β-Adrenergic Blocking Agents. 11. Heterocyclic Analogs of Pronethalol [2-Isopropylamino-1-(2-naphthyl)ethanol]

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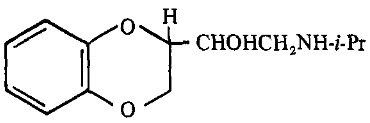
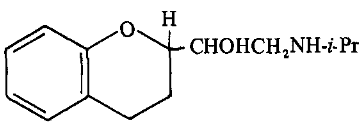
The synthesis and biological properties of further heterocyclic analogs of pronethalol (**3**) are reported. Examples are given in which the side chain is attached to the benzenoid part and to the heterocyclic part of a heterocyclic system. Many of the compounds have the pronethalol level of potency as β-adrenergic blocking agents. The most potent compounds contain features of the propranolol (**4**) type.

We have previously reported[1] the synthesis and β-adrenergic blocking potencies of a series of 1-(1,4-benzodioxan-2-yl)- (**1**) and 1-(chroman-2-yl)-2-aminoethanols (**2**) which contain features of both pronethalol (**3**)† and propranolol (**4**)‡. In this paper we report the synthesis and properties of further heterocyclic analogs of pronethalol.[2-4]



1



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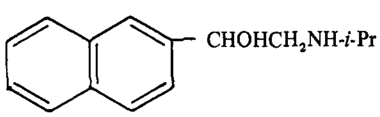

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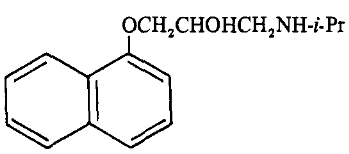


4

In Table I the side chain is always the same as it is in pronethalol (**3**), and examples are given where it is attached to the benzenoid part (**5** to **21**), and where it is attached to the heterocyclic part of a heterocyclic system (**22** to **39**). In Table II the substituents on N are varied.

The most general method used (A, eq 1, Scheme I) was reductive ($NaBH_4$) amination of a glyoxal.[5] The side chain attached to the 2 or 3 positions of indole analogs (**22-28** and **44-47**) was always formed by reduction (LAH) of an intermediate glyoxylamide (B, eq 2).[6] The indole analog **23** was obtained by removal (Na-NH_3) of the benzyl group from the indole N of **27**. Several compounds were made by reduction ($NaBH_4$) of an intermediate amino ketone (C, eq 3).[5] Compds **6** and **29** were prepared by reductive alkylation of an amino ketone with Me_2CO and $NaBH_4$ or Pt-H_2 (D, eq 4).[5] Related routes gave **43** by reductive (Pt-H_2) alkylation of an amino alcohol with a ketone (eq 5) and **34**

Scheme I

$$RCOCHO \xrightarrow{H_2NR^1} [RCOCH{=}NR^1 \xrightarrow{NaBH_4} RCOCH_2NHR^1] \xrightarrow{NaBH_4} RCHOHCH_2NHR^1 \quad (1)$$

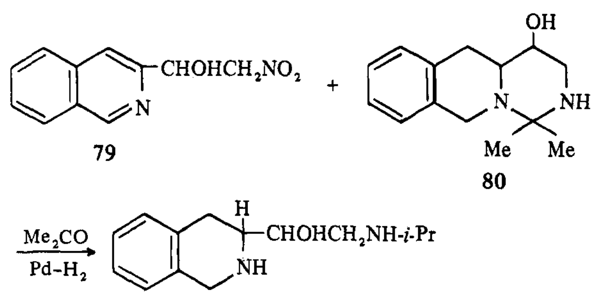
$$RCOCONR^1R^2 \xrightarrow{LAH} RCHOHCH_2NR^1R^2 \quad (2)$$

$$RCOCH_2NR^1R^2 \xrightarrow{NaBH_4} RCHOHCH_2NR^1R^2 \quad (3)$$

$$RCOCH_2NH_2 \xrightarrow{Me_2CO} [RCOCH_2N{=}CMe_2] \xrightarrow[\text{or Pt-}H_2]{NaBH_4} RCHOHCH_2NH\text{-}i\text{-}Pr \quad (4)$$

$$RCHOHCH_2NH_2 \xrightarrow{R^1R^2CO} [RCHOHCH_2N{=}CR^1R^2] \xrightarrow{Pt\text{-}H_2} RCHOHCH_2NHCHR^1R^2 \quad (5)$$

$$RCOCHN_2 \xrightarrow{Me_2CO + Pd\text{-}H_2} RCHOHCH_2NH\text{-}i\text{-}Pr \quad (6)$$



79 **80** **31** (7)

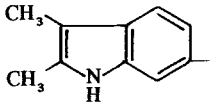
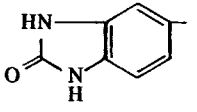
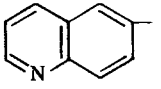
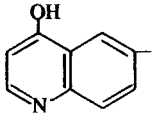
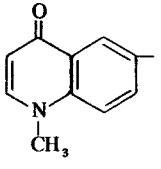
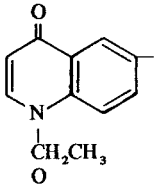
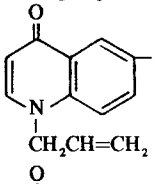
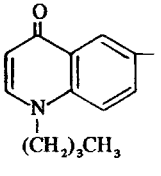
$$RCHOHCH_2X \xrightarrow{HNR^1R^2} \left[RCH\overset{O}{—}CH_2 \right] \xrightarrow{HNR^1R^2} RCHOHCH_2NR^1R^2 \quad (8)$$

by reductive (Pd-H_2) alkylation of a diazo ketone with Me_2CO (eq 6).[5] Reductive (Pd-H_2) alkylation of the nitro alcohol **79** with Me_2CO gave **31** and **80**; partial saturation of the isoquinoline and addition of the NH thus formed to the azomethine intermediate in the reductive alkylation would give **80** (eq 7). In method E (eq 8) a halohydrin was treated with an amine to give, *via* an oxirane, the desired amino alcohol.[5] For **30** an intermediate oxirane **81**, prepared by the action of dimethyloxosulfonium methylide on an aldehyde,[7] was used in place of a halohydrin.

Compound **32** was obtained by treating either 2-acetoxyacetylquinoxaline (**82**) or 2-(α,β-diacetoxyvinyl)quinoxaline (**83**) with *i*-$PrNH_2$ and then $NaBH_4$.[3] These two intermediates were obtained by acetylation of the compound, which we regard as the polymer **84**, obtained by treatment of 2-(D-*arabino*-tetrahydroxybutyl)quinoxaline with base.[8]

† Alderlin.
‡ Inderal.

Table I. RCHOHCH$_2$NH-*i*-Pr

Compound	R	Methods[a]	Form	Crystn solvent[b]	Mp, °C	Formula	Analyses	Infusion rate, μg/kg per min	% change in heart rate	% inhibition of tachycardia
5		A[c]	Base	P(100)	157–158	$C_{15}H_{22}N_2O$	C, H	100	−10	20
6		D[d] (Pt-H_2)	HBr	H_2O + Me_2CO	210	$C_{12}H_{18}BrN_3O_2$	C, H; N[e]	100	−10	35
7		A	Dipicrate	BuOH	235–236	$C_{26}H_{24}N_8O_{15}$	N	100[f]	−10	43
8		A[g]	Oxalate	MeOH–EtOAc	200–202	$C_{16}H_{20}N_2O_6 \cdot 1.5H_2O$	C, H, N	50	−12	53
9		A[h]	Tartrate	MeOH–EtOAc	200	$C_{19}H_{26}N_2O_8 \cdot H_2O$	H, N; C[i]	25	−4	82
10		A[j]	Tartrate	MeOH–EtOAc	164	$C_{20}H_{28}N_2O_8 \cdot 0.5H_2O$	C, H, N	100	−18	90
11		A[k]	Tartrate	EtOH–EtOAc	126	$C_{21}H_{28}N_2O_8 \cdot 0.5H_2O$	C, H, N	100	−16	80
12		A[l]	Tartrate	EtOH–EtOAc	123 dec	$C_{22}H_{32}N_2O_8 \cdot 0.5H_2O$	C, H, N	200	−29	58

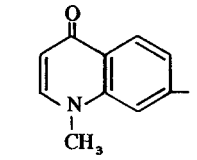
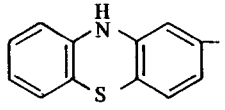
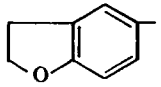
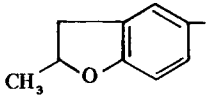
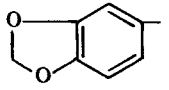
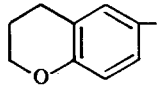
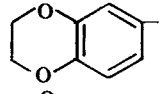
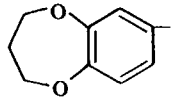
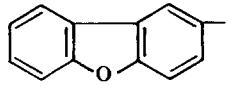
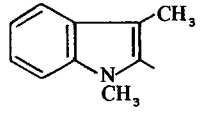
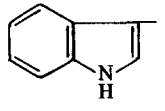
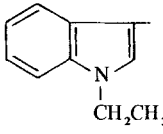
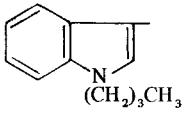
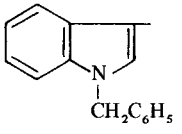
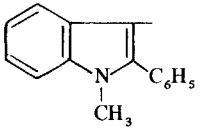
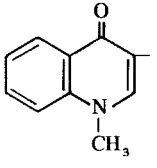
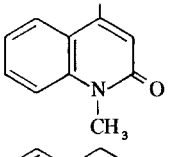
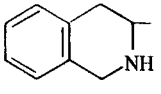
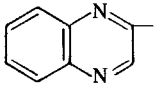
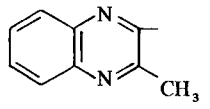
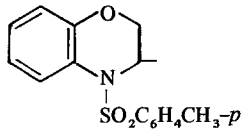
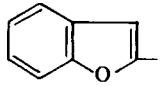
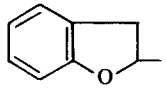
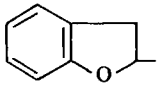
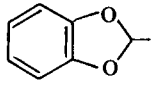
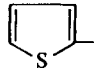
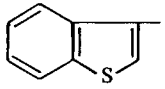
13		A[m]	Oxalate	MeOH–EtOAc	189 dec	$C_{17}H_{22}N_2O_6 \cdot H_2O$	C, H, N	500	0	12
14		E	Base	EtOAc	144–145	$C_{17}H_{20}N_2OS$	C, H, N, S	400	−21	Nil
15		A[n]	Base	EtOAc	108	$C_{13}H_{19}NO_2$	C, H, N	100	−23	69
16		A[o]	Oxalate	Et_2O	188–190	$C_{30}H_{44}N_2O_8$	H, N; C[p]	100	+5	19
17		C	Base	EtOAc	93–94	$C_{12}H_{17}NO_3$	C, H, N	25	+34	80
18		A[q]	Base	EtOAc	105–106	$C_{14}H_{21}NO_2$	C, H, N	100	−18	71
19		C	HCl	MeOH + Et_2O	184–185	$C_{13}H_{20}ClNO_3$	C, H, Cl, N	25	−3	45
20		C	HCl	MeOH + EtOAc	163–164	$C_{14}H_{22}ClNO_3$	C, H, Cl, N	100	−14	54
21		A[r]	Oxalate	EtOH	251	$C_{36}H_{40}N_2O_8$	C, H	100	−13	44
22		B[s]	Base	C_6H_6	126–127	$C_{15}H_{22}N_2O$	C, H, N	400	−32	Nil
23		See Expt'l	Base	P(80)	134–136	$C_{13}H_{18}N_2O$	C, H, N	50	0	35
24		B[t]	Base	EtOAc	114–115	$C_{14}H_{20}N_2O$	C, H, N	100	+2	70

Table I (*Continued*)

Compound	R	Methods[a]	Form	Crystn solvent[b]	Mp, °C	Formula	Analyses	Infusion rate, μg/kg per min	% change in heart rate	% inhibition of tachycardia
25		B	Base	EtOAc	125–126	$C_{15}H_{22}N_2O$	C, H, N	50	−6	38
26		B	Base	P(80)	66–68	$C_{17}H_{26}N_2O$	C, H, N	100 400	−18 −22	Nil 11
27		B	Base	EtOAc	120	$C_{20}H_{24}N_2O$	C, H, N	100	−14	Nil
28		B	Base	P(80)	110	$C_{20}H_{24}N_2O$	C, H, N	200	−14	Nil
29		D $NaBH_4$	Oxalate	MeOH–EtOAc	176–178	$C_{17}H_{22}N_2O_6 \cdot H_2O$	N; C, H[u]	100 500	+2 −15	Nil 16
30		See Exptl	Base	EtOAc	152–154	$C_{15}H_{20}N_2O_2$	C, H, N	50	+24	68
31		See Exptl	Di-HCl	MeOH + EtOAc	272–274	$C_{14}H_{24}Cl_2N_2O$	C, H, Cl, N	100	+22	50
32		See Exptl	Base	P(60)	98–99	$C_{13}H_{17}N_3O$	C, H, N	50	0	93

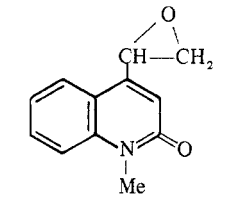
33		E[v]	Base	EtOAc + P(40)	89–90	$C_{14}H_{19}N_3O$	C, H, N	100	+7	33
34		See Exptl	Base	EtOAc + P(40)	150–151	$C_{20}H_{26}N_2O_4S$	C, H, N, S	50 200	+7 +22	Nil 17
35		A[w]	Base	P(80)	108–109	$C_{13}H_{17}NO_2$	C, H, N	5	+23	80
36A		E[x]	Base	P(60)	116–118	$C_{13}H_{19}NO_2$	C, H, N	10	−1	80
36B		E[x]	Base	P(40)	85–86		*y*	10	+12	90
37		E[z]	Base	C_6H_6	110	$C_{12}H_{17}NO_3$	C, H, N	10	0	63
38		E[aa]	Oxalate	EtOH–EtOAc	198–199	$C_{20}H_{32}N_2O_6S_2$	C, N, S; H[bb]	200	−8	16
39		A	Base	EtOH–EtOAc	193–194	$C_{13}H_{18}ClNOS$	C, H, N	50	+7	42

[a]Methods refer to Experimental Section. [b]P(40), P(60), P(80), and P(100) refer to petroleum ether bp 40–60°, bp 60–80°, bp 80–100°, and bp 100–120°. [c]Crude 2,3-dimethylindol-6-ylglyoxal obtd by method F (dioxane) from 1-acetyl-2,3-dimethylindol-6-yl methyl ketone [W. Borsche and H. Groth, *Justus Liebigs Ann. Chem.*, **549**, 238 (1941)]. The 1-Ac group was removed by the condns used in method A. [d]Crude aminomethyl benzimidazol-2-on-5-yl ketone hydrobromide was obtd by method J from bromomethyl benzimidazol-2-on-5-yl ketone.[13] [e]N: calcd, 13.3; found, 12.7. [f]Administered as free base. [g]Crude 4-hydroxyquinolin-6-ylglyoxal hydrate obtd by method F (AcOH) from 4-hydroxyquinolin-6-yl methyl ketone.[19] [h]Crude 1-methyl-4-quinolon-6-ylglyoxal hydrate obtd by method F (AcOH) from **49**. [i]C: calcd, 53.3; found, 52.8. [j]Crude 1-ethyl-4-quinolon-6-ylglyoxal hydrate obtd by method F (AcOH) from **50**. [k]Crude 1-allyl-4-quinolon-6-ylglyoxal hydrate obtd by method F (AcOH) from **51**. [l]Crude 1-*n*-butyl-4-quinolon-6-ylglyoxal hydrate obtd by method F (AcOH) from **52**. [m]Crude 1-methyl-4-quinolon-7-ylglyoxal hydrate obtd by method F (AcOH) from **53**. [n]Crude 2,3-dihydrobenzofuran-5-ylglyoxal obtd by method F (dioxane) from 2,3-dihydrobenzofuran-5-yl methyl ketone [G. Baddeley and M. A. Vickars, *J. Chem. Soc.*, 4665 (1958)]. [o]Crude 2-methyl-2,3-dihydrobenzofuran-5-ylglyoxal obtd by method F (dioxane) from methyl 2-methyl-2,3-dihydrobenzofuran-5-yl ketone (ref in footnote *n*). No attempt was made to sep geometric isomers. [p]C: calcd, 64.3; found, 63.8. [q]Crude chroman-6-ylglyoxal obtd by method F (dioxane) from chroman-6-yl methyl ketone [G. Chatelus, *Ann. Chim. (Paris)*, **4**, 505 (1949)]. [r]Crude dibenzofuran-2-ylglyoxal obtd by method F (dioxane) from dibenzofuran-2-yl methyl ketone [P. Galewski, *Justus Liebigs Ann. Chem.*, **264**, 187 (1891)]. [s]Crude *N*-isopropyl-1,3-dimethylindol-2-ylglyoxylamide obtd by method H from 1,3-dimethylindole [J. Meisenheimer, L. Angermann, O. Finn, and E. Vieweg, *Ber.*, **57**, 1744 (1924)]. [t]Crude *N*-isopropyl-1-methylindol-2-ylglyoxylamide obtd by method H from 1-methylindole [K. T. Potts and J. E. Saxton, *Org. Synth.*, **40**, 68 (1960)]. Literature on **20** gives mp 114.5–115.5° (ref 6). [u]C: calcd, 55.4; found, 54.7. H: calcd, 6.5; found, 6.0. [v]2-Bromo-1-(3-methylquinoxalin-2-yl)ethanol obtd by $NaBH_4$ reduction of **73** was not characterized. [w]Benzofuran-2-ylglyoxal [S. Fatutta, *Gazz. Chim. Ital.*, **89**, 1598 (1959)]. [x]2-Chloro-1-(2,3-dihydrobenzofuran-2-yl)ethanol [D. Misiti, A. Amato, and V. Rosnati, *ibid.*, **93**, 1128 (1963)]; chloromethyl 2,3-dihydrobenzofuran-2-yl ketone [V. Rosnati, F. De Marchi, D. Misiti, and C. Francescaglia, *ibid.*, **94**, 979 (1964)]. [y]No anal. τ ($CDCl_3$), 2.6–3.3 (multiplet, Ar H, 4), 5.35 (multiplet, H at C_2, 1), 6.25 (multiplet, CH(OH), 1), 6.75 (doublet, H's at C_3, 2), 7.0–7.5 (multiplet, $CH_2NHCH<$, 3), 7.54 (singlet, OH and NH, 2), 8.9 (doublet, $CH(CH_3)_2$, 6). The spectrum of **36A** had signals at 5.25, 6.8, and 7.65 in place of those at 5.35, 6.75, and 7.54; the shape of the multiplets for H at C_2 and CH(OH) differed for **36A** and **36B**, but no stereochem assignments were possible. [z]1,3-Benzodioxole-2-carbonyl chloride[20] was converted to 1,3-benzodioxol-2-yl diazomethyl ketone by the method given for **77**. Treatment of the diazomethyl ketone with HBr gave the bromomethyl ketone which was reduced by $NaBH_4$ to give crude 2-bromo-1-(1,3-benzodioxol-2-yl)ethanol (see Experimental Section). [aa]Crude 2-bromo-1-(2-thienyl)ethanol was obtd by $NaBH_4$ reduction (as in footnote *z*) of bromomethyl 2-thienyl ketone [H. Brunswig, *Ber.*, **19**, 2890 (1886)]. [bb]H: calcd, 7.0; found, 7.5.

Table II. $RCHOHCH_2NR^1R^2$

Compound	R	R^1	R^2	Method[a]	Form	Crystn solvent[b]	Mp, °C	Formula	Analyses	Infusion rate, μg/kg per min	% change in heart rate	% inhibition of tachycardia
40	As 17	CH_3	$CH(CH_3)_2$	C	HCl	MeOH + EtOAc	198–199	$C_{13}H_{20}ClNO_3$	C, H, Cl, N	100	+21	68
41	As 19	H	H	C	Base hydrate	EtOAc	82–83	$C_{10}H_{13}NO_3 \cdot H_2O$	C, H, N	250	−12	25
42	As 19	H	$C(CH_3)_2CH_2OH$	A	Base	EtOAc	101–102	$C_{14}H_{21}NO_4$	C, H, N	100	+8	85
43	As 19	H	$CH(CH_3)(CH_2)_2C_6H_5$	See Exptl	HCl	MeOH + EtOAc	158–159	$C_{20}H_{26}ClNO_3$	H, Cl, N; C[c]	100	+22	94
44	As 24	H	$C(CH_3)_3$	B	Base	EtOAc	124–126	$C_{15}H_{22}N_2O$	H, N; C[d]	100	−2	85
45	As 24	H	$C(CH_3)_2CH_2OH$	B[e]	Picrate	Me_2CO	146	$C_{21}H_{25}N_5O_9$	C, H, N	10[f]	+14	55
46	As 24	H	$(CH_2)_3N(CH_3)_2$	B	Oxalate	EtOH + H_2O	128–130dec	$C_{20}H_{29}N_3O_9$	C, H, N	250	−14	8
47	As 27	CH_2CH_3	CH_2CH_3	B	Base	P(40)	62–64	$C_{21}H_{26}N_2O$	C, H, N	10[g]		Not active

[a]Methods refer to Experimental Section. [b]P(40) stands for petroleum ether bp 40–60°. [c]C: calcd, 66.0; found, 65.5. [d]C: calcd, 73.2; found, 72.6. [e]Crude *N*-2-hydroxy-1,1-dimethylethyl-1-methylindol-3-ylglyoxylamide was prepd by method H. [f]Administered intraduodenally, 10 mg/kg. [g]Administered sc in the rat, 10 mg/kg.



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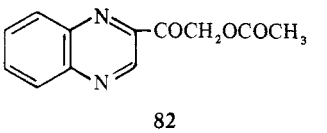

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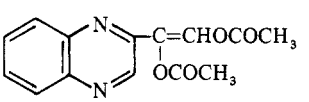

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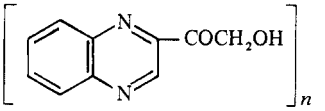

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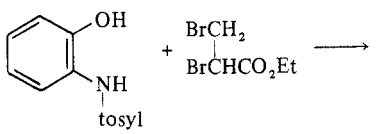
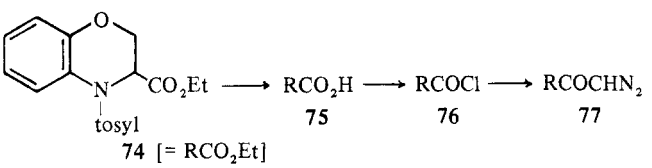
Other intermediates which were characterized are given in Table III. The intermediate glyoxals were prepared by oxidation of a methyl ketone with SeO_2 in the solvent specified (method F) or by treatment of a bromomethyl ketone with DMSO (method G).[5] The glyoxylamide intermediates **64–70** were prepared by the action of $(COCl)_2$ on the appropriate indole, followed by treatment with an amine (method H).[6] Bromomethyl ketones were obtained by brominating methyl ketones in the solvent specified (method I). Substituted aminomethyl ketones were prepared by the action of an amine on a bromomethyl ketone (method J); the hexamine route gave unsubstituted aminomethyl ketones (method K).[5] The *N*-alkylquinolin-4-ones **49–53** were obtained by the action of a dialkyl sulfate (method L) or an alkyl halide (method M) on the appropriate 4-hydroxyquinoline derivative. The diazo ketone **77** was made by the route





74 [= RCO_2Et]

The orientation of the acid **75** is based on nmr evidence. Had the CO_2H been at C_2, then the H at C_2 signal (H_B of an ABX system) would have been expected at lower field than H_A and H_X. Attempts to detosylate the ester **74** with H_2SO_4 failed; water-soluble derivatives were formed, presumably by sulfonation. With Na in NH_3,[9] the ester was degraded to *o*-aminophenol in good yield.

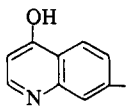
One compd, **86**, in which C-1 of an ethanolamine side chain attached to benzene forms part of the heterocyclic system, was prepared by treating *N*-methylisatin with dimethyloxosulfonium methylide[7] to give the oxirane **85** which with *i*-$PrNH_2$ gave **86**.

The diasteroisomers **36A** and **36B** were separated by fractional crystallization. No attempt was made to separate the diastereoisomers corresponding to **16**, **31**, **34**, and **43**.

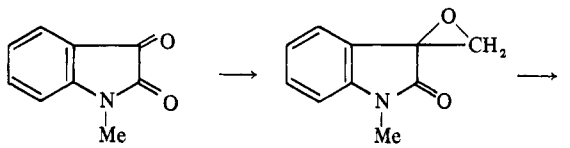
Biological Results. The results of the biological screening tests[§] are given in Tables I and II. β-Adrenergic blocking potency was determined in the usual way.

[§] Biological testing was carried out by Drs. J. W. Black and R. G. Shanks and Mr. D. Dunlop. For further information see ref 10.

Table III. RCOX

Compound	R	X	Method[a]	Crystn solvent[b]	Mp, °C	Formula	Analyses
48	As 7	CHO	F(AcOH)[c]	H_2O	145	$C_{11}H_7NO_2 \cdot H_2O$	N
49	As 9	CH_3	L[d]	PhCl	184	$C_{12}H_{11}NO_2$	N
50	As 10	CH_3	L[d]	BuOH	156-158	$C_{13}H_{13}NO_2$	N
51	As 11	CH_3	M[d]	H_2O	166	$C_{14}H_{13}NO_2 \cdot 0.25H_2O$	C, H, N
52	As 12	CH_3	M[d]	CCl_4	126-128	$C_{15}H_{17}NO_2$	H, N; C[e]
53	As 13	CH_3	L[f]	PhCl	178	$C_{12}H_{11}NO_2$	C, H, N
54		CH_3	g	DMF	280	$C_{11}H_9NO_2$	C, H, N
55	As 17	CH_2NH-*i*-Pr · HCl	J[h]	MeOH + EtOAc	227-228	$C_{12}H_{16}ClNO_3$	C, H, Cl, N
56	As 17	CH_2NMe-*i*-Pr · HCl	J[h]	MeOH + EtOAc	180-181	$C_{13}H_{18}ClNO_3$	C, H, Cl, N
57	As 19	CH_2NH-*i*-Pr · HCl	J[i]	EtOH-Et_2O	204-205	$C_{13}H_{18}ClNO_3$	C, H, N
58	As 19	$CH_2NH_2 \cdot HCl$	K[i]	EtOH-H_2O	248	$C_{10}H_{12}ClNO_3$	C, H, Cl, N
59	As 19	CHO	G[i]	H_2O	99-103 dec	$C_{10}H_8O_4 \cdot H_2O$	C, H
60	As 19	CH_2Br	I(CS_2)[j]	C_6H_6	119-120	$C_{10}H_9BrO_3$	C, H, Br
61	As 20	CH_2NH-*i*-Pr · HCl	J	EtOH + Et_2O	204-205	$C_{14}H_{20}ClNO_3$	C, H, Cl, N
62	As 20	CH_2Br	I(CS_2)	C_6H_6 + P(40)	75-76	$C_{11}H_{11}BrO_3$	C, H, Br
63	As 20	CH_3	See Exptl		120 (0.5 mm)	$C_{11}H_{12}O_3$	C, H
64	As 24	CONH-*tert*-Bu	H[k]	EtOH	143	$C_{15}H_{18}N_2O_2$	C, H; N[l]
65	As 24	$CONH(CH_2)_3NMe_2$	H[k]	Cyclohexane	83	$C_{16}H_{21}N_3O_2$	C, H, N
66	As 25	CONH-*i*-Pr	H[m]	P(80)	96	$C_{15}H_{18}N_2O_2$	H, N; C[n]
67	As 26	CONH-*i*-Pr	H[o]	EtOH	196-198	$C_{17}H_{22}N_2O_2$	C, H, N
68	As 27	CONH-*i*-Pr	H[p]	P(100)	132-134	$C_{20}H_{20}N_2O_2$	C, H, N
69	As 27	$CONEt_2$	H[p]	P(100)	93	$C_{21}H_{22}N_2O_2$	C, H, N
70	As 28	CONH-*i*-Pr	H[q]	EtOH	181-183	$C_{20}H_{20}N_2O_2$	C, H, N
71	As 29	$CH_2NH_2 \cdot HBr$	K[r]	EtOH + H_2O	284	$C_{12}H_{13}BrN_2O_2 \cdot 0.5H_2O$	C, H, Br, N
72	As 32	CH_2Br	I (48% HBr)[s]	MeOH + H_2O	116-117	$C_{10}H_7BrN_2O$	C, H, N
73	As 33	CH_2Br	I(HBr)[t]	MeOH + H_2O	107	$C_{11}H_9BrN_2O$	C, H, N; Br[u]
74	As 34	OEt	See Exptl	MeOH	135-136	$C_{18}H_{19}NO_5S$	C, H, N, S
75	As 34	OH	See Exptl	MeOH + EtOAc	181-182	$C_{16}H_{15}NO_5S$	C, H, N, S
76	As 34	Cl	See Exptl	P(60)	103-104	$C_{16}H_{14}ClNO_4S$	C, H, Cl, N, S
77	As 34	CHN_2	See Exptl	Et_2O	132-134	$C_{17}H_{15}N_3O_4S$	C, H, N, S
78	As 39	CHO	F (dioxane)[v]	Moist $CHCl_3$	128-130	$C_{10}H_8O_2S \cdot H_2O$	C, H

[a]Methods refer to the Experimental Section. [b]P(40) etc. see footnote *b* of Table I. [c]Quinolin-6-yl methyl ketone [S. G. Waley, *J. Chem. Soc.*, 2008 (1948)]. [d]4-Hydroxyquinolin-6-yl methyl ketone (footnote *g*, Table I). [e]C: calcd, 74.0; found, 73.4. [f]Prepd from **54**. [g]Prepd from 3-aminoacetophenone by the method of Riegel, *et al.*, ref 19. [h]Bromomethyl 3,4-methylenedioxyphenyl ketone [N. L. Drake and W. B. Tuemmler, *J. Amer. Chem. Soc.*, **77**, 1204 (1955)]. [i]Prepd from compound **60**. [j]1,4-Benzodioxan-6-yl methyl ketone [J. J. Denton, R. J. Turner, W. B. Neier, V. A. Lawson, and H. P. Schedl, *J. Amer. Chem. Soc.*, **71**, 2048 (1949)]. [k]1-Methylindole [K. T. Potts and J. E. Saxton, *Org. Syn.*, **40**, 68 (1960)]. [l]N: calcd, 10.9; found, 10.4. [m]1-Ethylindole [A. Michaelis, *Ber.*, **30**, 2809 (1897)]. [n]C: calcd, 69.8; found, 69.3. [o]1-*n*-Butylindole [J. v. Braun and O. Bayer, *Ber.*, **58**, 387 (1925)]. [p]1-Benzylindole [H. Plieninger, *ibid.*, **87**, 127 (1954)]. [q]2-Benzyl-1-methylindole [A. F. Ames, D. E. Ames, C. R. Coyne, T. F. Grey, I. M. Lockhart, and R. S. Ralph, *J. Chem. Soc.*, 3388 (1959)]. [r]Crude bromomethyl 1-methylquinol-4-on-3-yl ketone was obtd by method I (48% HBr) from methyl 1-methylquinol-4-on-3-yl ketone which was prepd by method L from 4-hydroxyquinolin-3-yl methyl ketone [R. K. Mapara and C. M. Desai, *J. Indian Chem. Soc.*, **31**, 951 (1954)]. [s]Methyl quinoxalin-2-yl ketone [G. Henseke and K. J. Bähner, *Ber.*, **91**, 1605 (1958)]. [t]Methyl 3-methylquinoxalin-2-yl ketone [F. Sachs and A. Röhmer, *ibid.*, **35**, 3307 (1902)]. [u]Br: calcd, 30.2; found, 29.7. [v]Benzo[*b*]thiophen-3-yl methyl ketone [M. W. Farrar and R. Levine, *J. Amer. Chem. Soc.*, **72**, 4433 (1950)].



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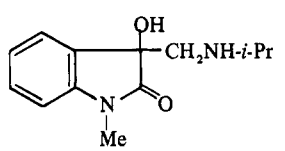

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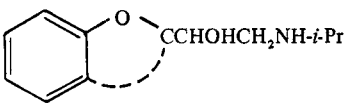
It is clear from Table I that the naphthalene ring of pronethalol can be replaced by many heterocyclic ring systems to give compds which have the pronethalol level of potency, *e.g.*, **8**, **10**, **11**, **15**, **17**, **18**, **23**, **24**, **25**, **30**, and **39**. Pronethalol infused at 50 μg/kg per min produces a 45% inhibition of isoproterenol-induced tachycardia in the cat.[5] A few compds showed a slightly higher potency, *i.e.*, **9**, **19**, and **32**. The level of potency of **15**, **17**, **18**, **19**, and **39** was as expected, because the group replacing naphthalene was about the same size and without functionality. The 4 most potent compds, **35**, **36A**, **36B**, and **37**, which were from 5 to 10 times more potent than pronethalol, all contained those features of the propranolol type (**87**) common to the highly potent 1,4-benzodioxan and chroman analogs described in part 7.[1] That the 1,4-benzodioxan and chroman ring systems are not responsible *per se* follows from a comparison of **18** and **19** with **2** and **1** (this paper). Compd **2** is the same as **5** (in part 7, 5 μg/kg per min, 32% inhib) and **1** corresponds with the geometric isomers **3** or **4** (in part 7, 1 and 1 μg/kg per min, 80 and 36% inhib, respectively). As in the



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1,4-benzodioxan series,[1] there was no marked difference in potency between the geometric isomers **36A** and **36B**.

At the other end of the scale the absence of or low potencies of **14**, **26**, **27**, **28**, and **34** suggest once more that the group replacing naphthalene can be made too large. This has previously been commented upon for the phenanthrene and anthracene analogs in part 4,[11] and for the naphthol[2,3-*b*]-1,4-dioxane analogs in part 7.[1] The low potencies of **13**, **22**, and **29** cannot be so explained.

Changes made to the substituent on the side chain nitrogen (Table II) followed the expected pattern. The tertiary amine **40** and the primary amine **41** were less potent than the corresponding secondary amines **17** and **19**.[5,11] Replacement of *i*-Pr by *tert*-Bu retained potency (**44** and **24**), by 2-hydroxy-1,1-dimethylethyl slightly lowered potency (**42** and **19**), and by 3-dimethylaminopropyl virtually eliminated β-blocking activity altogether (**46** and **24**).[5]

A few compds, **17**, **30**, **31**, **35**, **40**, and **43**, caused a marked tachycardia, which tends to exaggerate the observed degree of β blockade.

Biological results on **17** and **19** in the dog have been reported by Marchetti, *et al.*[12] Compd **19** had activity similar to that of pronethalol, but **17** had very low activity.

Experimental Section

Methods A–M are representative for compds reported in the tables. Melting points and recrystg solvents given in the tables are usually not repeated in the text. Hydrogenations were carried out at room temp and atm pressure, unless stated otherwise.

A. 1-(1,4-Benzodioxan-6-yl)-2-(2-hydroxy-1,1-dimethylethylamino)ethanol (42). $NaBH_4$ (0.6 g, 0.016 mole) was added during 30 min to a stirred soln of **59**·H_2O (1.3 g, 0.006 mole) and 2-amino-2-methylpropanol (1.2 g, 0.014 mole) in MeOH (30 ml) at 0°. The mixt was stirred at 0° for 2 hr and then the solvent was evapd *in vacuo*. HCl (0.5 *N*, 100 ml) was added, and then the mixt was washed with Et_2O. NaOH (4 *N*, 20 ml) was added to the aq acidic soln and then the product **(42)** was isolated by Et_2O extn.

B. 1-(*N*-Benzylindol-3-yl)-2-isopropylaminoethanol (27). A soln of **68** (9.3 g, 0.029 mole) in THF (150 ml) was added during 30 min to a stirred suspension of $LiAlH_4$ (5 g, 0.13 mole) in THF (150 ml). The mixt was heated under reflux for 2 hr and then 200 ml of solvent was evapd. The mixt was cooled, and wet Et_2O (200 ml) was cautiously added, followed by NaOH (2 *N*, 20 ml). The mixt was shaken and filtered, and the filtrate was sepd. The Et_2O soln yielded **27**.

1-(Indol-3-yl)-2-isopropylaminoethanol (23). Na (0.1 g, 0.0043 g-atom) was added to a stirred soln of **27** (0.5 g, 0.0016 mole) in NH_3 (100 ml). After 25 min NH_4Cl (1.5 g) was added and the NH_3 was allowed to evap. The residual solid **23** was stirred with a little H_2O to remove inorg material and then crystd.

C. 1-(3,4-Dihydro-1,5-benzodioxepin-7-yl)-2-isopropylaminoethanol (20). $NaBH_4$ (0.75 g, 0.02 mole) was added during 30 min to a stirred soln of **61**·HCl (2 g, 0.007 mole) in MeOH (50 ml) at 0–10°. After 2 hr the MeOH was evapd under reduced pressure, HCl (1 *N*, 100 ml) was added, and the mixt was washed with Et_2O (100 ml). NaOH (10 *N*, 15 ml) was added to the aq acid layer, and the product **(20)** was isolated with Et_2O. Treatment with Et_2O–HCl gave **20**·HCl.

D. 2-Isopropylamino-1-(1-methyl-4-quinolon-3-yl)ethanol (29). $NaBH_4$ (1.5 g, 0.04 mole) was added during 1 hr to a stirred suspension of **71** (2 g, 0.0065 mole) in Me_2CO (16 g, 0.28 mole) and MeOH (40 ml) at 5–10°. After 16 hr the MeOH and excess of Me_2CO were evapd. **29** was isolated ($CHCl_3$) in the same way as **20** (method C) and converted to the oxalate salt.

D. 1-(Benzimidazol-2-on-5-yl)-2-isopropylaminoethanol (6). A soln of crude aminomethyl benzimidazol-2-on-5-yl ketone·HBr[13] (5 g) in H_2O (300 ml) and Me_2CO (80 ml) was hydrogenated in the presence of Pt_2O (1 g). The mixt was filtered, and the filtrate was evapd to dryness to give **6**·HBr.

1-(1,4-Benzodioxan-6-yl)-2-(1-methyl-3-phenylpropylamino)-ethanol (43). A soln of **41**·H_2O (2 g, 0.0095 mole) in 1-phenylbutan-3-one (2.25 g, 0.015 mole), EtOH (30 ml), and concd HCl (1 ml) was hydrogenated in the presence of Pt_2O (0.3 g). The mixt was filtered, and the filtrate was evapd to dryness. The residual gum was stirred with Et_2O and solid **43**·HCl sepd.

Ethyl *N*-*p*-Toluenesulfonylbenzomorpholine-2-carboxylate (74). Ethyl α,β-dibromopropionate (15 g, 0.0057 mole) was added to a stirred mixt of 2-*p*-toluenesulfonylaminophenol[14] (50 g, 0.19 mole), anhyd K_2CO_3 (25 g), and Me_2CO (700 ml) which was being heated under reflux. After 30 min, more K_2CO_3 (25 g) and more ester (15 g) were added. The procedure described in the last sentence was repeated twice more. After 16 hr heating the mixt was cooled and filtered, and the filtrate was evapd to remove Me_2CO. **74** remained as a solid.

***N*-*p*-Toluenesulfonylbenzomorpholine-2-carboxylic Acid (75).** A soln of **74** (90 g) in NaOH (10%, 135 ml) was heated at 100° for 16 hr, cooled, acidified with concd HCl, and then extd with Et_2O. The ext gave **75**: τ (TFA) 2.1–3.0 (multiplet, Ar **H**, 8), 5.3 (H_A = H at C_2), 5.6 (H_B = H at C_3), 6.25 (H_X = H at C_2) (ABX system, $OCH_2CH(CO_2H)N$, J_{AB} = 3, J_{AX} = 12, J_{BX} = 8 cps, 3), 7.54 (singlet, $ArCH_3$, 3).

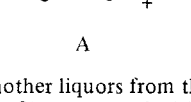
***N*-*p*-Toluenesulfonylbenzomorpholine-2-carbonyl Chloride (76).** **75** (15 g), $SOCl_2$ (150 ml), and $CHCl_3$ (450 ml) were heated under reflux for 16 hr. $CHCl_3$ and excess of $SOCl_2$ were evapd to leave **76** as a solid.

Diazomethyl *N*-*p*-Toluenesulfonylbenzomorpholin-3-yl Ketone (77). A slight excess of ethereal CH_2N_2 was added to a soln of **76** (13.5 g) in Et_2O (350 ml) and after 16 hr the Et_2O was evapd to leave **77** as a solid.

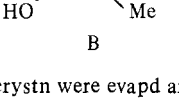
2-Isopropylamino-1-(*N*-*p*-toluenesulfonylbenzomorpholin-3-yl)ethanol (34). A soln of **77** (1 g) in Me_2CO (8 g) and EtOH (20 ml) was hydrogenated in the presence of Pt_2O (0.3 g). The mixt was filtered, and the filtrate was evapd to dryness. The residue was shaken with HCl (1 *N*, 200 ml) and Et_2O (50 ml). The acidic aq soln was made alk with NaOH (2 *N*) and then extd with Et_2O. The ext gave **34**.

Attempted Detosylation of 74. Small pieces of Na were added to a soln of **74** (3 g) in liq NH_3 until a blue color persisted for 3 min. Excess Na was destroyed with $AcONH_4$ and then the NH_3 was allowed to evap. H_2O was added, and the mixt was extd with EtOAc. The ext gave *o*-aminophenol, mp 174° (0.8 g, 89%).

2-*N*-Isopropylamino-1-(1,2,3,4-tetrahydroisoquinol-3-yl)-ethanol (31) and 4,4-Dimethyl-1-hydroxy-2,3,4,6,11,11α-hexahydro-1*H*-pyrimido[1,6-*b*]isoquinoline (80). A soln of 1-(isoquinol-3-yl)-2-nitroethanol **(79)**# (1 g) in HCl (2 *N*, 5 ml), H_2O (40 ml), and Me_2CO was hydrogenated at room temp and 100 atm pressure for 16 hr in the presence of Pd/C (5%, 1 g). The mixt was filtered, the filtrate was basified, and the org material (770 mg) was isolated with Et_2O. Fractional crystn from EtOAc gave **80**: mp 188–190°; τ (D_2O) 2.51 (singlet, Ar **H**, 4) 8.32 and 8.75 (singlets, CH_3, 3 each); m/e 232 ($C_{14}H_{20}N_2O$), 130 (C_9H_8N(A), 72.8%), 101 ($C_5H_{11}NO$ (B), 43.9%), 58, $Me_2C{=}NH_2^+$, 33.3%). *Anal.* ($C_{14}H_{20}N_2O$) C, H, N.



A



B

The mother liquors from the above crystn were evapd and the gum (in Et_2O) was treated with Et_2O–HCl. The hydrochloride was fractionally crystd to give **31** · 2HCl.

E. 2-Isopropylamino-1-(2-phenothiazinyl)ethanol (14). A soln of 2-chloro-1-(2-phenothiazinyl)ethanol[15] (5 g, 0.018 mole) and *i*-$PrNH_2$ (10 ml, 0.12 mole) in MeOH (250 ml) was heated under reflux for 66 hr and then the MeOH and excess *i*-$PrNH_2$ were evapd. The residue was dissolved in dil HCl, and the soln was washed with Et_2O. The aq acid soln was made alk and extd with Et_2O. The ext gave **14**.

1-(1,2-Dihydro-1-methyl-2-oxo-4-quinolyl)-2-isopropylaminoethanol (30). A soln of trimethyloxosulfonium iodide[7] (2.4 g, 0.011 mole) in DMSO (50 ml) was stirred under N_2 while a 50% mineral oil dispersion of NaH (0.52 g, 0.011 mole) was added in small portions. The mixt was stirred under N_2 at 50–60° for 30 min and then a soln of 1,2-dihydro-1-methyl-2-oxoquinoline-4-carbaldehyde[16] (1.87 g, 0.01 mole) in DMSO (30 ml) was added. The mixt was stirred at 50–60° for 2 hr, cooled, dild with H_2O (200 ml), and extd with $CHCl_3$. The ext gave the intermediate oxirane as a gum. This was dissolved in EtOH (80 ml) and *i*-$PrNH_2$ (8 ml), and the mixt was refluxed for 3 hr. EtOH and excess *i*-$PrNH_2$ were evapd and then **30** was isolated in the same way as **14**.

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2-(α,β-Diacetoxyvinyl)quinoxaline (83) and 2-Acetoxyacetylquinoxaline (82). A suspension of 2-(D-*arabino*-tetrahydroxybutylquinoxaline[8] (15 g) in dry C_5H_5N (40 ml) was added to a soln of Na (3 g) in MeOH (40 ml), and the mixt was heated under reflux for 2 hr. The solid which sepd after 4 hr at 0° was isolated and dissolved in H_2O (100 ml), and the soln was acidified with H_2SO_4 (6 *N*, 20 ml). The red solid (**84**) which sepd was isolated and dried. A soln of this solid (5.9 g) in C_5H_5N (18 ml) and Ac_2O (18 ml) was kept at room temp for 18 hr, poured into H_2O (200 ml), and extd 5 times with Et_2O (100 ml each time). The combined Et_2O exts were washed successively with HCl (1 *N*, 100 ml), satd $NaHCO_3$ soln (100 ml), and then H_2O (100 ml). The ext gave **83**, mp 117°, and **82**, mp 113–114°, by fractional crystn from petr ether, bp 60–80°: **83**, nmr τ ($CDCl_3$) 1.10 (singlet, N=CCH=N, 1), 1.54 (singlet, C(OAc)=CHOAc, 1), 1.7–2.5 (multiplet, Ar **H**, 4), 7.57 and 7.73 (singlets, C(OCOCH$_3$)=CHOCOCH$_3$, 3 and 3); *Anal.* ($C_{14}H_{12}N_2O_4$) C, H, N; **82**, nmr τ ($CDCl_3$), 0.50 (singlet, N=CCH=N, 1), 1.65–2.25 (multiplet, Ar **H**, 4), 4.25 (singlet, $COCH_2OAc$, 2), 7.62 (singlet, $OCOCH_3$, 3); *Anal.* ($C_{12}H_{10}N_2O_3$) C, H, N.

2-Isopropylamino-1-(2-quinoxalyl)ethanol (32). *i*-$PrNH_2$ (10 ml, 0.12 mole) was added during 10 min to a stirred soln of **82** (0.5 g, 0.0022 mole) in EtOH (30 ml) at 0°; 5 min later a soln of $NaBH_4$ (1 g, 0.027 mole) in EtOH (10 ml) was added. After 1 hr glac AcOH (15 ml) was added slowly, followed by H_2O (100 ml) and HCl (6 *N*, 5 ml). The EtOH was evapd, and the residual aq soln was washed 3 times with Et_2O. The aq soln was made alk with NaOH (6 *N*, 20 ml) and extd with Et_2O. The ext gave **32**. In a similar way (MeOH soln) **32** was obtd from **83**.

F. Quinolin-6-ylglyoxal Hydrate (48). Methyl 6-quinolyl ketone[17] (3.4 g, 0.02 mole), SeO_2 (2.26 g, 0.02 mole), and AcOH (80%, v/v, 20 ml) were heated at 90° for 4 hr. The mixt was filtered and the filtrate was evapd to dryness. The residual gum was stirred with $NaHCO_3$ (2%, 100 ml), and the solid **48** which sepd was isolated.

G. 1,4-Benzodioxan-6-ylglyoxal Hydrate (59). A soln of **60** (10 g) in DMSO (80 ml) was kept at room temp for 3 days and then poured onto ice; **59** was isolated by Et_2O extn.

H. *N*-Isopropyl-1-benzylindole-3-ylglyoxylamide (68). A soln of 1-benzylindole (26 g, 0.125 mole) in Et_2O (200 ml) was added during 1 hr to a stirred soln of $(COCl)_2$ (9 ml, 0.105 mole) in Et_2O (100 ml) at 5°. After 30 min a soln of *i*-$PrNH_2$ (31 ml, 0.37 mole) in Et_2O (200 ml) was added. After 16 hr the mixt was filtered, the solid was stirred with NaOH (4 *N*, 100 ml) and then filtered. The solid **68** was recrystd.

3,4-Dihydro-1,5-benzodioxepin-7-yl Methyl Ketone (63). A soln of 3,4-dihydro-1,5-benzodioxepine[18] (20 g, 0.133 mole) and AcCl (11 g, 0.14 mole) in CS_2 (60 g) was added during 1 hr to a stirred mixt of $AlCl_3$ (26 g, 0.2 mole) and CS_2 (80 g) at 10–15°. After 2 days the mixt was poured onto ice. The CS_2 phase was sepd, and the aq phase was extd with Et_2O. The combined CS_2–Et_2O solns were washed with NaOH (2 *N*, 50 ml), dried ($MgSO_4$), and distd to give **63**, bp 120° (0.5 mm).

I. Bromomethyl 3,4-Dihydro-1,5-benzodioxepin-7-yl Ketone (62). Br_2 (9.6 g, 0.06 mole) was added during 30 min to a stirred soln of **63** (11.4 g, 0.06 mole) in CS_2 (135 ml) at 0°. After 2 hr the CS_2 was evapd and the residual **62** recrystd.

J. 3,4-Dihydro-1,5-benzodioxepin-7-yl Isopropylaminomethyl Ketone (61). *i*-$PrNH_2$ (4 g, 0.068 mole) was added to a soln of **62** (7.6 g, 0.028 mole) in Et_2O (200 ml) at 0°. After 2 hr the mixt was filtered, and the filtrate was evapd. HCl (1 *N*, 100 ml) was added, and the mixt was washed with Et_2O (100 ml). NaOH (8 *N*, 20 ml) was added to the aq acid soln. The product (**61**) was isolated by Et_2O extn and converted to **61** · HCl with Et_2O–HCl.

K. Aminomethyl 1,4-Benzodioxan-6-yl Ketone (58). A soln of hexamine (6 g, 0.043 mole) in $CHCl_3$ (100 ml) was added to a soln of **60** (10 g, 0.039 mole) in $CHCl_3$ (100 ml), and the mixt was shaken for 30 min. The hexaminium salt was isolated and shaken with EtOH (250 ml) and concd HCl (15 ml) at room temp for 3 days; **58** · HCl sepd as a solid.

L. 1-Methylquinol-4-on-6-yl Methyl Ketone (49). 4-Hydroxyquinol-6-yl methyl ketone (30 g), aq NaOH (40% w/v, 100 ml), and H_2O (400 ml) were stirred vigorously while Me_2SO_4 (40 ml) was added. The mixt was stirred for 2 hr and then extd with $CHCl_3$ (4 times, 100 ml each time). The ext was washed with H_2O, dried ($MgSO_4$), and then evapd to give **49**.

M. 1-Allylquinol-4-on-6-yl Methyl Ketone (51). 4-Hydroxyquinol-6-yl methyl ketone[19] (5.4 g, 0.029 mole) was dissolved in a soln of Na (0.7 g, 0.03 g-atom) in EtOH (50 ml) and then allyl bromide (6.3 g, 0.052 mole) was added. The soln was heated under reflux for 16 hr and then evapd to dryness. The residue was extd with C_6H_5Cl. Petr ether (bp 40–60°) was added to the ext to ppt **51**, which was then recrystd from H_2O.

1-(1,3-Benzodioxol-2-yl)-2-bromoethanol. A soln of 1,3-benzodioxol-2-carbonyl chloride[20] (5 g) in Et_2O (50 ml) was added to a soln of CH_2N_2 (6.5 g) in Et_2O (180 ml) at −10°, and then the soln was allowed to warm to room temp. After 64 hr the solvent was evapd to give crude 1,3-benzodioxol-2-yl diazomethyl ketone which was dissolved in Et_2O (100 ml), cooled to −5°, and treated with aq HBr (S.G. 1.46, 5 ml). The mixt was stirred for 1 hr and then evapd to dryness under reduced pressure to give crude 1,3-benzodioxol-2-yl bromomethyl ketone. This (2.2 g) was dissolved in EtOH (15 ml), cooled to 0°, and then $NaBH_4$ (0.5 g) was added during 30 min. After 2 hr the mixt was added to ice (50 g) and HCl (11 *N*, 5 ml). Extn with EtOAc gave crude 1-(1,3-benzodioxol-2-yl)-2-bromoethanol.

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