in an oil bath maintained at 120°. After cooling the residue was crystd from AcOH to yield XIII (X = Br) (0.06 g, 60%) as orange prisms: mp 140–142°. *Anal.* ($C_6H_2BrN_3O_4$) C, H, N.

Biological Testing. Compounds were freshly dissolved in DMSO and added to 2-ml suspensions of freshly isolated and twice-washed rabbit thymocytes (0.5–1.0 × 10^5 cells/ml) in Hanks medium buffered with 0.2 vol of 0.1 *M* sodium phosphate buffer, pH 7.4. The final DMSO concns did not exceed 1% (v/v). Cells and drugs were then incubated at 37° with uridine-*5-t* or thymidine-*6-t* (0.25 μCi/ml) for 40 min. Radioactivity incorporated into the acid-insoluble fraction was determined after adding 1 vol of 10% (w/v) CCl_3COOH to each incubation, washing the pptd material twice with 5% CCl_3COOH and redissolving the ppt in 0.4 ml of 0.5 *N* NaOH. After decolorization with H_2O_2 (1 drop, 30% vol H_2O_2), 0.1-ml aliquots of the alkaline digest were assayed for ^3H by liquid scintillation counting.

Radioactivity incorporated into RNA (from uridine-*t*) or DNA (from thymidine-*t*) in control incubations containing DMSO only, in replicate incubations with a given preparation of thymus lymphocytes varied by not more than ±5%. The mean radioactivity of RNA or DNA from these replicated drug-free control incubations was assigned the value of 100%. Each compd was assayed in duplicate incubations at any one drug level. Drug activity was computed as the per cent inhibition of nucleic acid labeling with ^3H. For reference purposes a standard drug (maleimide or 4-nitrobenzofurazan) was included in each series of incubations with a new preparation of lymphocytes. The reproducibility of the drug response to these standard compds with different preparation of lymphocytes was generally within 8–10%. Data obtained with cell preparations which responded abnormally to these standard compds were not used for compiling Table II.

Acknowledgment. The biological testing of these compounds was supported by a grant from the National Institutes of Health, Bethesda, Md. (GM-15759).

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β-Adrenergic Blocking Agents. 12. Heterocyclic Compounds Related to Propranolol

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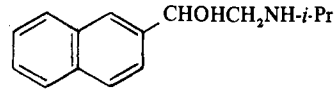
Received September 20, 1971

The synthesis and biological properties of some heterocyclic compounds related to propranolol (2) are described. Most compounds have the side chain attached to the benzenoid part of a heterocyclic system, and activity is highest when the position of attachment is α. Also included is a series of phenoxypropanolamines with a heterocyclic substituent. Many compounds have the same level of β-adrenergic blocking potency as propranolol.

In our previous paper[1] we described the synthesis and properties of a series of heterocyclic analogs of pronethalol (1).† We now report the synthesis of some heterocyclic compounds related to propranolol (2).‡,[2-4]

In most of these compounds (Tables I–VI) the oxypropanolamine side chain is attached to the benzenoid ring of a heterocyclic system, but a series of carbostyrils is also described (Table VII) in which the side chain is attached to the heterocyclic ring. We have also included a series of compounds (Table VIII) in which the heterocyclic nucleus is a substituent on the 1-amino-3-phenoxy-2-propanol molecule.

Chemistry. The methods used to prepare these compounds were in general analogous with those previously reported[5] (Scheme I). In routes A and B (those most frequently employed) the intermediate chlorohydrin or epoxide was not usually characterized, the crude product being treated immediately with the appropriate amine. As before,[5a,b] we confirmed that the epoxide opened in the desired manner by the use in one or two instances of the alternative synthesis (method C).



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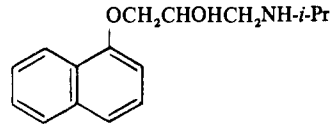

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In one case the use of method D led also to hydrogenation of a quinoline ring to give **49**.

Reaction of **5** with AcCl gave the ester **18**, while the oxazolidines **36** and **80** were obtained from **35** and **67**, respectively, by treatment with CH_2O. Bromination of **34** gave a monobromo derivative which we consider from spectroscopic evidence to be either the 6- or 8-Br compound **44**.

When the heterocyclic nucleus carried a strongly basic N atom, side reactions (presumably quaternization) were a serious complication. Thus, the quinoline compounds in

†Alderlin.
‡Inderal.

Table I

Compd No.	R^1	R^2	R^3	R^4	Position of side chain	Salt	Mp, °C	Crystn solvent	Empirical formula[a]	Method of prepn	Infusion rate, μg/kg per min	% inhibn of tachycardia
						$R^3R^4NCH_2CHOHCH_2O$–						
3[b]	Me	H	$CHMe_2$	H	4	HCl	158–162	EtOAc–EtOH	$C_{15}H_{21}NO_3$[c]·HCl	A, C, D	2.5	63
4	Me	H	CH(Me)Et	H	4	Base	74.5–76.5	Hexane	$C_{16}H_{23}NO_3$	A	2.5	56
5	Me	H	CMe_3	H	4	Base	107.5–108.5	Hexane	$C_{16}H_{23}NO_3$	A, B	2	71
6	Me	H	$CH(Me)C_7H_{15}$	H	4	Base	*d*			A	25	59
7	Me	H	$CH(Me)(CH_2)_2Ph$	H	4	Base	*d*			A	2.5	50
8	Me	H	$C(Me_2)CH_2Ph$	H	4	Oxalate	203.5–204.5	EtOAc–EtOH	$C_{22}H_{27}NO_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$	A	50	91
9	Me	H	Allyl	H	4	Base	75–77.5	P(60)[e]	$C_{15}H_{19}NO_3$	A	10	64
10	Me	H	Cyclopentyl	H	4	Base	110–113	P(60)[e]	$C_{17}H_{23}NO_3$	A	10	54
11[f]	H	H	$CHMe_2$	H	4	Base	83–84	P(60)[e]	$C_{14}H_{19}NO_3$	A	5	62
12	H	H	CMe_3	H	4	Base	103–104.5	P(60)[e]	$C_{15}H_{21}NO_3$	A	2.5	65
13[g]	Me	H	$CHMe_2$	H	5	Base	108–109.5	Hexane	$C_{15}H_{21}NO_3$	A	50	62
14[h]	H	H	$CHMe_2$	H	6	Base	86.5–88	Hexane	$C_{14}H_{19}NO_3$	A	10	48
15[i]	H	Me	$CHMe_2$	H	6	Base	108–112	Hexane	$C_{15}H_{21}NO_3$	A	100	43
16[j]	H	H	$CHMe_2$	H	7	Base	80–81.5	Hexane	$C_{14}H_{19}NO_3$	A	2	70
17	Me	H	Et	Et	4	Oxalate	124.5–127	EtOAc–MeOH	$C_{16}H_{23}NO_3 \cdot C_2H_2O_4$	A	25	50
18[k]	Me	H	CMe_3	H	4	HCl	158–160	Hexane–EtOAc	$C_{18}H_{25}NO_4$·HCl	See Exptl	25	95

[a] All compds analyzed for C, H, N. [b] Starting material, 4-hydroxy-2-methylbenzofuran. See Exptl Section. [c] C: calcd, 60.1; found, 59.5. [d] Not analyzed; characterized by nmr–see exptl. [e] P(60) refers to petr ether, bp 60–80°. [f] Starting material, 4-hydroxybenzofuran.[8] [g] Starting material, 5-hydroxy-2-methylbenzofuran.[9] [h] Starting material, 6-hydroxybenzofuran.[10] [i] Starting material, 6-hydroxy-3-methylbenzofuran.[11] [j] Starting material, 7-hydroxybenzofuran.[12] [k] Acetate ester of **5**.

Table II

Compd No.	R^1	R^2	R^3	Position of side chain	Salt	Mp, °C	Crystn solvent	Empirical formula[a]	Method of prepn	Infusion rate, μg/kg per min	% inhibn of tachycardia
					$R^3NHCH_2CHOHCH_2O$–						
19[b]	H	H	$CHMe_2$	4	Base	85	P(60)[c]	$C_{14}H_{19}NO_2S$	A	2.5	89
20	H	H	CMe_3	4	Base	115–116	P(60)[c]	$C_{15}H_{21}NO_2S$	A	1	52
21	H	H	Cyclopentyl	4	Base	96–98	P(80)[c]	$C_{16}H_{21}NO_2S$	B	20	62
22[d]	H	H	$CHMe_2$	5	Base	117	P(80)[c]	$C_{14}H_{19}NO_2S$	A	10	52
23	H	H	CH_2CH_2Me	5	Base	104	P(60)[c]	$C_{14}H_{19}NO_2S$[e]	A	50	29
24	H	H	Allyl	5	Oxalate	166–168	*n*-BuOAc	$C_{14}H_{17}NO_2S \cdot C_2H_2O_4$[f]	A	5	58
25[g]	H	Me	$CHMe_2$	7	Base	96–97	Cyclohexane	$C_{15}H_{21}NO_2S$	B	40	63
26	H	Me	CMe_3	7	Base	72–73	Hexane	$C_{16}H_{23}NO_2S$	B	20	83

[a] All compds analyzed for C, H, N. [b] Starting material, 4-hydroxybenzothiophen.[13] [c] P(60) and P(80) refer to petr ether (bp 60–80° and 80–100°, respectively). [d] Starting material, 5-hydroxybenzothiophen.[13] [e] N: calcd, 5.3; found 4.8. [f] C: calcd, 54.4; found 53.8. [g] Starting material, 7-hydroxy-3-methylbenzothiophen.[14]

Table III

Compd No.	R^1	R^2	Position of side chain	Salt	Mp, °C	Crystn solvent	Empirical formula[a]	Method of prepn	Infusion rate, μg/kg per min	% inhibn of tachycardia
				$R^2NHCH_2CHOHCH_2O$–						
27[b]	H	$CHMe_2$	4	Base	170–172	EtOH	$C_{14}H_{20}N_2O_2$	A	0.2	81
28[c]	Me	$CHMe_2$	4	Base	81.5–82.5	Hexane	$C_{15}H_{22}N_2O_2$	A	2	51
29	Me	Cyclopentyl	4	Base	82–84	Cyclohexane	$C_{17}H_{24}N_2O_2$	A	10	56
30	Me	Allyl	4	Base	74–75	Hexane	$C_{15}H_{20}N_2O_2$	A	20	74
31	Me	$C(Me)_2CH_2CH_2Ph$	4	Base	79–80	Hexane	$C_{23}H_{30}N_2O_2$	A	20	87
32	Me	$C(Me)_2CH_2OH$	4	Base	128–130	Cyclohexane	$C_{16}H_{24}N_2O_3$	A	10	98

[a] All compds analyzed for C, H, N. [b] Starting material, 4-hydroxyindole–see Exptl Section. [c] Starting material, 4-hydroxy-1-methylindole–see Exptl Section.

Table V could be obtained pure only after preparative tlc, while reaction of 3-hydroxypyridine and 4-hydroxyquinoline with the chlorohydrin **81**[6] gave exclusively N-alkylation products **82** and **83**, respectively.

The starting phenols were mostly known compounds but a few were novel and their methods of preparation are described in the Experimental Section.

Biological Results. The results of the biological screening

Table IV

Compd No.	R^1	X	*n*	Position of side chain	Salt	Mp, °C	Crystn solvent	Empirical formula[a]	Method of prepn	Infusion rate, μg/kg per min	% inhibn of tachycardia
					$R^1NHCH_2CHOHCH_2O$–						
33	$CHMe_2$	O	1	5	Base	76–77	P(60)[b]	$C_{13}H_{19}NO_4$	A	20	83
34[c]	$CHMe_2$	O	2	5	Base	104–105	EtOAc	$C_{14}H_{21}NO_4$	A	1	53
35	CMe_3	O	2	5	Base	71–72	P(40)[b]-EtOAc	$C_{15}H_{23}NO_4$	A	2.5	74
36[d]	CMe_3	O	2	5	Base	65–66	P(40)[b]	$C_{16}H_{23}NO_4$	See Exptl	2.5	64
37	$C(Me)_2CH_2OH$	O	2	5	Base	91–92	P(40)[b]-EtOAc	$C_{15}H_{23}NO_5$	A	10	62
38	$CH(Me)C_7H_{15}$	O	2	5	Base	57–58	P(40)[b]	$C_{20}H_{33}NO_4$	A	20	73
39	Cyclopentyl	O	2	5	Base	87–88	P(60)[b]	$C_{16}H_{23}NO_4$	A	20	47
40	Allyl	O	2	5	Oxalate	146–147	MeOH-EtOAc	$C_{14}H_{19}NO_4 \cdot C_2H_2O_4$	A	2.5	52
41[e]	$CHMe_2$	O	3	6	Base	67–68	P(40)[b]	$C_{15}H_{23}NO_4$	A	2	43
42	CMe_3	O	3	6	Base	86–87	P(40)[b]	$C_{16}H_{25}NO_4$	A	1	50
43[f]	CMe_3	O	4	7	HCl	118–119	EtOAc	$C_{17}H_{27}NO_4$[g]·HCl	A	1	57
44[h]	$CHMe_2$	O	2	5	Base	98–99	P(40)[b]	$C_{14}H_{20}BrNO_4$	See Exptl	20	48
45[i]	$CHMe_2$	C=O	2	8	Base	90–91	PhH-P(60)[b]	$C_{15}H_{21}NO_4$	B	5	52

[a] All compds analyzed for C, H, N. [b] P(40) and P(60) refer to petr ether, bp 40–60° and 60–80°, resp. [c] Starting material, 5-hydroxy-1,4-benzodioxan.[15] [d] Oxazolidine formed from 35. [e] Starting material, 6-hydroxy-3,4-dihydro-2*H*-1,5-benzodioxepin–see Exptl Section. [f] Starting material, 7-hydroxy-2,3,4,5-tetrahydro-1,6-benzodioxocin–see Exptl Section. [g] C: calcd, 59.0; found 58.0. [h] Bromination product of 34. [i] Starting material 8-hydroxy-4-oxochroman–see Exptl Section.

Table V

Compd No.	R^1	Position of side chain	Salt	Mp, °C	Crystn solvent	Empirical formula[a]	Method of prepn	Infusion rate, μg/kg per min	% inhibn of tachycardia
				$R^1NHCH_2CHOHCH_2O$–					
46	CMe_3	8	Base	128	EtOAc	$C_{16}H_{22}N_2O_2$	B, C	12.5	55
47	$CHMe_2$	5	Dipicrate[b]	200–202	EtOH	$C_{15}H_{20}N_2O_2 \cdot 2C_6H_3N_3O_7 \cdot H_2O$[c]	B	1	61
48	CMe_3	5	Base	56–57	Et_2O-P(40)[d]	$C_{16}H_{22}N_2O_2 \cdot 2H_2O$	C	0.5	60
49[e]	$CHMe_2$	8	Base	95–97	P(40)[d]	$C_{15}H_{24}N_2O_2$	C, D	20	55

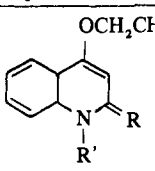
[a] All compds analyzed for C, H, N. [b] Assayed as free base. [c] N: calcd, 15.1; found 14.5. [d] P(40) refers to petr ether, bp 40–60°. [e] 1,2,3,4-tetrahydro compd–see Exptl Section.

Table VI

Compd No.	R^1	X	Salt	Mp, °C	Crystn solvent	Empirical formula[a]	Method of prepn	Infusion rate, μg/kg per min	% inhibn of tachycardia
				$OCH_2CHOHCH_2NHR^1$					
50[b]	$CHMe_2$	C=O	Base	145–146	EtOAc	$C_{19}H_{21}NO_4$	A	2	51
51	$CHMe_2$	CH_2	Base	128–129	Cyclohexane	$C_{19}H_{23}NO_3$	A, C, D and see Exptl	1	57
52	$CHMe_2$	CH(OH)	Base	136–138	EtOAc	$C_{19}H_{23}NO_4$	See Exptl	2	61
53	CMe_3	C=O	Base	119–120	EtOAc-P(40)[c]	$C_{20}H_{23}NO_4$	A	2	46
54	$C(Me)_2CH_2OH$	C=O	Base	128	PhH	$C_{20}H_{23}NO_5$	A	5	56
55	$C(Me)_2CH_2OH$	CH_2	Base	126	PhH-P(60)[c]	$C_{20}H_{25}NO_5$	See Exptl	5	75
56[d]	$CH(Me)CH_2CH_2Ph$	C=O	Base	106–108	Cyclohexane	$C_{26}H_{27}NO_4$	A	10	52

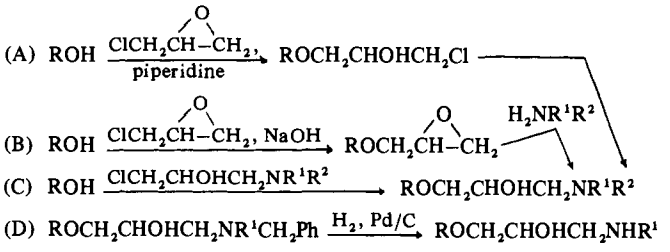
[a] All compds analyzed for C, H, N. [b] Starting material, 4-hydroxy-9-oxoxanthen.[16] [c] P(40) and P(60) refer to petr ether, bp 40–60° and 60–80°, resp. [d] Single diastereoisomer.

Table VII

Compd No.	R^1	R^2	R^3	Salt	Mp, °C	Crystn solvent	Empirical formula[a]	Method of prepn	Infusion rate, μg/kg per min	% inhibn of tachycardia
										
57[b]	Me	$CHMe_2$	H	HCl	228–229 dec	EtOAc–EtOH	$C_{16}H_{22}N_2O_3 \cdot HCl$	A, D	40	80
58[c]	Et	$CHMe_2$	H	Oxalate	224–225 dec	EtOAc–MeOH	$C_{17}H_{24}N_2O_3 \cdot 0.5C_2H_2O_4H_2O$	A	80	29
59[d]	Allyl	$CHMe_2$	H	HCl	184–185 dec	EtOAc–MeOH	$C_{18}H_{24}N_2O_3 \cdot HCl \cdot 0.5H_2O$	A	40	32
60[e]	Ph	$CHMe_2$	H	Base	135–136	EtOAc	$C_{21}H_{24}N_2O_3$	A	50	0
61	Me	CMe_3	H	HCl	156–158 dec	EtOAc–EtOH	$C_{17}H_{24}N_2O_3$[f] $\cdot 1.5HCl \cdot H_2O$	A	20	59
62	Me	$C(Me)_2CH_2OH$	H	HCl	143–144 dec	Acetone–MeOH	$C_{17}H_{24}N_2O_4$[g] $\cdot 1.5HCl \cdot H_2O$	A	20	92
63	Et	CH_2Ph	H	HCl	198–199 dec	EtOAc–EtOH	$C_{21}H_{24}N_2O_3 \cdot 2HCl$	A	100	3
64	Et	$CHMe_2$	$CHMe_2$	Oxalate	170–171 dec	EtOAc–EtOH	$C_{20}H_{30}N_2O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$	A	100	0
65	Me	CH_2Ph	$CHMe_2$	Oxalate	190–191 dec	EtOAc–EtOH	$C_{23}H_{28}N_2O_3 \cdot C_2H_2O_4$	A	10	71

[a] All compds analyzed for C, H, N. [b] Starting material, 4-hydroxy-1-methylcarbostyril.[17] [c] Starting material, 1-ethyl-4-hydroxycarbostyril (Lutz, *et al.*[17]), mp 268–271°, lit.[18] mp 255–264°. [d] Starting material, 1-allyl-4-hydroxycarbostyril (Lutz, *et al.*[17]), mp 232–234°, lit.[19] mp 234–235°. [e] Starting material, 4-hydroxy-1-phenylcarbostyril (Lutz, *et al.*[17]), mp 300–303°, lit.[20] mp 295–296°. [f] C: calcd, 54.2; found, 54.7; loses 0.5HCl on drying under vacuum. [g] C: calcd, 52.0; found, 52.5; N: calcd, 7.1; found, 7.6; loses 0.5HCl on drying under vacuum.

Scheme I



tests are given in the tables. β-Adrenergic blocking potency was determined in the usual way.§

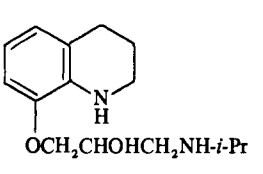
Tables I to VI show that replacement of the naphthalene ring of propranolol by a variety of heterocyclic ring systems is possible without loss of potency. It is interesting to note that in the cases where comparison is possible higher activity is observed in compounds where the oxypropanolamine side chain is in an α-position. Thus the 4-substituted benzofuran **3** is much more active than the corresponding 5-substituted derivative **13**, the 7-substituted **16** is more potent than the 6 analog **14** and in the benzothiophen series **19** is more active than **22**. This was not really unexpected (*cf.* propranolol and its β isomer),[5a] so we have concentrated on compounds which possess this substitution pattern and in general biological activity is high.

Variation of the side chain follows the pattern of our previous work[5] in that highest activity is observed when the substituent on N is *i*-Pr or *tert*-Bu and lengthening of the C chain of the N substituent leads to lowered potency.

The 4-substituted carbostyrils shown in Table VII are of a much lower order of activity.

The heterocyclic-substituted oxypropanolamines in Table VIII follow the order of potency shown by the *o*-Ph analog (**31** in Paper 5) and activity is not very much lower in the *m*-thienyl (**73**) and *p*-thiazolyl (**72**) compounds. A

§ Biological testing was carried out by Dr. R. G. Shanks, Mr. D. D. Dunlop, and Mr. J. Carter. For further information see Black, *et al.*[7]



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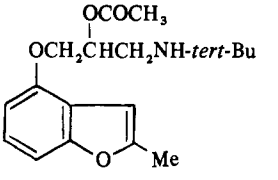

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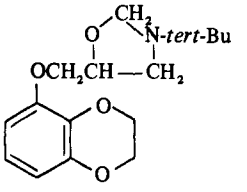

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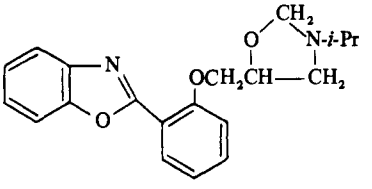

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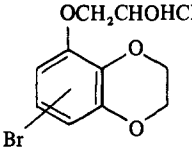

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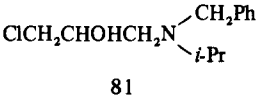
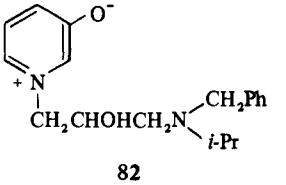


81



82

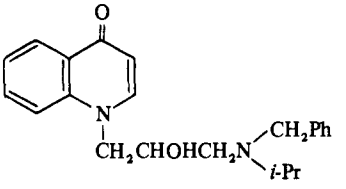


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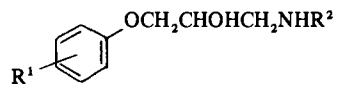
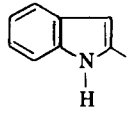
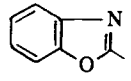
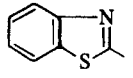
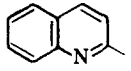
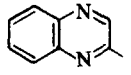
Table VIII

Compd No.	R^1	R^2	Position of side chain	Salt	Mp, °C	Crystn solvent	Empirical formula[a]	Method of prepn	Infusion rate, μg/kg per min	% inhibn of tachycardia
										
66[b]		$CHMe_2$	2	Base	132–134	Cyclohexane	$C_{20}H_{24}N_2O_2$	B	5	57
67[c]	 (I)	$CHMe_2$	2	Base	106–107	Hexane	$C_{19}H_{22}N_2O_3$	A	10	71
68[d]	 (II)	$CHMe_2$	2	Base	125–126	EtOH	$C_{19}H_{22}N_2O_2S \cdot H_2O$	A	10	55
69[e]		$CHMe_2$	2	Dipicrate[f]	162–164	EtOH	$C_{21}H_{24}N_2O_2 \cdot 2C_6H_3N_3O_7$	A	50	62
70[g]		$CHMe_2$	2	Dipicrate[f]	168–170	*i*-PrOH	$C_{20}H_{23}N_3O_2 \cdot 2C_6H_3N_3O_7$	B	20	76
71[h]	II	$CHMe_2$	4	Base	142–144	Cyclohexane	$C_{19}H_{22}N_2O_2S \cdot 0.5H_2O$	A	20	54
72[i]		$CHMe_2$	4	Base	99–100	P(60)[j]	$C_{15}H_{20}N_2O_2S$	B	20	60
73[k]		$CHMe_2$	3	Base	110–111	P(60)[j]	$C_{16}H_{21}NO_2S$	B	10	53
74	I	CMe_3	2	Di-HCl	150–152(d)	*n*-PrOH–EtOAc	$C_{20}H_{24}N_2O_3 \cdot 2HCl$	A	10	75
75	I	$C(Me)_2CH_2OH$	2	Oxalate	168–170	*n*-PrOH	$C_{20}H_{24}N_2O_4$[l] $\cdot C_2H_2O_4$	A	5	68
76	I	$C(Me)_2C_7H_{15}$	2	Oxalate	166	EtOAc–EtOH	$C_{26}H_{36}N_2O_3$[m] $\cdot 0.5C_2H_2O_4 \cdot 0.5H_2O$	A	40	31
77	II	Allyl	2	Oxalate	195–196(d)	H_2O	$C_{19}H_{20}N_2O_2S \cdot C_2H_2O_4$	A	100	57
78	II	Cyclopentyl	2	Base	104–106	Cyclohexane	$C_{21}H_{24}N_2O_2S$[n]	A	50	73
79	II	$CH(Me)CH_2CH_2Ph$	2	HCl	236	EtOH	$C_{26}H_{28}N_2O_2S \cdot HCl \cdot 0.5H_2O$	A	5	39
80[o]	I	$CHMe_2$	2	Oxalate	199(d)	EtOH	$C_{20}H_{22}N_2O_3 \cdot C_2H_2O_4 \cdot H_2O$	See Exptl	20	58

[a] All compds analyzed for C, H, N. [b] Starting material, 2-(2-hydroxyphenyl)indole.[21] [c] Starting material, 2-(2-hydroxyphenyl)benzoxazole.[22] [d] Starting material, 2-(2-hydroxyphenyl)benzothiazole.[23] [e] Starting material, 2-(2-hydroxyphenyl)quinoline.[24] [f] Compds assayed as the free base. [g] Starting material, 2-(2-hydroxyphenyl)quinoxaline.[25] [h] Starting material, 2-(4-hydroxyphenyl)benzothiazole.[26] [i] Starting material, 4-(4-hydroxyphenyl)thiazole.[27] [j] P(60) refers to petr ether, bp 60–80°. [k] Starting material, 2-(3-hydroxyphenyl)thiophene.[28] [l] C: calcd, 59.0; found, 58.5. [m] H: calcd, 8.0; found, 8.5. [n] H: calcd, 6.5; found, 7.0. [o] Oxazolidine formed from 67.

few compounds, **8**, **18**, **31**, **32**, **33**, **40**, **65**, and **77**, caused a marked tachycardia, which tends to exaggerate the observed degree of β-blockade.

Experimental Section

1-(Benzofuran-4-yloxy)-3-isopropylaminopropan-2-ol (11) (Method A). 4-Hydroxybenzofuran[8] (0.7 g), epichlorohydrin (4.0 g), and piperidine (0.01 g) were heated on the steam bath for 6 hr. Excess of epichlorohydrin was distilled off, and the residual oil was dissolved in EtOAc (40 ml) and washed with 2 *N* NaOH (20 ml). The organic phase was evaporated to dryness to give the crude chlorohydrin which was dissolved in MeOH (20 ml) and *i*-$PrNH_2$ (10 ml) was added. The mixt was heated in a sealed vessel for 12 hr at 110° and then evaporated to dryness and the residue was partitioned between EtOAc (40 ml) and 2 *N* NaOH (20 ml). The organic phase was separated, dried, and evaporated and the product was crystd; yield 0.6 g (46%).

1-Isopropylamino-3-(3-methylbenzothien-7-yloxy)propan-2-ol (25) (Method B). 7-Hydroxy-3-methylbenzothiophene[14] (7 g) and NaOH (2.2 g) were dissolved in H_2O (50 ml) and epichlorohydrin (5.6 ml) was added slowly at 20° to the stirred soln. The mixt was stirred at room temp for 70 hr and extd with $CHCl_3$ (3 × 30 ml), and the organic soln was washed with H_2O, dried, and evapd to give the epoxide, which was distd; bp 152–160° (0.8 mm), yield 7.6 g (81%). The epoxide (3.8 g) and *i*-$PrNH_2$ (10 ml) in EtOH (5 ml) were heated in a sealed vessel for 10 hr at 100°. Work-up was essentially the same as in method A; yield 3.4 g (79%).

1-Isopropylamino-3-(2-methylbenzofuran-4-yloxy)propan-2-ol (3) (Method C). A mixt of 2-methyl-4-hydroxybenzofuran (0.47 g), 1-chloro-3-isopropylaminopropan-2-ol hydrochloride (0.6 g), and NaOH (0.38 g) in EtOH (15 ml) was heated in a sealed vessel for 10 hr at 100°. Work-up was essentially the same as in methods A and B and the product was converted to its hydrochloride.

Method D. Reaction of 2-methyl-4-hydroxybenzofuran with epichlorohydrin by method A followed by treatment of the crude chlorohydrin with *N*-benzylisopropylamine gave 1-(*N*-benzylisopropylamino)-3-(2-methylbenzofuran-4-yloxy)propan-2-ol as an oil. A soln of this compd (3.95 g) in EtOH (100 ml) and concd HCl (5 ml) was hydrogd over Pd/C (5%, 1 g) at room temp and atmospheric pressure until the uptake of H_2 ceased. The mixt was filtered, the filtrate was evapd to dryness, and the product was crystd.

1-*tert*-Butylaminomethyl-2-(2-methylbenzofuran-4-yloxy)ethyl Acetate Hydrochloride (18). A mixt of **5** (0.5 g) and AcCl (3 g) was heated under reflux for 2 hr. The excess of acid chloride was evapd and the residue was stirred with hexane. The solid product was filtered and crystd.

5-(1,4-Benzodioxan-5-yloxymethyl)-3-*tert*-butyloxazolidine (36). A soln of **35** (0.27 g) and 40% formalin (2 g) in PhH (25 ml) was heated under reflux in a Dean–Stark apparatus for 24 hr. The solvent was removed and the residual oil was triturated with petr ether (bp 40–60°), filtered, and crystd.

5-(2-Benzoxazol-2-ylphenoxymethyl)-3-isopropyloxazolidine (80). A soln of **67** (0.2 g) and 40% formalin (1 ml) in EtOH (20 ml) was heated under reflux for 24 hr. The crude product obtained by evapn of the solvents gave a cryst oxalate salt.

6- or 8-Bromo-5-(2-hydroxy-3-isopropylaminopropoxy)-1,4-benzodioxan (44). A soln of Br_2 (0.3 g) in AcOH (30 ml) was added dropwise over 15 min to a stirred soln of **34** (0.5 g) in AcOH (25 ml). When addn was complete the soln was warmed to 40° for 5 min and then allowed to stand at room temp for 1 hr. The AcOH was removed under reduced pressure and the residual gum was dissolved in H_2O (20 ml). The soln was basified and the product was obtained by extn with Et_2O; nmr τ ($CDCl_3$) 2.92–3.66 (AB quartet, J = 10 Hz, ArH).

1-(1-Methyloctylamino)-3-(2-methylbenzofuran-4-yloxy)propan-2-ol (6) was prepd by method A and the crude product was purified by prep tlc on 40 cm × 20 cm × 2 mm plates of silica gel (Kieselgel P.F. 254; Code No. Merck 7749) developed with EtOAc–EtOH–Et_3N (100:20:3), and the product was obtained as an oil having R_f 0.6 in this system; nmr τ 2.70–3.70 (multiplet, ArH, 4), 5.70–6.10 (multiplet, OCH_2CHOH, 3), 6.44 (broad singlet, OH, NH, 2), 7.00–7.50 (multiplet, $CH_2NHCH(CH_3)$, 3), 7.59 (singlet, $ArCH_3$, 3), 8.20–9.20 (multiplet, $CHCH_3(CH_2)_6CH_3$, 18).

1-(1-Methyl-3-phenylpropylamino)-3-(2-methylbenzofuran-4-yloxy)propan-2-ol (17) was also prepd by method A and was obtained as an oil after prep tlc as above; R_f 0.4, nmr τ 2.70–3.70 (multiplet, ArH, 9), 5.80–6.20 (multiplet, OCH_2CHOH, 3), 6.85 (broad singlet, OH, NH, 2), 7.10–7.60 (multiplet, $CH_2NHCH(CH_3)$-CH_2CH_2Ph, 5), 7.63 (singlet, $ArCH_3$, 3), 8.00–8.65 (multiplet, $CHCH_3CH_2CH_2Ph$, 2), 8.91 (doublet, J = 6 Hz, $CHCH_3$, 3).

1-*tert*-Butylamino-3-(quinol-8-yloxy)propan-2-ol (46). Epichlorohydrin (4.7 ml) was added to a stirred soln of 8-hydroxyquinoline (2.9 g) and NaOH (2.4 g) in H_2O (100 ml) at room temp and the mixt was stirred for 1.5 hr. *tert*-$BuNH_2$ (50 ml) was then added and the mixt was stirred at room temp for 2 hr, evapd under reduced pressure to about one half the original vol, and extd with EtOAc (50 ml). The ext was dried and evapd and the residue was stirred with H_2O. The aq phase was decanted off, the residue was dissolved in 2 *N* HCl (50 ml), and the soln was treated with C and filtered. The filtrate was basified with 18 *N* NaOH and filtered and the solid residue was washed with Et_2O. The Et_2O washings were combined and evapd to dryness and the residue was extd with petr ether (bp 60–80°). The crude product, obtained by evapn of the petr ether exts was purified by chromatog on two 40 cm × 20 cm × 2 mm silica gel plates using MeOH–NH_3 (99:1) as developing solvent, R_f 0.65.

1-Isopropylamino-3-(1,2,3,4-tetrahydroquinol-8-yloxy)propan-2-ol (49). A mixt of the Na salt of 8-hydroxyquinoline [prepd from 8-hydroxyquinoline (18.2 g) and Na (3.0 g)] and 1-*N*-benzylisopropylamino-3-chloro-2-propanol (31.2 g) in *n*-PrOH (250 ml) was stirred and heated at 100° for 18 hr. The reaction mixt was cooled and filtered, and the filtrate was evapd. The residual oil was dissolved in Et_2O, washed with H_2O, and dried, and the Et_2O was removed. The residual oil was chromatogd on Florisil (2 kg) in EtOAc. Elution was carried out successively with EtOAc (4 l.), and mixts of EtOAc–EtOH (19:1, 1 l.; 9:1, 2 l.; and 4:1, 6 l.). Evapn of the last 6 l. of mixed solvent gave an oil which was dissolved in H_2O (50 ml) and Me_2CO (100 ml). 1-(*N*-Benzylisopropylamino)-3-(quinol-8-yloxy)-2-propanol crystd as a monohydrate, yield 14.6 g, mp 95–96°.

A mixt of this compd (13 g), EtOH (25 ml), and 1 *N* HCl (8 ml) was hydrogd over Pd/C (5%, 0.1 g). The crude base obtained by basificaton of the filtrate and extn with $CHCl_3$ was purified by prep tlc (silica gel, EtOAc), R_f 0.1.

1-Isopropylamino-3-(quinol-5-yloxy)propan-2-ol (47). A mixt of 5-hydroxyquinoline (1.45 g), NaOH (4.0 g), and epichlorohydrin (23.4 ml) in H_2O (100 ml) was stirred at room temp for 4 hr then extd with $CHCl_3$ (2 × 50 ml). Evapn of the dried exts gave the crude epoxide (1.5 g) which was refluxed in *i*-$PrNH_2$ (40 ml) for 2 hr, allowed to stand at room temp for 3 days, and then evapd to dryness. The residue was dissolved in 2 *N* HCl (25 ml), treated with C, and filtered, and the filtrate was basified with a mixt of ice (10 g) and 18 *N* NaOH (5 ml). The crude product was obtained by extn with EtOAc and purified by prep tlc (MeOH–NH_3, 99:1), R_f 0.6.

1-*tert*-Butylamino-3-(quinol-5-yloxy)propan-2-ol (48). A mixt of 5-hydroxyquinoline (2.9 g), NaOH (8.8 g), and 1-*tert*-butylamino-3-chloropropan-2-ol hydrochloride[5a] (16.5 g) in H_2O (500 ml) was allowed to stand at room temp for 3 days. The product was obtained by extn with EtOAc and was purified by prep tlc R_f 0.35 (EtOAc–EtOH–Et_3N, 100:30:3).

4-(2-Hydroxy-3-isopropylaminopropoxy)xanthene (51). A soln of **50** (1 g) in EtOH (25 ml) was stirred while Na (2.5 g) was added in small pieces over 30 min. The mixt was stirred and refluxed for 1 hr, cooled, and dild with ice–H_2O (100 ml). The product was obtained by Et_2O extn.

4-[2-Hydroxy-3-(2-hydroxy-1,1-dimethylethylamino)propoxy]-xanthene (55) was obtained in the same manner by redn of **54**.

9-Hydroxy-4-(2-hydroxy-3-isopropylaminopropoxy)xanthene (52). A mixt of **50** (1 g), NaOH (4 g), and EtOH (40 ml) was stirred and refluxed and Zn dust (4 g) was added in small portions over 1 hr Refluxing and stirring were contd for 18 hr and the cooled mixt was filtered. The filtrate was dild with H_2O (400 ml), and the product was obtained by Et_2O extn.

4-Hydroxy-2-methylbenzofuran. A mixt of 2-methyl-4-oxo-4,5,6,7-tetrahydrobenzofuran[29] (19.1 g) and Pd/C (10%, 4 g) in cumene (500 ml) was stirred and heated under reflux under N_2 for 24 hr. It was filtered, and the filtrate was extd with 2 *N* KOH (3 × 150 ml). The exts were combined and acidified, and the product was obtained by extn with Et_2O as an oil which was not purified further.

4-Hydroxyindole. A mixt of 4-oxo-4,5,6,7-tetrahydroindole[30] (10 g) and Pd/C (10%, 4.0 g) in cumene (500 ml) was stirred and heated under reflux under N_2 in the dark for 2 days. Evapn of the solvent followed by chromatography of the residue on Florisil (700 g) in $CHCl_3$ gave the product which was crystd from PhH–petr ether (bp 60–80°); yield 5.3 g (54%), mp 98–100° (lit.[31] mp 97–99°)

4-Hydroxy-1-methylindole. A mixt of 1-methyl-4-oxo-4,5,6,7-tetrahydroindole[30] (0.92 g) and Pd/C (5%, 0.16 g) in cumene (25

ml) was stirred and heated under reflux under N_2 for 36 hr. The mixt was filtered and the filtrate was extd with 2 *N* KOH (3 × 10 ml). The combined exts were washed with Et_2O (10 ml), filtered, and cooled, and the product was obtained by careful acidification to pH 1–2, extn with Et_2O, and crystn from EtOAc–hexane, mp 87–91° (lit.[32] mp 90°).

6-Hydroxy-3,4-dihydro-2*H*-1,5-benzodioxepin (84). 1,3-Dibromopropane (200 g) was added to a stirred soln of pyrogallol (62 g) and KOH (55 g) in abs EtOH (330 ml) at room temp. When the initial exothermic reaction had subsided, the mixt was heated under reflux under N_2 for 16 hr, cooled, and filtered and the filtrate was evapd to dryness. The crude product was obtd by extn with Et_2O and distn, bp 128–140° (1 mm). The distillate was stirred with PhH (300 ml) and filtered, the filtrate was evapd to dryness, and the product was obtained by crystn of the residue from petr ether (bp 60–80°), mp 109–110°. *Anal.* ($C_9H_{10}O_3$) C, H.

7-Hydroxy-2,3,4,5-tetrahydro-1,6-benzodioxocin (85) was prepd the same way as the benzodioxepin from pyrogallol and 1,4-dibromobutane; crude product, bp 138–142° (0.8 mm), mp 64–65° from petr ether (bp 60–80°). *Anal.* ($C_{10}H_{12}O_3$) C, H.

8-Hydroxy-4-oxochroman (86). 8-Methoxy-4-oxochroman[33] (1.0 g) was dissolved in dry xylene (10 ml) and anhyd $AlCl_3$ (1.5 g) was added. The mixt was heated at 100° for 1 hr, then decompd with ice-cold 2 *N* HCl and the product was obtained by extn with $CHCl_3$ and crystn from a mixt of PhH and petr ether (bp 60–80°), mp 166–167°. *Anal.* ($C_9H_8O_3$) C, H.

4-Hydroxyxanthene (87). Na (5.0 g) was added in small pieces over 1 hr to a refluxing soln of 4-methoxy-9-oxoxanthene[16] (2.26 g) in *n*-BuOH (80 ml). The mixt was refluxed for 1 hr, the solvent was removed under reduced pressure, and Et_2O extn gave 4-methoxyxanthen, mp 60–61° (crystd from *i*-PrOH). *Anal.* ($C_{14}H_{12}O_2$) C, H. A soln of this product (1.0 g) in dry xylene (25 ml) was treated with anhyd $AlCl_3$ (1.5 g) and the mixt was heated at 100° for 1 hr. After cooling and decompn with ice and 2 *N* HCl, the xylene was removed by steam distn and the product was obtained by filtration and crystn from aq EtOH, mp 121–122°. *Anal.* ($C_{13}H_{10}O_2$) C, H.

1-*N*-Benzylisopropylamino-3-(1,4-dihydro-4-oxo-1-quinolyl)-propan-2-ol (83). 4-Hydroxyquinoline (2.9 g) and the chlorohydrin 81[6] (4.8 g) were dissolved in EtOH (30 ml) contg NaOEt (2.72 g) and the soln was heated in a sealed tube at 100° for 10 hr. The EtOH was removed under reduced pressure and the product was obtained by extn with $CHCl_3$ and crystn from EtOAc; mp 126–127°, ir ν_{max} (C=O) 1630 cm^{-1}. *Anal.* ($C_{22}H_{26}N_2O_2$) C, H, N.

Anhydro-(3-*N*-benzylisopropylamino-2-hydroxypropyl)-3-hydroxypyridinium Hydroxide (82). 3-Hydroxypyridine (0.95 g) and 81 (2.3 g) were heated on the steam bath for 3 hr. The cooled mixt was dissolved in 2 *N* HCl (30 ml) and the acidic soln was washed with $CHCl_3$ (2 × 20 ml) and basified, and the product was obtained by extn with $CHCl_3$ and crystn from EtOAc; mp 142–143°, uv λ_{max} (H_2O) 217 mμ (ε 25,620), 253 (7110), 327 (5430); (1 *N* NaOH) 252 (7320), 325 (5040); (1 *N* HCl) 231 (4830), 292 (4380). *Anal.* ($C_{18}H_{24}N_2O_2$) C, H, N. 3-Hydroxypyridine methochloride[34] had λ_{max} (H_2O) 213 mμ (24,640), 249 (8120), 320 (57,810); (0.1 *N* NaOH) 245 (9000), 322 (5100); (0.1 *N* HCl) 288 (5860). The same product was obtained in the presence of NaOEt.

Acknowledgments. We thank Dr. A. H. Todd for compounds **25** and **26**, Dr. H. Tucker for compound **48**, and Mr. R. Farrand for compound **49**.

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Synthesis and Biological Activity of Acronycine Analogs

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The synthesis and biological activity of compounds related to acronycine (**3a**) are reported. None of the derivatives and analogs prepared showed enhanced activity against experimental tumors in mice and rats over the parent alkaloid.

Acronycine (**3a**), an acridone alkaloid, has been reported to have broad spectrum antitumor activity in experimental animals.[1-3] The structure of acronycine was confirmed by numerous workers[4-6,†] and by the synthetic work

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