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β-Adrenergic Blocking Agents. VII. 2-(1,4-Benzodioxanyl) and 2-Chromanyl Analogs of Pronethalol [2-Isopropylamino-1-(2-naphthyl)ethanol]

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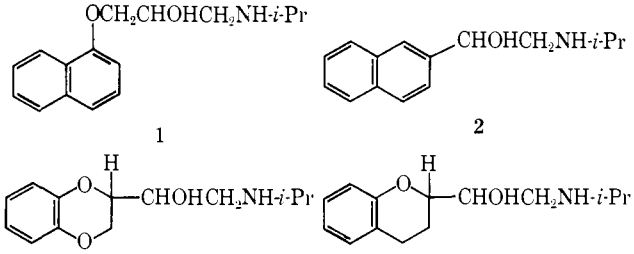
A series of 1-(1,4-benzodioxan-2-yl)- and 1-(chroman-2-yl)-2-aminoethanols, *e.g.*, **3** and **5**, which contain features of both pronethalol (**2**) and propranolol (**1**), has been synthesized by standard methods. Several pairs of geometric isomers have been separated by fractional crystallization, and related by nmr and chemical methods, and relative configurations assigned. The *RR* racemate of 1-(1,4-benzodioxan-2-yl)-2-*t*-butylaminoethanol **16** is the most potent β-adrenergic blocking agent yet reported. Structure–potency relationships are discussed.

When it became clear[1] that compounds of the propranolol[2] (**1**) type were considerably more potent as β-adrenergic blocking agents than those of the pronethanol[3] (**2**) type it became of interest to prepare 1,4-



1 2 3 (and 4) 5

benzodioxan[4] and chroman[5] analogs, such as **3** and **5**, which contain features of both types. Rosnati and de Marchi[6,7] had previously prepared a series of 1,4-benzodioxans related to, and including a mixture of, the racemic isomers **3** and **4**. They reported that the compounds were not markedly active as α-adrenergic blocking agents, but had some stimulant action on the central nervous system.

Most of the compounds in Table I (**6** to **53**) were prepared from an amine and the appropriate halohydrin (which with base forms the epoxide) (eq **1**, Scheme I). When this method was used in the pronethalol series[1a,d] a mixture of position isomers was obtained because the oxirane ring of the intermediate epoxide opened in two ways. In the propranolol series only the secondary alcohol was formed.[1b,e] It was assumed that only the secondary alcohol would be obtained in the 1,4-benzodioxan and chroman series, and the assumption held for those compounds which were made by alternative unambiguous methods (eq 2, 4, and 5), and for those prepared by methods A and B whose structures were checked by nmr. A third main method (C, eq 2) was reductive amination ($NaBH_4$) of a glyoxal.[1a] In addition, certain compounds were prepared by methods described in previous parts of this series. Compound **5** was obtained by reductive alkylation of either **39** with acetone and $NaBH_4$ (eq 3),[1a] or of the diazoketone **54** with acetone and Pt-H_2 (eq 4).[1a] Reduction of the aminoketone **55** with $NaBH_4$ gave **16** (eq 5). This route could not be used generally because the intermediate aminoketones could not be obtained. Bromination of **16** gave **37**, and of **42** gave **52** (eq 6).

All the compounds reported here have at least two centers of asymmetry. In five cases the two possible racemates were obtained by fractional crystallization, *i.e.*, **3** and **4**, **6** and **7**, **15** and **16**, **32** and **33**, and **41** and **42**. No deliberate attempt was made to separate the isomers of the other compounds. Catalytic reductive alkylation of **6** in the presence of acetone gave **3**, and in t he same way **7** gave **4** (eq 3, R = 1,4-benzodioxan 2-yl). Thus **3** and **6** belong to the same stereochemica series, and **4** and **7** belong to a different series.

It was thought at first that **20** and **21** were geometric isomers,[4a] but **21** is now considered (on nmr and mass

(1) (a) Part I: R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, **11**, 1,000 (1968). (b) Part II: A. F. Crowther and L. H. Smith, *ibid.*, **11**, 1,009 (1968). (c) Part III: R. Howe and B. S. Rao, *ibid.*, **11**, 1,118 (1968). (d) Part IV: R. Howe, B. J. McLoughlin, B. S. Rao, L. H. Smith, and M. S. Chodnekar, *ibid.*, **12**, 452 (1969). (e) Part V: A. F. Crowther, D. J. Gilman, B. J. McLoughlin, L. H. Smith, R. W. Turner, and T. M. Wood, *ibid.*, **12**, 638 (1969). (f) Part VI: R. Howe, *ibid.*, **12**, 642 (1969).

(2) Inderal(R).

(3) Alderlin, Trademark.

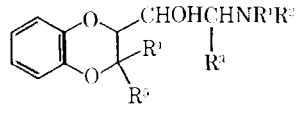
(4) (a) M. S. Chodnekar, A. F. Crowther, and R. Howe, British Patent 1,038,332 (1966). (b) M. S. Chodnekar, A. F. Crowther, and R. Howe, British Patent 1,038,333 (1966). (c) R. Howe, British Patent 1,038,336 (1966).

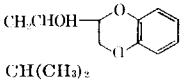
(5) R. Howe, British Patent 1,054,655 (1966).

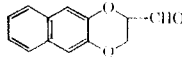
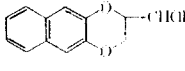
(6) V. Rosnati and F. de Marchi, *Gazz. Chim. Ital.*, **91**, 605 (1961).

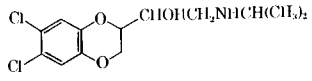
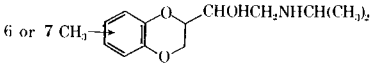
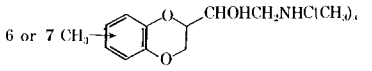
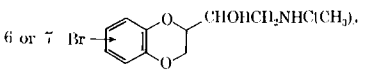
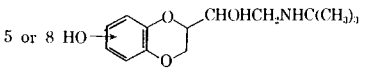
(7) V. Rosnati, F. de Marchi, and D. Misiti, *ibid.*, **91**, 1365 (1961).

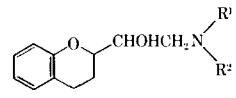
TABLE I



Compound	R⁴	R²	R³	R⁴	R⁵	Methods[a]	Form	Crystn solvent[b]	Mp, °C, of amine or salt	Formula	Analyses	Infusion rate, μg/kg per min	% change in heart rate	% inhibition of *Tachycardia*
6	H	H	H	H	H	A	HCl	MeOH + EtOAc	248–249	$C_{16}H_{14}ClNO_3$	C, H, N	10	+5	33
7	H	H	H	H	H	A	HCl	MeOH + EtOAc	234–238[c]	$C_{10}H_{14}ClNO_3$	C, H, Cl, N	10	−8	21
8	H	CH_2CH_3	H	H	H	A, C	Base	P(80)	85–90[d]	$C_{12}H_{17}NO_3$	C, H, N	2.5	+1	18
9	CH_2CH_3	CH_2CH_3	H	H	H	A, C	Base		Oil	$C_{14}H_{21}NO_3$	C, N, H[e]	10	+3	46
10	H	CH_2CH_3	CH_3	H	H	A[f]	HCl	MeOH + EtOH	192–193	$C_{13}H_{20}ClNO_3$	H, Cl, C[g]	5	+8	50
3	H	$CH(CH_3)_2$	H	H	H	A, C[h]	Base	P(40)	88–89[i]	$C_{13}H_{19}NO_3$	C, H, N	1	+1	80
							HCl	MeOH + EtOAc	180–181	$C_{13}H_{20}ClNO_3$	C, H, Cl, N			
4	H	$CH(CH_3)_2$	H	H	H	A[h]	Base	P(40)	56–57[c]	$C_{13}H_{19}NO_3$	C, H, N	1	−6	36
							HCl	MeOH + EtOAc	144–145	$C_{13}H_{20}ClNO_3$	C, H, Cl, N			
11	H	$CH(CH_3)_2$	CH_3	H	H	A[f]	Oxalate	MeOH + EtOH	215–217	$C_{30}H_{44}N_2O_{10}$	C, H, N	2.5	+1	17
12	H	$(CH_2)_3CH_3$	H	H	H	A, C	Base	P(40)	67–70[i]	$C_{14}H_{21}NO_3$	H, N, C[g]	10	−23	57
13	H	$(CH_2)_3CH_3$	CH_3	H	H	A[f]	Base	P(40)	101–102	$C_{15}H_{23}NO_3$	C, H, N	10	−13	57
14	H	$CH(CH_3)CH_2CH_3$	H	H	H	A	Oxalate	MeOH + Et_2O	204–206	$C_{30}H_{44}N_2O_{10}$	C, H, N	2.5	−17	65
15	H	$C(CH_3)_3$	H	H	H	A, B, C	Base	P(40)	104–105	$C_{14}H_{21}NO_3$	C, H, N	0.5	−5	43
							HCl	MeOH + EtOAc	162–163	$C_{14}H_{22}ClNO_3$	C, H, Cl, N			
16	H	$C(CH_3)_3$	H	H	H	A, C[h]	Base	P(40)	91–92	$C_{14}H_{21}NO_3$	C, H, N	0.5	−6	64
							HCl	MeOH + EtOAc	193–194	$C_{14}H_{22}ClNO_3$	C, H, Cl, N			
17	H	$CH_2CH{=}CH_2$	H	H	H	C	Hydrogen oxalate	EtOH + Me_2CO	161–162	$C_{15}H_{19}NO_7$	C, H, N	10	5	32
18	H	$C(CH_3)_2CH_2OH$	H	H	H	A	Base	EtOAc	137–140	$C_{14}H_{21}NO_4$	C, H, N	2	−1	58
19	H	$(CH_2)_3OCH_3$	H	H	H	C	Hydrogen oxalate	MeOH + EtOAc	163–165	$C_{16}H_{23}NO_8$	C, H, N	2.5	−10	48
20	H	$C(CH_3)_2CH_2C_6H_5$	H	H	H	A	HCl[j]	MeOH	237–238	$C_{20}H_{26}ClNO_3$	C, H, Cl, N	5	−13	47
21		*m*				A	Base	P(40)	111–112	$C_{21}H_{25}NO_3$	C, H, N	60	−5	18
							HCl[j]	MeOH + EtOAc	196–197	$C_{21}H_{26}ClNO_3$	C, H, Cl, N			
22	H	$CH(CH_3)(CH_2)_2C_6H_5$	H	H	H	A	HCl[j]	MeOH + EtOAc	220–221	$C_{20}H_{26}ClNO_3$	C, H, N	2	+6	53
23	H	$C(CH_3)_2(CH_2)_2$-C_6H_4Cl-*p*	H	H	H	B	HCl[j]	MeOH + EtOAc	203–204	$C_{21}H_{27}Cl_2NO_3$	C, H, Cl, N	20	8	67
24	H	$(CH_2)_2C_6H_3$-$(OCH_3)_2$-*m,p*	H	H	H	C	HCl	MeOH + EtOAc	172–173	$C_{20}H_{26}ClNO_5$	C, H, Cl, N	20	9	15
25	H	$CH_2CH(OCH_3)C_6H_5$ (OCH_3)-*m*	H	H	H	C[k]	Hydrogen oxalate[l]	MeOH + EtOAc	150–151	$C_{22}H_{27}NO_8$	H, N, C[g]	50	1	16
26	H	CH_2CHOH- 	H	H	H	A[m]	HCl	MeOH + EtOAc	224–225	$C_{20}H_{24}ClNO_5$	C, H, N	2.5	+22	15
27	H	$CH(CH_3)_2$	H	CH_3	H	A	Base	P(40)	114–115	$C_{14}H_{21}NO_3$	C, H, N	80	+7	26
28	H	$C(CH_3)_3$	H	CH_3	H	A	Base	P(40)	89–90	$C_{15}H_{23}NO_3$	C, H, N	10	+10	17
29	H	$C(CH_3)_2CH_2OH$	H	CH_3	H	A	Base	EtOAc	111–112	$C_{15}H_{23}NO_4$·0.5H_2O	C, H, N	10	−8	5
30	$CH_2CH_2OCH_2CH_2$		H	CH_3	H	A	HCl	MeOH + Et_2O	184–185	$C_{15}H_{22}ClNO_4$	C, H, Cl, N	20	+2	9
31	H	$CH(CH_3)_2$	H	CH_3	CH_3	A	HCl	MeOH + EtOAc	223–224	$C_{15}H_{24}ClNO_2$	C, H, Cl, N	80	+2	30

Compound	Formula	Methods[a]	Form	Crystn solvent[b]	Mp, °C, of amine or salt	Formula	Analyses	Infusion rate, μg/kg per min	% change in heart rate	% inhibition of *Tachycardia*
32		A	Base	P(60)	125–126	$C_{17}H_{21}NO_3$	C, H, N	25	−2	62
			HCl	MeOH + EtOAc	218–219	$C_{17}H_{22}ClNO_3$	C, H, Cl, N			
33		A	Base	P(60)	98–99	$C_{17}H_{21}NO_3$	C, H, N	10	+1	20
			HCl	MeOH + EtOAc	236–237	$C_{17}H_{22}ClNO_3$	C, H, Cl, N			

34[r]			B	HCl	EtOH + Et_2O	221–226	$C_{13}H_{18}Cl_3NO_3$	C, H, Cl, N	20	+16	14
35			A	HCl	MeOH + EtOAc	130–132	$C_{14}H_{22}ClNO_3$	C, H, N, H_2O	10	−1	26
36			A	HCl	MeOH + EtOAc	204–205	$C_{15}H_{24}ClNO_3$	C, H, Cl, N	4	−7	39
37[s]			As for 50[t]	HCl	EtOAc	190	$C_{14}H_{20}BrClNO_3$	C, H, N	5	−21	84
38			A	Base	P(60)	135–136	$C_{14}H_{21}NO_4$	C, H, N	10	−7	37



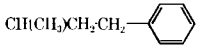
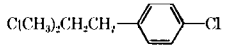
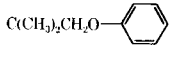
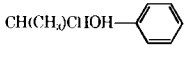
	R_1	R_2									
39	H	H	B[u]	HCl	MeOH + EtOAc	226–228	$C_{11}H_{16}ClNO_2$	C, H, Cl, N	80	+16	80
40	CH_2CH_3	CH_2CH_3	B	Picrate	EtOAc + P(40)	123–124	$C_{21}H_{26}N_4O_9$	C, H, N	50	−6	None
5	H	$CH(CH_3)_2$	A[h]	HCl	MeOH + EtOAc	171–173	$C_{14}H_{22}ClNO_2 \cdot 0.25H_2O$	C, H, Cl, N, H_2O	5	+6	32
41	H	$C(CH_3)_3$	A, C[v]	HCl Base	MeOH + EtOAc P(40)	248–249 108–109	$C_{15}H_{24}ClNO$ $C_{15}H_{23}NO_2$	C, H, Cl, N C, H, N	5	−10	66
42	H	$C(CH_3)_3$	A Base	HCl Base	MeOH + EtOAc P(60)	193–194 112–113	$C_{15}H_{24}ClNO_2$ $C_{15}H_{23}NO_2$	C, H, Cl, N C,[bb] H, N	20	−35	44
43	H	$C(CH_3)_2CH_2OH$	B	Base	EtOAc	146–147	$C_{15}H_{23}NO_3$	C, H, N	100	−20	68
44	H	$(CH_2)_2OCH_3$	B	HCl	MeOH + EtOAc	129–130	$C_{15}H_{24}ClNO_3 \cdot {}^1/_3H_2O$	C, H, Cl, N, H_2O	50	−20	40
45	H		A[l]	HCl	MeOH + EtOAc	192–194	$C_{21}H_{28}ClNO_2$	C, H, Cl, N	5	−1	25
46	H		B[l]	HCl	MeOH + EtOAc	153–155	$C_{22}H_{29}Cl_2NO_2 \cdot 0.5H_2O$	C, H, Cl, N, H_2O	200	−26	50
47	H		B[w]	HCl	MeOH + EtOAc	116–117	$C_{21}H_{28}ClNO_3 \cdot 0.5H_2O$	C, H, Cl, N	50	+6	40
48	H		B[l,x]	Hydrogen oxalate	MeOH + EtOAc	188–189	$C_{22}H_{27}NO_7 \cdot 0.25H_2O$	C, H, N, H_2O	25	+8	62
49	H	$CH_2CH{=}CH_2$	B	Base	P(60)	96–97	$C_{14}H_{19}NO_2$	C, H, N	50	−19	55
50	H		B	Base	P(60)	113–114	$C_{16}H_{23}NO_2$	C, H, N	100	−28	48
51	$CH_2CH_2OCH_2CH_2$		B	Hydrogen oxalate	MeOH + EtOAc	120–121	$C_{17}H_{23}NO_7$	C, H, N	100	0	33

Table I (*Continued*)

Compound	Formula	Methods[a]	Form	Cryst solvent[b]	Mp, °C, of amine or salt	Formula	Analyses	Infusion rate, μg/kg per min	% change in heart rate	% inhibition of *Tachycardia*
		See	Base	P(40)	108–109	$C_9H_{12}BrNO_2$	C, H, Br, N	100	+16	78
52		Expt[d]								
53[e]		A	DCl	MeOH + EtOAc	193–195	$C_9H_{14}ClNO_2$	H, Cl, N, C[cc]	100	0	8

[a] Methods refer to Experimental Section. [b] P(40), P(60), and P(80) refer to petroleum ether bp 40–60°, bp 60–80°, and bp 80–100°. [c] Sinters 200–202°. [d] Lit.[6] mp 89–90°. [e] II: calcd, 8.33; found 7.8. [f] Intermediate chlorohydrin, ref 7. [g] C: calcd, 57.0; found, 56.1. [h] See also Experimental Section. [i] Lit.[6] mp 68–68.5° for mixture of **3** and **4**. [j] Lit.[6] mp 69–71°. [k] C: calcd, 66.9; found 66.3. [l] HCl salt very slightly soluble in H_2O; isolated by extraction into $CHCl_3$. [m] See discussion and formula **21**. Nmr τ ($CDCl_3$), 2.70–2.95 (multiplet, Ar-**H**, 3), 3.10–3.25 (multiplet, Ar-**H**, 1), 5.45–6.06 (multiplet, 11 at C_2 and 11a and **H**s at C_3, 3); not changed by double irradiation over the range 6.3–6.9), 5.5–6.5 (broad, **NH** 1), 6.44 and 6.77 (2AB patterns, CH_2O and CH_2N, 4; not changed by double irradiation over the range 5.45–6.06), 6.44 (singlet, $CH_3C_6H_2$, 2) 9.08 (shoulder, CH_3, 6); m/e 339 (weak), 324 ($C_{9}H_{12}NO_2$, *m*-CH_3), 248 (base peak, C_6H_8-NO_2, *m*-$CH_3C_6H_3$). [n] Compound **20** had the expected m/e 327. [o] The amine used has been described by A. D. Ainley and R. Howe, British Patent 1,017,691 (1962); *J. Med. Chem.*, **12**, 642 (1969). [p] HCl salt very slightly soluble in H_2O; isolated by extraction into $CHCl_3$ and then converted *in* (free base to hydrogen oxalate. [q] C: calcd, 58.8; found 58.3. [r] A by-product in the preparation of **6** and **7** and separated from them by fractional crystallization. [s] Compound kindly prepared by Dr. T. W. Thompson. 1,4-Benzodioxan-2-yl methyl ketone in D_2O was chlorinated in the presence of $AlCl_3$ to give the 6,7-dichloro analog, which was then brominated in the side chain by the method used for **52**. [t] Compound kindly prepared by Mr. L. H. Smith. [u] **16** was starting material. [v] Chroman-2-carboxylic acid converted to acid chloride by oxalyl chloride. [w] Intermediate glyoxal prepared by the action of DMSO on the bromo ketone obtained from the diazo ketone and HBr. [x] The amine used was described by L. B. Clapp, *J. Amer. Chem. Soc.*, **73**, 2584 (1951). [y] Norephedrine was the amine used. [z] **42** was the starting material. [aa] Ir shows no >C=O; nmr (60 Mc, $CDCl_3$) τ 5.4–5.9 (multiplet, 3 protons on carbon next to oxygen), no olefinic protons. [bb] C: calcd, 59.7; found, 60.2. [cc] C: calcd, 72.25; found, 72.8.

Scheme I

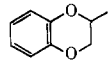
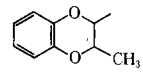
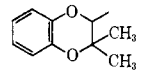
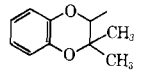
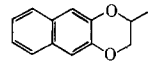
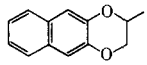
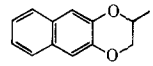
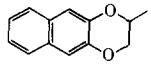
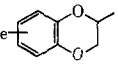
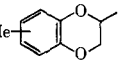
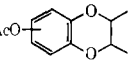
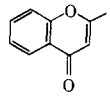
spectrum evidence) to have the structure shown. It must have been formed from a trace of **56** in the intermediate chlorohydrin. Compound **56** would be formed

21 **56**

from further reaction of the intermediate chloromethyl ketone (in Eq 7) with CH_2N_2.

Many of the intermediates were gums which failed to crystallize, probably because they consisted of two or more racemic isomers. Those new intermediates which did crystallize are listed in Table II (**57** to **69**). New intermediates not listed were characterized only by ir spectra. The halohydrin intermediates were

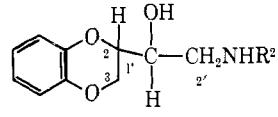
TABLE II
RCOX

Compd	R	X	Crystn solvent	Mp, °C	Formula	Analysis
57		CH_2Br[a]	P(60)	80–81	$C_{10}H_9BrO_3$	C, H, Br
58	H	CHO	Et_2O + P(40)	92–94	$C_{10}H_8O_4 \cdot 0.75H_2O$	C, H
59		CH_2Cl[b]	P(60)	94–96	$C_{11}H_{11}ClO_3$	C, H, Cl
60		OH[c]	MeOH	225–226	$C_{11}H_{12}O_4$	C, H
61		CHN_2	P(40)	106–107	$C_{12}H_{12}N_2O_3$	C, H, N
62		OEt[d]	EtOAc + P(60)	61–62	$C_{15}H_{14}O_4$	C, H
63		OH[d]	EtOAc	186	$C_{13}H_{10}O_4$	C, H
64		Cl[d]	P(60)	88–89	$C_{13}H_9ClO_3$	C, H, Cl
65		CH_2Cl[d]	EtOAc + P(60)	121–122	$C_{14}H_{11}ClO_3$	C, H, Cl
66	6 or 7 Me- 	OH	Et_2O + P(40)	94–95	$C_{10}H_{10}O_4$	C, H
67	6 or 7 Me- 	CH_2Cl	P(60)	71–72	$C_{11}H_{11}ClO_3$	C, H, Cl
68	5 or 8 AcO- 	OH	Et_2O	146–147	$C_{11}H_{10}O_6$	C, H
69		CH_2Cl	EtOAc	166–168	$C_{11}H_7ClO_3$	C, H, Cl

[a] Intermediate Me ketone, D. Misiti and F. De Marchi, *Gazz. Chim. Ital.*, **93**, 46 (1963). [b] Intermediate acid chloride, J. Koo. S. Avakian, and G. J. Martin, *Chem. Ind. (London)*, 832 (1958). [c] Intermediate Et ester, J. Augstein, S. M. Green, A. M. Monro, G. W. H. Potter, C. R. Worthing, and T. I. Wrigley, *J. Med. Chem.*, **8**, 446 (1965). [d] See Experimental Section.

generally made by the route exemplified for the naphtho[2,3-*b*]-1,4-dioxan analogs (eq 7). The bromo ketone **57** was also made by brominating the corresponding methyl ketone.[8] $NaBH_4$ reduction of the chloromethyl ketone **69** also reduced the chromenone ring system to the hydroxychroman system exemplified in **53**. Treatment of the chloromethyl ketone derived from the acid **68** with $NaBH_4$ also removed the acetyl group. The glyoxals were made either by oxidation of the corresponding methyl ketone with SeO_2 or by oxidation of the corresponding bromomethyl ketone with DMSO.[1a,9] The 1,4-benzodioxans were prepared by the general route (eq 8) which gave the intermediates **66** and **67** of uncertain orientation. Compound **68**, also of uncertain orientation, was prepared by acetylating the hydroxy acid obtained by using pyrogallol in the above condensation. Chroman-2-carboxylic acid was prepared from 2-bromo-1-tetralone,[10] and also by reduction of chromen-4-one-2-carboxylic acid[11] with amalgamated Zn and HCl.

Stereochemical Relationships.—It has been shown above by a chemical correlation that **3** and **6** belong to the same stereochemical series, and **4** and **7** belong to another stereochemical series. These two series differ in the relative stereochemical configurations at C_2 and C_1', and for convenience may be referred to as the *RR* and the *RS* series. (Because the compounds are racemates they could equally well be called the *S,S* and the *SR* series.)



(8) First carried out by a colleague, Dr. A. G. McGregor, British Patent 1,038,334 (1966).
(9) R. Howe, British Patent 1,038,335 (1966).
(10) G. Baddeley and J. R. Cooke, *J. Chem. Soc.*, 2797 (1958).
(11) R. Heywang and St. v. Kostaneki, *Ber.*, **35**, 2887 (1902).

By analysis of nmr data, relative configurations have been assigned to centers C_2 and C_1'. It was necessary to identify the signal due to H at C_1', and to measure the coupling constant to H at C_2.

The spectrum of **15** was: τ ($CDCl_3$), 3.15–3.30 (multiplet, Ar-**H**, 4), 5.55–6.20 (multiplet, H at C_2 and H_A and H_B at C_3, 3), 6.30–6.53 (triplet of doublets, X part of ABXY, J = 7.0, 7.0, and 3.7 cps, C**H**(OH), 1), 7.00–7.45 (four doublets, AB pattern of ABX, J = 3.7, 7.0, and 12.0 cps, C**H**$_2$N, 2), 7.10–7.60 (broad, O**H** and N**H**, 2), 8.90 [singlet, C(C**H**$_3$)$_3$, 9]. The important coupling H at C_2 to H at C_1' was 7.0 cps. The spectrum of **16** was: τ ($CDCl_3$), 3.15–3.30 (multiplet, Ar-**H**, 4), 5.65–6.00 (multiplet, H at C_2 and H_A and H_B at C_3, 3), 6.20–6.40 (triplet of doublets, X part of A_2XY, J = 5.5, 5.5, and 3.0 cps, C**H**OH, 1); 7.23 (doublet A_2 part of A_2X, J = 5.5 cps, C**H**$_2$N, 2), 7.60–8.00 (broad, O**H** and N**H**, 2), 8.90 [singlet, C(C**H**$_3$)$_3$, 9]. The important coupling H at C_2 to H at C_1' was 3.0 cps, and a characteristic feature of the spectrum was that the H atoms at C_2' happened to have the same chemical shift. Partial nmr spectra of **15** and **16**, together with the expanded spectra are shown in Figure 1.

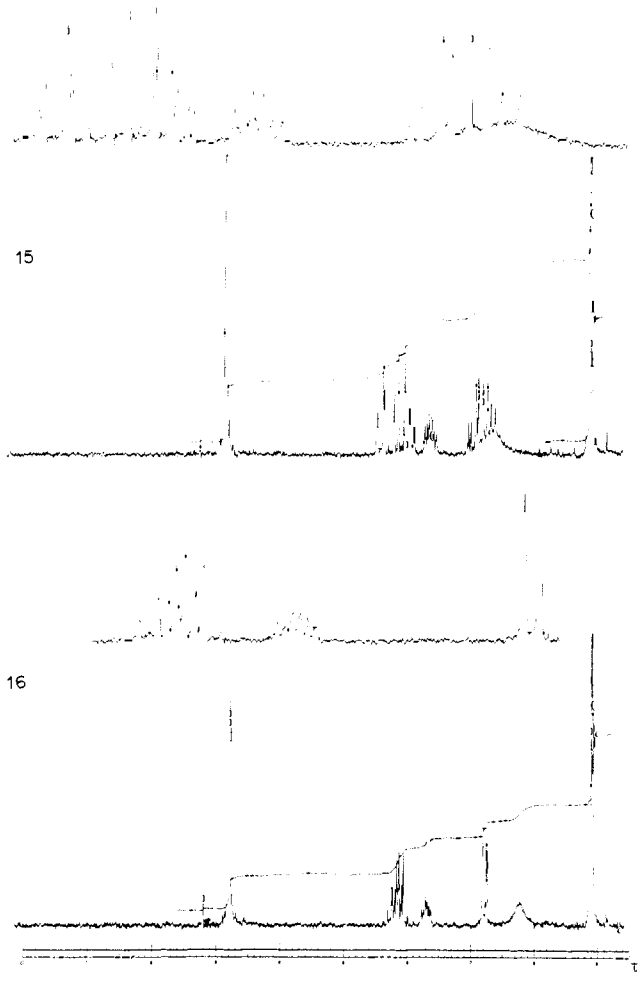


Figure 1.—Nmr spectra of **15** and **16**, measured in $CDCl_3$ at 100 Mcps, with expansion of the region τ 5.5–7.5.

The spectrum of **4** was essentially similar to that of **15**, after allowing for the change *t*-butyl into *i*-Pr: τ ($CDCl_3$) 7.20 (septet, *i*-Pr C**H**, 1), 8.96 (doublet, *i*-Pr C**H**$_3$, 6). The coupling H at C_2 to H at C_1' was 7.0 cps. The spectrum of **3** was essentially similar to that of **16**: τ ($CDCl_3$) 7.20 (septet, *i*-Pr C**H**, 1), 8.95 (doublet, *i*-Pr C**H**$_3$, 6). The coupling H at C_2 to H at C_1' was 3.0 cps, and again the H atoms at C_2' had the same chemical shift.

The spectrum of **20** was: τ ($CDCl_3$) 2.65–2.95 (multiplet, Ar-**H**, 5), 3.10–3.30 (multiplet, Ar-**H**, 4), 5.60–6.00 (multiplet, H at C_2 and H_A and H_B at C_3, 3), 6.15–6.35 (triplet of doublets, X part of A_2XY, J = 6.0, 6.0, and 3.0 cps, C**H**OH, 1); 7.14 (doublet, A_2 part of A_2X, J = 6.0 cps, C**H**$_2$N, 2), 7.31 (singlet, C**H**$_2$C$_6$H$_5$, 2), 7.2–7.8 (broad, O**H** and N**H**, 2, exchanged with D_2O), 8.92 [singlet, C(C**H**$_3$)$_2$, 6]. The coupling H at C_2 to H at C_1' was 3.0 cps, and again the H atoms at C_2' had the same chemical shift.

The spectrum of **42** was: τ ($CDCl_3$) 2.90–3.35 (multiplet, Ar-**H**, 4), 6.08–6.28 (multiplet, H at C_2, 1), 6.32–6.60 (triplet of doublets, X part of ABXY, J = 7.0, 7.0, and 3.7 cps, C**H**OH, 1), 7.02–8.50 [multiplet containing 8 protons, H's at C_3 and C_4, N**H**, O**H**, and C**H**$_2$N, the latter appearing as four doublets, AB pattern of ABX (7.0–7.5), J = 3.7, 7.0, and 12.0 cps, converted by double irradiation at τ 6.45 into an AB pattern, J = 12.0 cps], 8.90 [singlet, C(C**H**$_3$)$_3$, 9]. The important coupling H at C_2 to H at C_1' was 7.0 cps. The spectrum of **41** was: τ ($CDCl_3$) 2.90–3.35 (multiplet, Ar-**H**, 4), 5.97–6.20 (multiplet, H at C_2, 1, unchanged after double irradiation at τ 7.25), 6.25–6.40 [triplet of doublets, X part of ABXY, J = 4.5, 4.5, and 7.0 cps, C**H**OH, 1, converted into a doublet, J = 4.5 cps, by double irradiation at τ 7.25], 7.10–7.30 (multiplet, AB part of ABX, C**H**$_2$N, and H's at C_3, 4), 7.60 (broad, N**H** and O**H**, 2) 7.95–8.20 (multiplet, H's at C_3, 2), 8.90 [singlet, C(C**H**$_3$)$_3$, 9]. The important coupling H at C_2 to H at C_1' was 4.5 cps.

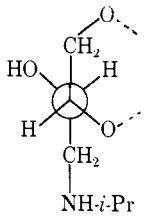
The chemical conversions and the nmr correlations show that **3**, **6**, **16**, **20**, **37**, and **41** belong to the same stereochemical series and **4**, **7**, **15**, **42**, and **52** belong to the other stereochemical series.

In attempting to assign relative configurations to centers C_2 and C_1', the assumption can not be made that the ethanolamine side chain adopts an equatorial conformation.[12,13] It was necessary therefore to know the ratio axial:equatorial side chain for each geometric isomer of a pair. The appropriate coupling constants H_2H_{3A} and H_2H_{3B} could not be obtained from the above spectra, which were all run at 100 Mc. In the nmr spectrum of **15** (220 Mc, C_6D_6), $J_{2,3A}$ was 2.5 cps and $J_{2,3B}$ was 6.75 cps, *i.e.*, $J_{2,3A} + J_{2,3B}$ = 9.25 ± 0.25 cps. For **16**, $J_{2,3A} + J_{2,3B}$ was 9.5 ± 0.25 cps (by subtraction of $J_{2,1}'$ from the measured sum of $J_{2,3A}$, $J_{2,3B}$, and $J_{2,1}'$); the separate coupling constants could not be identified with certainty. Thus both **15** and **16** have the side chain in the same axial:equatorial ratio. If the eq/ax and eq/eq coupling constants are 2.3 cps and the ax/ax coupling constant is 11.0 cps[12] then the ratio axial:equatorial side chain is approximately 1:1.

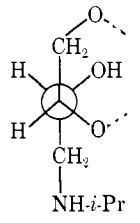
Assuming that the OH group will prefer to H bond to N rather than to an O of the benzodioxan ring, then relative configurations can be assigned to the two geometric isomers based on the coupling constants of

(12) A. R. Katritzky, A. M. Monro, G. W. H. Potter, R. E. Reavill, and M. J. Sewell, *Chem. Commun.*, 59 (1965).
(13) G. Pfundt and S. Farid, *Tetrahedron*, **22**, 2237 (1966).

the **H** atoms at C_2 and C_1', and the relative sizes of the groups attached to C_2 and C_1'. Thus, provided that the interactions are purely steric in orgin, the isomer **15** which has the higher coupling constant will have the configuration **70** which inspection shows has the *RS* (or *SR*) absolute configuration. **16** will have the *RR* (or *SS*) configuration **71**.



70



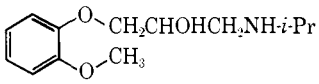
71

Thus **4**, **7**, **15**, **42**, and **52** are RS (or SR) racemates and **3**, **6**, **16**, **20**, **37**, and **41** are RR (or SS) racemates.

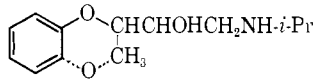
Biological Results and Discussion.—The results of the biological screening tests[14] are given in Table I. The test procedure was identical with that reported previously.[1a]

The benzodioxans **15** and **16** are the most potent β-adrenergic blocking agents so far reported and are five to ten times more potent than propranolol. Structure-potency relationships in the benzodioxan series resembled those in the propranolol series.[1b] Potency was highest when the N substituent was an alkyl group of 3–4 C atoms branched at the α-C, *e.g.*, **3**, **4**, **15**, and **16**. As in the propranolol series, potency was not improved by appending Ar to the alkyl group *e.g.*, **20**, **22**, and **23**, whereas in the pronethalol series[1a] and the isoproterenol series[15] the presence of such an aryl group often increased the potency. Introduction of Me (R^3) (Table I) appeared to lower potency,[1f] but caution is required because the compounds being compared may not belong to the same stereochemical series. Introduction of Me groups R^4 or R^4 and R^5 markedly lowered the potency. Substitution in the benzene ring, *e.g.*, **32** to **38** lowered potency with respect to the unsubstituted analog.

Comparison of the potencies of **3** and **4** with that of **72** (**6** in ref 1e, 55% block at 5 μg/kg per min)



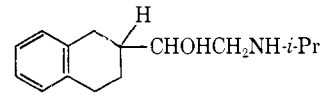
72



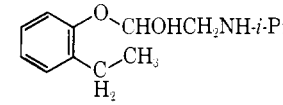
73

shows that a useful increase in potency is achieved by joining the OCH_3 of **72** to the propanolamine side chain to form the more rigid molecule **3** or **4**. The increase in potency is the more remarkable because substitution of Me in the propanolamine side chain as in structure **73** might be expected to markedly decrease potency as in the propranolol series.[1f]

Fewer chroman analogs were prepared but once again *t*-Bu and *i*-Pr substituents on N gave compounds of highest potency. Compounds in the chroman series were generally at least five to ten times less potent than their benzodioxan analogs. Comparison of **3** and **4** with **5** and with the tetrahydronaphthalene analog **74** (**24** in ref 1d; 45% block at 50 μg/kg per min) is interesting. Replacement of O-4 of **3** and **4** by CH_2 reduces potency by about 10 times and replacement of O-1 and 4 by CH_2's reduces it by about 75 times. The comparative potencies of **5** and **74** are in line with the



74



75

observation that replacement of the ethereal O of the propranolol side chain by CH_2 markedly lowers potency.[16] The comparison between **3** and **4**, and **5** is not in line with that between **72** and **75** (**3** in ref 1e; 74% block at 2.5 μg/kg per min), where a similar structural change is involved in a less rigid molecule.

The difference in potencies between the pairs of racemates was not particularly marked, except perhaps for the chromans **41** and **42**. The *RR* (or *SS*) racemates were the more potent.

Experimental Section[17]

When diastereoisomers were separated by fractional crystallization the salt or base mentioned first in Table I crystallized first from the solvent given. Hydrogenations were carried out at room temperature and atmospheric pressure. Methods A, B, and C are representative for the compounds listed in Table I.

A. 1-(1,4-Benzodioxan-2-yl)-2-*t*-butylaminoethanol (15, 16).—A mixture of 1-(1,4-benzodioxan-2-yl)-2-chloroethanol[6] (18.8 g) and *t*-$BuNH_2$ (120 ml) was heated in a sealed vessel at 100° for 10 hr, and then the excess of *t*-$BuNH_2$ was evaporated. The residual oil was shaken with 2 *N* HCl and Et_2O. The acidic aqueous solution was made alkaline with 8 *N* NaOH and then extracted with Et_2O. The dried extract was evaporated and the residual oil (15.6 g) was stirred with petroleum ether (bp 40–60°) (60 ml). The solid which separated was fractionally crystallized from petroleum ether (bp 40–60°) and gave **15**, mp 104–105°. **15**·HCl, prepared by adding a slight excess of ethereal HCl to a solution of **15** in Et_2O, was crystallized twice from MeOH–EtOAc, mp 162–163°. An aqueous solution of this **15**·HCl was made alkaline with 2 *N* NaOH and then extracted with Et_2O. The extract gave **15**, mp 104–105°.

The mother liquors remaining from the fractional crystallization which gave **15** yielded crude **16**, mp 79–81°, not changed by four crystallizations from petroleum ether (bp 40–60°). Crude **16**·HCl, mp 168–178°, was fractionally crystallized to give pure **16**·HCl, mp 193–194°, which gave pure **16**, mp 91–92°.

B.—In method B, 1-(1,4-benzodioxan-2-yl)-2-bromoethanol was used in place of 1-(1,4-benzodioxan-2-yl)-2-chloroethanol.

Bromomethyl 1,4-Benzodioxan-2-yl Ketone (57).—Br_2 (7.5 g) was added during 2 hr to a stirred solution of 1,4-benzodioxan-2-yl methyl ketone (8.36 g) in Et_2O (250 ml) at 10°. When the Br_2 color had been discharged the solution was washed with 3 *N* $NaHCO_3$ solution and then with H_2O. The Et_2O solution was dried and then evaporated to give **57** (9 g, 75%).

1-(1,4-Benzodioxan-2-yl)-2-bromoethanol.—$NaBH_4$ (4 g) was added during 1 hr to a stirred solution of **57** (14.0 g) in MeOH (150 ml) at 0°. After 18 hr the MeOH was evaporated, H_2O was added, and then the product was isolated by Et_2O extraction. It had mp 85–87° (from petroleum ether, bp 60–80°) (11.4 g, 81%). *Anal.* ($C_{10}H_{11}BrO_3$) H, Br; C: calcd, 46.35; found, 46.8.

C. 1-(1,4-Benzodioxan-2-yl)-2-isopropylaminoethanol (3).—$NaBH_4$ (2.0 g) was added during 1 hr to a stirred solution of **58** (2 g) and *i*-$PrNH_2$ (20 ml) in MeOH (50 ml) at 0°. After 18 hr the MeOH and the excess of *i*-$PrNH_2$ were evaporated. The residue

(14) Biological testing was carried out by Drs. J. W. Black, R. G. Shanks, and Mr. D. Dunlop. For further information see J. W. Black, W. A. M. Duncan, and R. G. Shanks, *Brit. J. Pharmacol.*, **25**, 577 (1965).

(15) H. D. Moed, J. van Dijk, and H. Niewind, *Rec. Trav. Chim.*, **74**, 919 (1955).

(16) Part VIII of this series being prepared.

(17) Where analyses are indicated only by symbols of the elements or functions, analytical results obtained for those elements or functions were within ±0.4% of the theoretical values.

was shaken with 1 *N* HCl and Et_2O. The acidic aqueous solution was made alkaline with 2 *N* NaOH and then extracted with Et_2O. The extract gave **3**.

(1,4-Benzodioxan-2-yl)glyoxal (58) (a).—A solution of **57** (1.5 g) in DMSO (15 ml) was kept at room temperature for 6 days, poured onto ice, and then extracted with Et_2O. The extract was evaporated and the residual gum was crystallized from Et_2O–petroleum ether (bp 40–60°) (0.82 g, 95%). **(b)** A solution of 1,4-benzodioxan-2-yl methyl ketone (1 g) and SeO_2 (0.65 g) in AcOH (30 ml) was heated at 100° for 2 hr and then heated under reflux for 1 hr. The cooled mixture was filtered and the filtrate was evaporated to dryness. The residual oil was dissolved in Et_2O and washed with 10% $NaHCO_3$ solution and then with H_2O. The Et_2O solution gave **58** (0.82 g, 70%).

When heated with *o*-phenylenediamine in MeOH solution, **58** gave 2-(1,4-benzodioxan-2-yl)quinoxaline, mp 152–153° (from EtOH). *Anal.* ($C_{16}H_{12}N_2O_2$) C, H, N.

1-(2-Chromanyl)-2-isopropylaminoethanol (5) (a).—$NaBH_4$ (0.1 g) was added during 15 min to a stirred solution of **39** free base (0.1 g) in MeOH (20 ml) and Me_2CO (2 ml) at 0°. After 12 hr the MeOH was evaporated *in vacuo*, H_2O was added, and the mixture was extracted with Et_2O. Ethereal HCl was added to the dried extract and **5**·HCl separated, mp 175–176°, from MeOH–EtOAc. **(b)** A solution of 2-chromanyl diazomethyl ketone (**54**) (1 g) in EtOH (30 ml) and Me_2CO (15 ml) was hydrogenated in the presence of Pd (0.2 g). The mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was shaken with 1 *N* HCl and Et_2O. The acidic aqueous solution was made alkaline with 2 *N* NaOH and then extracted with Et_2O. Ethereal HCl was added to the dried extract and **5**·HCl separated.

1-(1,4-Benzodioxan-2-yl)-2-*t*-butylaminoethanol (16).—*t*-$BuNH_2$ (1.12 g, 0.0153 mol) was added to a stirred solution of bromomethyl 2-(1,4-benzodioxanyl) ketone (2 g, 0.0078 mol) in Et_2O (80 ml) at 0°. After 1 hr the mixture was filtered to remove *t*-$BuNH_2$·HCl. Ethereal HCl was added to the filtrate and the solid which separated was fractionally crystallized to give 2-(1,4-benzodioxanyl) *t*-butylaminomethyl ketone·HCl (**55**), mp 182–184° (79 mg), ν 1755 cm^{-1}.

$NaBH_4$ (0.25 g) was added during 15 min to a stirred solution of **55** (0.09 g) in MeOH (50 ml) at 0°. After 12 hr the MeOH was evaporated *in vacuo*; **16**·HCl was isolated in the same way as **5**·HCl (above).

1-(6-Bromo-2-chromanyl)-2-*t*-butylaminoethanol (52).—Br_2 (0.2 g) in AcOH (25 ml) was added to a solution of **42**·HCl in AcOH (25 ml) and then the solution was kept at 40° until the Br_2 color had largely been discharged. After 1 hr, AcOH was evaporated *in vacuo*. **52**·HCl was obtained by procedure b given for **5**·HCl.

1-(1,4-Benzodioxan-2-yl)-2-isopropylaminoethanol (3).—A solution of **6**·HCl (0.1 g) in EtOH (15 ml) and Me_2CO (10 ml) was hydrogenated in the presence of Pt catalyst (0.2 g). The mixture was filtered, the filtrate was evaporated to dryness, and then the residue was dissolved in H_2O (50 ml). The solution was made alkaline with 8 *N* NaOH and extracted with Et_2O. The extract gave **3**, mmp 88–89°.

7·HCl was used in place of **6**·HCl. The residue obtained after evaporation of the filtrate was crystallized from MeOH–EtOAc to give **4**·HCl, mmp 144–145°.

Ethyl Naphtho[2,3-*b*]-1,4-dioxan-2-carboxylate (62).—Ethyl 2,3-dibromopropionate (25 g) was added during 30 min to a mixture of 2,3-dihydroxynaphthalene (40 g), anhydrous K_2CO_3 (35 g), and Me_2CO (500 ml) which was being stirred and heated under reflux. More K_2CO_3 (35 g) was then added, followed by more ethyl 2,3-dibromopropionate (25 g) during 30 min. The procedure described in the last sentence was repeated twice more. The mixture was then stirred and heated under reflux for 18 hr, and then cooled and filtered. The Me_2CO was evaporated and the residue was extracted with H_2O (300 ml) and Et_2O (360 ml in three portions). The Et_2O extract was washed with 5% aqueous Na_2CO_3 (200 ml) and then H_2O. The extract was dried, the Et_2O was evaporated, and the residual oil was distilled to give **62**, bp 170–175° (0.7 mm), mp 61–62° (40 g, 63%).

Naphtho[2,3-*b*]-1,4-dioxan-2-carboxylic Acid (63).—Compound **62** (36 g) and 10% aqueous NaOH (200 ml) were heated at 100° for 45 min. The solution was cooled to 40° and maintained at 40° while concentrated HCl (50 ml) was added. The mixture was cooled and filtered, and the solid **63** (25.2 g, 95%) was washed with H_2O (50 ml).

Naphtho[2,3-*b*]-1,4-dioxan-2-carboxylic Acid Chloride (64). Compound **63** (61.2 g), $SOCl_2$ (44 g), and $CHCl_3$ (1,200 ml) were heated under reflux for 4 hr and then the $CHCl_3$ and the excess of $SOCl_2$ were evaporated. The residue was **64** (56.8 g, 86%).

Chloromethyl Naphtho[2,3-*b*]-1,4-dioxan-2-yl Ketone (65).—A solution of **64** (25 g) in Et_2O (300 ml) was treated with a slight excess of CH_2N_2 in Et_2O at 0°. After 18 hr excess CH_2N_2 and Et_2O were evaporated. A solution of the residual oil (20 g), which consisted of diazomethyl naphtho[2,3-*b*]-1,4-dioxan-2-yl ketone (ν 2120 cm^{-1}), in Et_2O (250 ml) was saturated with HCl gas at 0°. Ice (250 g) and Et_2O (200 ml) were added and the mixture was shaken. The Et_2O solution was washed successively with H_2O (50 ml, 3 times), 10% aqueous Na_2CO_3 (50 ml, 3 times), and H_2O (50 ml, 3 times). The dried Et_2O solution was evaporated to give **65** (19.2 g, 77%).

2-Chloro-1-(naphtho[2,3-*b*]-1,4-dioxan-2-yl)ethanol.—$NaBH_4$ (2 g) was added during 30 min to a stirred solution of **65** (5 g) in MeOH (120 ml) at 0°. After 16 hr the MeOH was evaporated, H_2O (50 ml) was added, and then the mixture was extracted with Et_2O (50 ml, 4 times). The extract was washed with H_2O, dried, and evaporated to give the chlorohydrin as an oil (3.2 g, 64%).

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