxy)anilino]tropone Derivatives (XII)——A typical synthesis is described for 2-[*p*-(2-diethylaminoethoxy)anilino]tropone (30). A mixture of 2.1 g of III (R^1=R^2=R^3=H), 4.1 g of diethylaminoethyl chloride, 4.2 g of anhyd. K_2CO_3 and 25 ml of MeCOEt was refluxed with stirring for 9 hr. The reaction mixture was filtered while hot and the residue left after evaporation of the filtrate was chromatographed over Al_2O_3 with $CHCl_3$–EtOH (9: 1) as eluent. The eluate was concentrated under reduced pressure. The residual oil was dissolved in HCl–EtOH, and then the resulting solution was evaporated to dryness. The crude crystals were recrystallized from iso-PrOH–ether to give yellow crystals, mp 148—150°. Yield 1 g. *Anal.* Calcd. for $C_{19}H_{26}O_2N_2\cdot 1/2H_2O$: C, 57.87; H, 6.90; N, 7.10; Cl, 17.98. Found: C, 57.46; H, 6.80; N, 7.22; Cl, 17.23. UV $\lambda_{\mathrm{max}}^{\mathrm{EtOH}}$ nm (log ε): 237 (4.38), 344.5 (4.27), 403 (4.43). IR (Nujol cm^{-1}): 3480, 1615.

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