

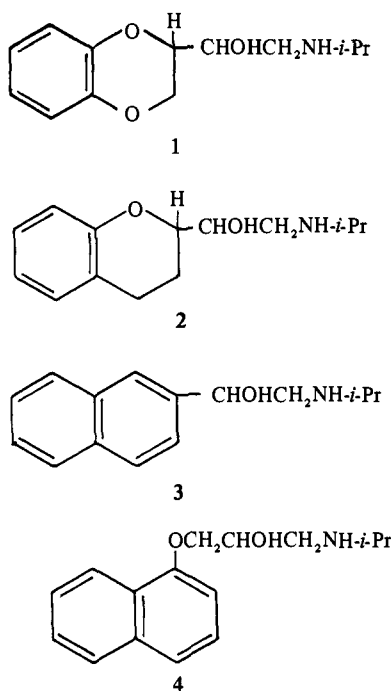
## β-Adrenergic Blocking Agents. 11. Heterocyclic Analogs of Pronethalol [2-Isopropylamino-1-(2-naphthyl)ethanol]

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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.

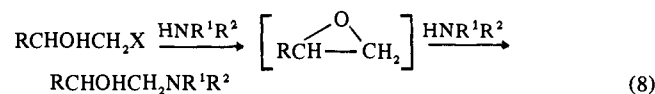
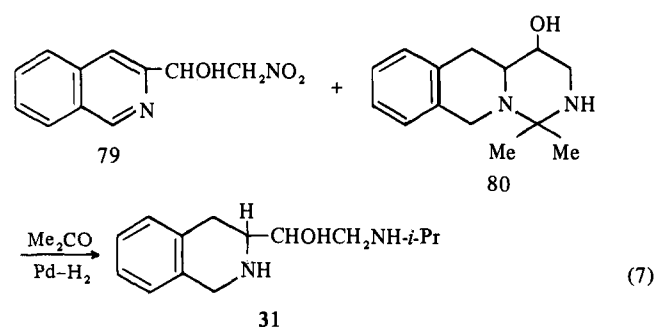
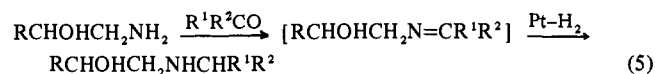
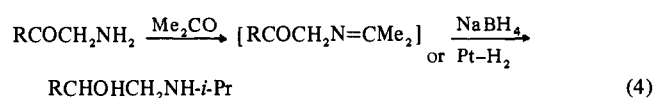
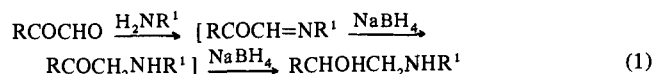
We have previously reported<sup>1</sup> the synthesis and β-adrenergic blocking potencies of a series of 1-(1,4-benzodioxan-2-yl)- (1) and 1-(chroman-2-yl)-2-aminoethanols (2) which contain features of both pronethalol (3)† and propranolol (4)‡. In this paper we report the synthesis and properties of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



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<sub>4</sub>) amination of a glyoxal.<sup>5</sup> 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).<sup>6</sup> The indole analog 23 was obtained by removal (Na-NH<sub>3</sub>) of the benzyl group from the indole N of 27. Several compounds were made by reduction (NaBH<sub>4</sub>) of an intermediate amino ketone (C, eq 3).<sup>5</sup> Compds 6 and 29 were prepared by reductive alkylation of an amino ketone with Me<sub>2</sub>CO and NaBH<sub>4</sub> or Pt-H<sub>2</sub> (D, eq 4).<sup>5</sup> Related routes gave 43 by reductive (Pt-H<sub>2</sub>) alkylation of an amino alcohol with a ketone (eq 5) and 34

### Scheme I

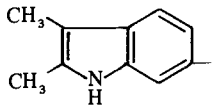
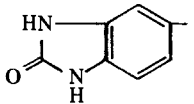
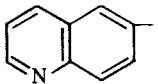
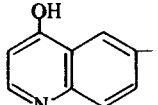
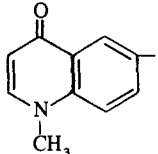
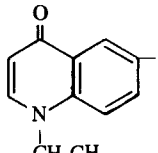
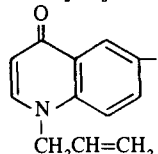
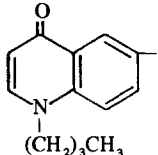


by reductive (Pd-H<sub>2</sub>) alkylation of a diazo ketone with Me<sub>2</sub>CO (eq 6).<sup>5</sup> Reductive (Pd-H<sub>2</sub>) alkylation of the nitro alcohol 79 with Me<sub>2</sub>CO gave 31 and 80; partial saturation of the isoquinoline and addition of the NH thus formed to the azomethine intermediate 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.<sup>5</sup> For 30 an intermediate oxirane 81, prepared by the action of dimethylloxosulfonium methylide on an aldehyde,<sup>7</sup> 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<sub>2</sub> and then NaBH<sub>4</sub>.<sup>3</sup> 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.<sup>8</sup>

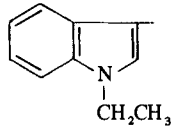
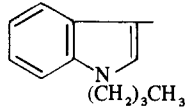
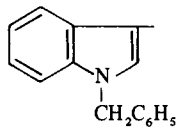
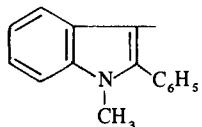
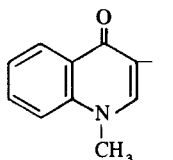
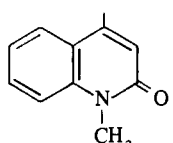
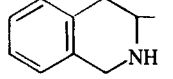
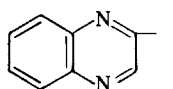
† Alderlin.  
‡ Inderal.

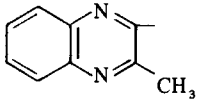
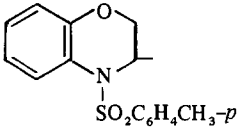
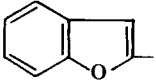
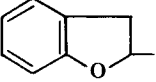
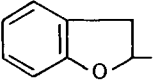
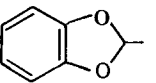
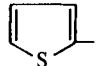
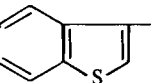
**Table I.** RCHOHCH<sub>2</sub>NH-*l*-Pr

Compound	R	Methods <sup>a</sup>	Form	Crystn solvent <sup>b</sup>	Mp, °C	Formula	Analyses	Infusion rate, μg/kg per min	% change in heart rate	% inhibition of tachycardia
5		A <sup>c</sup>	Base	P(100)	157-158	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O	C, H	100	-10	20
6		D <sup>d</sup> (Pt-H <sub>2</sub> )	HBr	H <sub>2</sub> O + Me <sub>2</sub> CO	210	C <sub>12</sub> H <sub>18</sub> BrN <sub>3</sub> O <sub>2</sub>	C, H; N <sup>e</sup>	100	-10	35
7		A	Dipicrate	BuOH	235-236	C <sub>26</sub> H <sub>24</sub> N <sub>8</sub> O <sub>15</sub>	N	100 <sup>f</sup>	-10	43
8		A <sup>g</sup>	Oxalate	MeOH-EtOAc	200-202	C <sub>16</sub> H <sub>20</sub> N <sub>2</sub> O <sub>6</sub> · 1.5H <sub>2</sub> O	C, H, N	50	-12	53
9		A <sup>h</sup>	Tartrate	MeOH-EtOAc	200	C <sub>19</sub> H <sub>26</sub> N <sub>2</sub> O <sub>8</sub> · H <sub>2</sub> O	H, N; C <sup>i</sup>	25	-4	82
10		A <sup>j</sup>	Tartrate	MeOH-EtOAc	164	C <sub>20</sub> H <sub>28</sub> N <sub>2</sub> O <sub>8</sub> · 0.5H <sub>2</sub> O	C, H, N	100	-18	90
11		A <sup>k</sup>	Tartrate	EtOH-EtOAc	126	C <sub>21</sub> H <sub>28</sub> N <sub>2</sub> O <sub>8</sub> · 0.5H <sub>2</sub> O	C, H, N	100	-16	80
12		A <sup>l</sup>	Tartrate	EtOH-EtOAc	123 dec	C <sub>22</sub> H <sub>32</sub> N <sub>2</sub> O <sub>8</sub> · 0.5H <sub>2</sub> O	C, H, N	200	-29	58

13		A <sup>m</sup>	Oxalate	MeOH-EtOAc	189 dec	C <sub>17</sub> H <sub>22</sub> N <sub>2</sub> O <sub>6</sub> · H <sub>2</sub> O	C, H, N	500	0	12
14		E	Base	EtOAc	144-145	C <sub>17</sub> H <sub>20</sub> N <sub>2</sub> OS	C, H, N, S	400	-21	Nil
15		A <sup>n</sup>	Base	EtOAc	108	C <sub>13</sub> H <sub>19</sub> NO <sub>2</sub>	C, H, N	100	-23	69
16		A <sup>o</sup>	Oxalate	Et <sub>2</sub> O	188-190	C <sub>30</sub> H <sub>44</sub> N <sub>2</sub> O <sub>8</sub>	H, N; CP	100	+5	19
17		C	Base	EtOAc	93-94	C <sub>12</sub> H <sub>17</sub> NO <sub>3</sub>	C, H, N	25	+34	80
18		A <sup>q</sup>	Base	EtOAc	105-106	C <sub>14</sub> H <sub>21</sub> NO <sub>2</sub>	C, H, N	100	-18	71
19		C	HCl	MeOH + Et <sub>2</sub> O	184-185	C <sub>13</sub> H <sub>20</sub> ClNO <sub>3</sub>	C, H, Cl, N	25	-3	45
20		C	HCl	MeOH + EtOAc	163-164	C <sub>14</sub> H <sub>22</sub> ClNO <sub>3</sub>	C, H, Cl, N	100	-14	54
21		A <sup>r</sup>	Oxalate	EtOH	251	C <sub>36</sub> H <sub>40</sub> N <sub>2</sub> O <sub>8</sub>	C, H	100	-13	44
22		B <sup>s</sup>	Base	C <sub>6</sub> H <sub>6</sub>	126-127	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O	C, H, N	400	-32	Nil
23		See Exptl	Base	P(80)	134-136	C <sub>13</sub> H <sub>18</sub> N <sub>2</sub> O	C, H, N	50	0	35
24		B <sup>t</sup>	Base	EtOAc	114-115	C <sub>14</sub> H <sub>20</sub> N <sub>2</sub> O	C, H, N	100	+2	70

Table I (Continued)

Compound	R	Methods <sup>a</sup>	Form	Crystn solvent <sup>b</sup>	Mp, °C	Formula	Analyses	Infusion rate, $\mu\text{g}/\text{kg}$ per min	% change in heart rate	% inhibition of tachycardia
25		B	Base	EtOAc	125-126	$\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}$	C, H, N	50	-6	38
26		B	Base	P(80)	66-68	$\text{C}_{17}\text{H}_{26}\text{N}_2\text{O}$	C, H, N	100 400	-18 -22	Nil 11
27		B	Base	EtOAc	120	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$	C, H, N	100	-14	Nil
28		B	Base	P(80)	110	$\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$	C, H, N	200	-14	Nil
29		D $\text{NaBH}_4$	Oxalate	MeOH-EtOAc	176-178	$\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_6 \cdot \text{H}_2\text{O}$	N; C, H <sup>u</sup>	100 500	+2 -15	Nil 16
30		See Exptl	Base	EtOAc	152-154	$\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_2$	C, H, N	50	+24	68
31		See Exptl	Di-HCl	MeOH + EtOAc	272-274	$\text{C}_{14}\text{H}_{24}\text{Cl}_2\text{N}_2\text{O}$	C, H, Cl, N	100	+22	50
32		See Exptl	Base	P(60)	98-99	$\text{C}_{13}\text{H}_{17}\text{N}_3\text{O}$	C, H, N	50	0	93

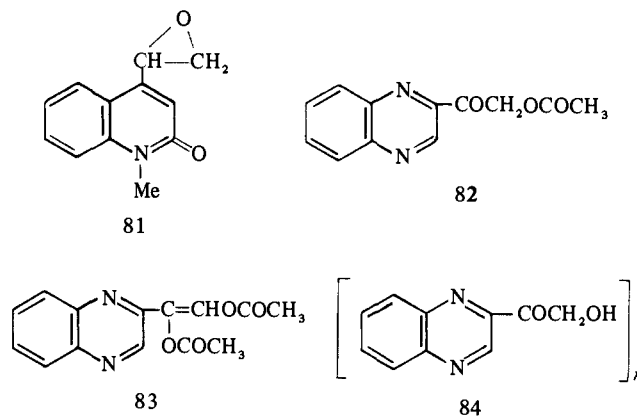
33		E <sup>v</sup>	Base	EtOAc + P(40)	89-90	C <sub>14</sub> H <sub>19</sub> N <sub>3</sub> O	C, H, N	100	+7	33
34		See Exptl	Base	EtOAc + P(40)	150-151	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>4</sub> S	C, H, N, S	50 200	+7 +22	Nil 17
35		A <sup>w</sup>	Base	P(80)	108-109	C <sub>13</sub> H <sub>17</sub> NO <sub>2</sub>	C, H, N	5	+23	80
36A		E <sup>x</sup>	Base	P(60)	116-118	C <sub>13</sub> H <sub>19</sub> NO <sub>2</sub>	C, H, N	10	-1	80
36B		E <sup>x</sup>	Base	P(40)	85-86		y	10	+12	90
37		E <sup>z</sup>	Base	C <sub>6</sub> H <sub>6</sub>	110	C <sub>12</sub> H <sub>17</sub> NO <sub>3</sub>	C, H, N	10	0	63
38		E <sup>aa</sup>	Oxalate	EtOH-EtOAc	198-199	C <sub>20</sub> H <sub>32</sub> N <sub>2</sub> O <sub>6</sub> S <sub>2</sub>	C, N, S; H <sup>bb</sup>	200	-8	16
39		A	Base	EtOH-EtOAc	193-194	C <sub>13</sub> H <sub>18</sub> ClNOS	C, H, N	50	+7	42

<sup>a</sup>Methods refer to Experimental Section. <sup>b</sup>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°. <sup>c</sup>Crude 2,3-dimethylindol-6-ylglyoxal obt'd 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. <sup>d</sup>Crude aminomethyl benzimidazol-2-on-5-yl ketone hydrobromide was obt'd by method J from bromomethyl benzimidazol-2-on-5-yl ketone.<sup>13</sup> <sup>e</sup>N: calcd, 13.3; found, 12.7. <sup>f</sup>Administered as free base. <sup>g</sup>Crude 4-hydroxyquinolin-6-ylglyoxal hydrate obt'd by method F (AcOH) from 4-hydroxyquinolin-6-yl methyl ketone.<sup>19</sup> <sup>h</sup>Crude 1-methyl-4-quinolon-6-ylglyoxal hydrate obt'd by method F (AcOH) from 49. <sup>i</sup>C: calcd, 53.3; found, 52.8. <sup>j</sup>Crude 1-ethyl-4-quinolon-6-ylglyoxal hydrate obt'd by method F (AcOH) from 50. <sup>k</sup>Crude 1-allyl-4-quinolon-6-ylglyoxal hydrate obt'd by method F (AcOH) from 51. <sup>l</sup>Crude 1-*n*-butyl-4-quinolon-6-ylglyoxal hydrate obt'd by method F (AcOH) from 52. <sup>m</sup>Crude 1-methyl-4-quinolon-7-ylglyoxal hydrate obt'd by method F (AcOH) from 53. <sup>n</sup>Crude 2,3-dihydrobenzofuran-5-ylglyoxal obt'd by method F (dioxane) from 2,3-dihydrobenzofuran-5-yl methyl ketone [G. Baddeley and M. A. Vickars, *J. Chem. Soc.*, 4665 (1958)]. <sup>o</sup>Crude 2-methyl-2,3-dihydrobenzofuran-5-ylglyoxal obt'd 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. <sup>p</sup>C: calcd, 64.3; found, 63.8. <sup>q</sup>Crude chroman-6-ylglyoxal obt'd by method F (dioxane) from chroman-6-yl methyl ketone [G. Chatelus, *Ann. Chim. (Paris)*, 4, 505 (1949)]. <sup>r</sup>Crude dibenzofuran-2-ylglyoxal obt'd by method F (dioxane) from dibenzofuran-2-yl methyl ketone [P. Galewski, *Justus Liebigs Ann. Chem.*, 264, 187 (1891)]. <sup>s</sup>Crude *N*-isopropyl-1,3-dimethylindol-2-ylglyoxyamide obt'd by method H from 1,3-dimethylindole [J. Meisenheimer, L. Angermann, O. Finn, and E. Vieweg, *Ber.*, 57, 1744 (1924)]. <sup>t</sup>Crude *N*-isopropyl-1-methylindol-2-ylglyoxyamide obt'd 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). <sup>u</sup>C: calcd, 55.4; found, 54.7. H: calcd, 6.5; found, 6.0. <sup>v</sup>2-Bromo-1-(3-methylquinoxalin-2-yl)ethanol obt'd by NaBH<sub>4</sub> reduction of 73 was not characterized. <sup>w</sup>Benzofuran-2-ylglyoxal [S. Fatutta, *Gazz. Chim. Ital.*, 89, 1598 (1959)]. <sup>x</sup>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)]. <sup>y</sup>No anal.  $\tau$  (CDCl<sub>3</sub>), 2.6-3.3 (multiplet, Ar H, 4), 5.35 (multiplet, H at C<sub>2</sub>, 1), 6.25 (multiplet, CH(OH), 1), 6.75 (doublet, H's at C<sub>3</sub>, 2), 7.0-7.5 (multiplet, CH<sub>2</sub>NHCH<, 3), 7.54 (singlet, OH and NH, 2), 8.9 (doublet, CH(CH<sub>3</sub>)<sub>2</sub>, 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<sub>2</sub> and CH(OH) differed for 36A and 36B, but no stereochem assignments were possible. <sup>z</sup>1,3-Benzodioxole-2-carbonyl chloride<sup>20</sup> 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<sub>4</sub> to give crude 2-bromo-1-(1,3-benzodioxol-2-yl)ethanol (see Experimental Section). <sup>aa</sup>Crude 2-bromo-1-(2-thienyl)ethanol was obt'd by NaBH<sub>4</sub> reduction (as in footnote *z*) of bromomethyl 2-thienyl ketone [H. Brunswig, *Ber.*, 19, 2890 (1886)]. <sup>bb</sup>H: calcd, 7.0; found, 7.5.

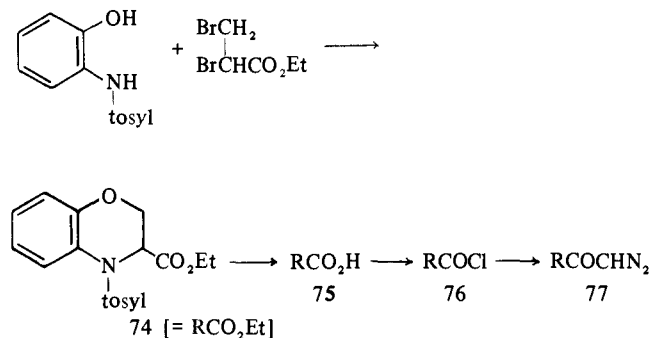
Table II. RCHOHCH<sub>2</sub>NR<sup>1</sup>R<sup>2</sup>

Compound	R	R <sup>1</sup>	R <sup>2</sup>	Method <sup>a</sup>	Form	Crystn solvent <sup>b</sup>	Mp, °C	Formula	Analyses	Infusion rate, μg/kg per min	% change in heart rate	% inhibition of tachycardia
40	As 17	CH <sub>3</sub>	CH(CH <sub>3</sub> ) <sub>2</sub>	C	HCl	MeOH + EtOAc	198-199	C <sub>13</sub> H <sub>20</sub> ClNO <sub>3</sub>	C, H, Cl, N	100	+21	68
41	As 19	H	H	C	Base hydrate	EtOAc	82-83	C <sub>10</sub> H <sub>13</sub> NO <sub>3</sub> · H <sub>2</sub> O	C, H, N	250	-12	25
42	As 19	H	C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> OH	A	Base	EtOAc	101-102	C <sub>14</sub> H <sub>21</sub> NO <sub>4</sub>	C, H, N	100	+8	85
43	As 19	H	CH(CH <sub>3</sub> ) <sub>2</sub> (CH <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	See Exptl	HCl	MeOH + EtOAc	158-159	C <sub>20</sub> H <sub>26</sub> ClNO <sub>3</sub>	H, Cl, N; C <sup>c</sup>	100	+22	94
44	As 24	H	C(CH <sub>3</sub> ) <sub>3</sub>	B	Base	EtOAc	124-126	C <sub>15</sub> H <sub>22</sub> N <sub>2</sub> O	H, N; C <sup>d</sup>	100	-2	85
45	As 24	H	C(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub> OH	B <sup>e</sup>	Picrate	Me <sub>2</sub> CO	146	C <sub>21</sub> H <sub>25</sub> N <sub>3</sub> O <sub>9</sub>	C, H, N	10 <sup>f</sup>	+14	55
46	As 24	H	(CH <sub>2</sub> ) <sub>3</sub> N(CH <sub>3</sub> ) <sub>2</sub>	B	Oxalate	EtOH + H <sub>2</sub> O	128-130dec	C <sub>20</sub> H <sub>29</sub> N <sub>3</sub> O <sub>9</sub>	C, H, N	250	-14	8
47	As 27	CH <sub>2</sub> CH <sub>3</sub>	CH <sub>2</sub> CH <sub>3</sub>	B	Base	P(40)	62-64	C <sub>21</sub> H <sub>26</sub> N <sub>2</sub> O	C, H, N	10 <sup>g</sup>	Not active	

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



Other intermediates which were characterized are given in Table III. The intermediate glyoxals were prepared by oxidation of a methyl ketone with SeO<sub>2</sub> in the solvent specified (method F) or by treatment of a bromomethyl ketone with DMSO (method G).<sup>5</sup> The glyoxylamide intermediates 64-70 were prepared by the action of (COCl)<sub>2</sub> on the appropriate indole, followed by treatment with an amine (method H).<sup>6</sup> 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).<sup>5</sup> 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



The orientation of the acid 75 is based on nmr evidence. Had the CO<sub>2</sub>H been at C<sub>2</sub>, then the H at C<sub>2</sub> signal (H<sub>B</sub> of an ABX system) would have been expected at lower field than H<sub>A</sub> and H<sub>X</sub>. Attempts to detosylate the ester 74 with H<sub>2</sub>SO<sub>4</sub> failed; water-soluble derivatives were formed, presumably by sulfonation. With Na in NH<sub>3</sub>,<sup>9</sup> the ester was degraded to *o*-aminophenol in good yield.

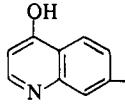
One comp'd, 86, in which C-1 of an ethanolamine side chain attached to benzene forms part of the heterocyclic system, was prepared by treating *N*-methylisatin with dimethylxosulfonium methylide<sup>7</sup> to give the oxirane 85 which with *i*-PrNH<sub>2</sub> gave 86.

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

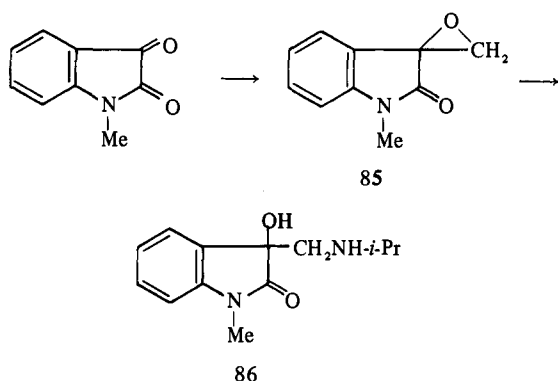
**Biological Results.** The results of the biological screening tests<sup>8</sup> are given in Tables I and II. β-Adrenergic blocking potency was determined in the usual way.

<sup>8</sup>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

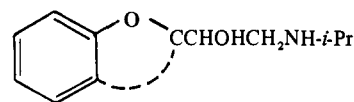
Compound	R	X	Method <sup>a</sup>	Crystn solvent <sup>b</sup>	Mp, °C	Formula	Analyses
48	As 7	CHO	F(AcOH) <sup>c</sup>	H <sub>2</sub> O	145	C <sub>11</sub> H <sub>7</sub> NO <sub>2</sub> · H <sub>2</sub> O	N
49	As 9	CH <sub>3</sub>	L <sup>d</sup>	PhCl	184	C <sub>13</sub> H <sub>11</sub> NO <sub>2</sub>	N
50	As 10	CH <sub>3</sub>	L <sup>d</sup>	BuOH	156–158	C <sub>13</sub> H <sub>13</sub> NO <sub>2</sub>	N
51	As 11	CH <sub>3</sub>	M <sup>d</sup>	H <sub>2</sub> O	166	C <sub>14</sub> H <sub>13</sub> NO <sub>2</sub> · 0.25H <sub>2</sub> O	C, H, N
52	As 12	CH <sub>3</sub>	M <sup>d</sup>	CCl <sub>4</sub>	126–128	C <sub>15</sub> H <sub>17</sub> NO <sub>2</sub>	H, N; C <sup>e</sup>
53	As 13	CH <sub>3</sub>	L <sup>f</sup>	PhCl	178	C <sub>12</sub> H <sub>11</sub> NO <sub>2</sub>	C, H, N
54		CH <sub>3</sub>	g	DMF	280	C <sub>11</sub> H <sub>9</sub> NO <sub>2</sub>	C, H, N
55	As 17	CH <sub>2</sub> NH- <i>i</i> -Pr · HCl	J <sup>h</sup>	MeOH + EtOAc	227–228	C <sub>12</sub> H <sub>16</sub> ClNO <sub>3</sub>	C, H, Cl, N
56	As 17	CH <sub>2</sub> NMe- <i>i</i> -Pr · HCl	J <sup>h</sup>	MeOH + EtOAc	180–181	C <sub>13</sub> H <sub>18</sub> ClNO <sub>3</sub>	C, H, Cl, N
57	As 19	CH <sub>2</sub> NH- <i>i</i> -Pr · HCl	J <sup>i</sup>	EtOH–Et <sub>2</sub> O	204–205	C <sub>13</sub> H <sub>18</sub> ClNO <sub>3</sub>	C, H, N
58	As 19	CH <sub>2</sub> NH <sub>2</sub> · HCl	K <sup>i</sup>	EtOH–H <sub>2</sub> O	248	C <sub>10</sub> H <sub>12</sub> ClNO <sub>3</sub>	C, H, Cl, N
59	As 19	CHO	G <sup>i</sup>	H <sub>2</sub> O	99–103 dec	C <sub>10</sub> H <sub>8</sub> O <sub>4</sub> · H <sub>2</sub> O	C, H
60	As 19	CH <sub>2</sub> Br	I(CS <sub>2</sub> ) <sup>j</sup>	C <sub>6</sub> H <sub>6</sub>	119–120	C <sub>10</sub> H <sub>9</sub> BrO <sub>3</sub>	C, H, Br
61	As 20	CH <sub>2</sub> NH- <i>i</i> -Pr · HCl	J	EtOH + Et <sub>2</sub> O	204–205	C <sub>14</sub> H <sub>20</sub> ClNO <sub>3</sub>	C, H, Cl, N
62	As 20	CH <sub>2</sub> Br	I(CS <sub>2</sub> )	C <sub>6</sub> H <sub>6</sub> + P(40)	75–76	C <sub>11</sub> H <sub>9</sub> BrO <sub>3</sub>	C, H, Br
63	As 20	CH <sub>3</sub>	See Exptl		120 (0.5 mm)	C <sub>11</sub> H <sub>12</sub> O <sub>3</sub>	C, H
64	As 24	CONH- <i>tert</i> -Bu	H <sup>k</sup>	EtOH	143	C <sub>15</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	C, H; N <sup>l</sup>
65	As 24	CONH(CH <sub>2</sub> ) <sub>3</sub> NMe <sub>2</sub>	H <sup>k</sup>	Cyclohexane	83	C <sub>16</sub> H <sub>21</sub> N <sub>3</sub> O <sub>2</sub>	C, H, N
66	As 25	CONH- <i>i</i> -Pr	H <sup>m</sup>	P(80)	96	C <sub>14</sub> H <sub>18</sub> N <sub>2</sub> O <sub>2</sub>	H, N; C <sup>n</sup>
67	As 26	CONH- <i>i</i> -Pr	H <sup>o</sup>	EtOH	196–198	C <sub>17</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N
68	As 27	CONH- <i>i</i> -Pr	H <sup>p</sup>	P(100)	132–134	C <sub>20</sub> H <sub>26</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N
69	As 27	CONEt <sub>2</sub>	H <sup>p</sup>	P(100)	93	C <sub>21</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N
70	As 28	CONH- <i>i</i> -Pr	H <sup>q</sup>	EtOH	181–183	C <sub>20</sub> H <sub>20</sub> N <sub>2</sub> O <sub>2</sub>	C, H, N
71	As 29	CH <sub>2</sub> NH <sub>2</sub> <sup>+</sup> HBr	K <sup>r</sup>	EtOH + H <sub>2</sub> O	284	C <sub>12</sub> H <sub>13</sub> BrN <sub>2</sub> O <sub>2</sub> · 0.5H <sub>2</sub> O	C, H, Br, N
72	As 32	CH <sub>2</sub> Br	I (48% HBr) <sup>s</sup>	MeOH + H <sub>2</sub> O	116–117	C <sub>10</sub> H <sub>9</sub> BrN <sub>2</sub> O	C, H, N
73	As 33	CH <sub>2</sub> Br	I(HBr) <sup>t</sup>	MeOH + H <sub>2</sub> O	107	C <sub>11</sub> H <sub>9</sub> BrN <sub>2</sub> O	C, H, N; Br <sup>u</sup>
74	As 34	OEt	See Exptl	MeOH	135–136	C <sub>18</sub> H <sub>19</sub> NO <sub>3</sub> S	C, H, N, S
75	As 34	OH	See Exptl	MeOH + EtOAc	181–182	C <sub>16</sub> H <sub>15</sub> NO <sub>3</sub> S	C, H, N, S
76	As 34	Cl	See Exptl	P(60)	103–104	C <sub>16</sub> H <sub>14</sub> ClNO <sub>4</sub> S	C, H, Cl, N, S
77	As 34	CHN <sub>2</sub>	See Exptl	Et <sub>2</sub> O	132–134	C <sub>17</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S	C, H, N, S
78	As 39	CHO	F (dioxane) <sup>v</sup>	Moist CHCl <sub>3</sub>	128–130	C <sub>10</sub> H <sub>8</sub> O <sub>2</sub> S · H <sub>2</sub> O	C, H

<sup>a</sup>Methods refer to the Experimental Section. <sup>b</sup>P(40) etc. see footnote b of Table I. <sup>c</sup>Quinolin-6-yl methyl ketone [S. G. Waley, *J. Chem. Soc.*, 2008 (1948)]. <sup>d</sup>4-Hydroxyquinolin-6-yl methyl ketone (footnote g, Table I). <sup>e</sup>C: calcd, 74.0; found, 73.4. <sup>f</sup>Prepd from 54. <sup>g</sup>Prepd from 3-aminoacetophenone by the method of Riegel, *et al.*, ref 19. <sup>h</sup>Bromomethyl 3,4-methylenedioxyphenyl ketone [N. L. Drake and W. B. Tuemmler, *J. Amer. Chem. Soc.*, 77, 1204 (1955)]. <sup>i</sup>Prepd from compound 60. <sup>j</sup>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)]. <sup>k</sup>1-Methylindole [K. T. Potts and J. E. Saxton, *Org. Syn.*, 40, 68 (1960)]. <sup>l</sup>N: calcd, 10.9; found, 10.4. <sup>m</sup>1-Ethylindole [A. Michaelis, *Ber.*, 30, 2809 (1897)]. <sup>n</sup>C: calcd, 69.8; found, 69.3. <sup>o</sup>1-*n*-Butylindole [J. v. Braun and O. Bayer, *Ber.*, 58, 387 (1925)]. <sup>p</sup>1-Benzylindole [H. Plieninger, *ibid.*, 87, 127 (1954)]. <sup>q</sup>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)]. <sup>r</sup>Crude bromomethyl 1-methylquinol-4-on-3-yl ketone was obt'd 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)]. <sup>s</sup>Methyl quinoxalin-2-yl ketone [G. Henseke and K. J. Böhner, *Ber.*, 91, 1605 (1958)]. <sup>t</sup>Methyl 3-methylquinoxalin-2-yl ketone [F. Sachs and A. Röhmer, *ibid.*, 35, 3307 (1902)]. <sup>u</sup>Br: calcd, 30.2; found, 29.7. <sup>v</sup>Benzo[*b*]thiophen-3-yl methyl ketone [M. W. Farrar and R. Levine, *J. Amer. Chem. Soc.*, 72, 4433 (1950)].



comps 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 comps, 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.<sup>1</sup> 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

It is clear from Table I that the naphthalene ring of pronethalol can be replaced by many heterocyclic ring systems to give comps 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.<sup>5</sup> A few



1,4-benzodioxan series,<sup>1</sup> 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,<sup>11</sup> and for the naphthol[2,3-*b*]-1,4-dioxane analogs in part 7.<sup>1</sup> 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**.<sup>5,11</sup> 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  $\beta$ -blocking activity altogether (**46** and **24**).<sup>5</sup>

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

Biological results on **17** and **19** in the dog have been reported by Marchetti, *et al.*<sup>12</sup> 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**).  $\text{NaBH}_4$  (0.6 g, 0.016 mole) was added during 30 min to a stirred soln of  $59 \cdot \text{H}_2\text{O}$  (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  $\text{Et}_2\text{O}$ . NaOH (4 *N*, 20 ml) was added to the aq acidic soln and then the product (**42**) was isolated by  $\text{Et}_2\text{O}$  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  $\text{LiAlH}_4$  (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  $\text{Et}_2\text{O}$  (200 ml) was cautiously added, followed by NaOH (2 *N*, 20 ml). The mixt was shaken and filtered, and the filtrate was sepd. The  $\text{Et}_2\text{O}$  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  $\text{NH}_3$  (100 ml). After 25 min  $\text{NH}_4\text{Cl}$  (1.5 g) was added and the  $\text{NH}_3$  was allowed to evap. The residual solid **23** was stirred with a little  $\text{H}_2\text{O}$  to remove inorg material and then crystd.

C. 1-(3,4-Dihydro-1,5-benzodioxepin-7-yl)-2-isopropylaminoethanol (**20**).  $\text{NaBH}_4$  (0.75 g, 0.02 mole) was added during 30 min to a stirred soln of  $61 \cdot \text{HCl}$  (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  $\text{Et}_2\text{O}$  (100 ml). NaOH (10 *N*, 15 ml) was added to the aq acid layer, and the product (**20**) was isolated with  $\text{Et}_2\text{O}$ . Treatment with  $\text{Et}_2\text{O}$ –HCl gave  $20 \cdot \text{HCl}$ .

D. 2-Isopropylamino-1-(1-methyl-4-quinolon-3-yl)ethanol (**29**).  $\text{NaBH}_4$  (1.5 g, 0.04 mole) was added during 1 hr to a stirred suspension of **71** (2 g, 0.0065 mole) in  $\text{Me}_2\text{CO}$  (16 g, 0.28 mole) and MeOH (40 ml) at 5–10°. After 16 hr the MeOH and excess of  $\text{Me}_2\text{CO}$  were evapd. **29** was isolated ( $\text{CHCl}_3$ ) 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  $\cdot \text{HBr}^{13}$  (5 g) in  $\text{H}_2\text{O}$  (300 ml) and  $\text{Me}_2\text{CO}$  (80 ml) was hydrogenated in the presence of  $\text{Pt}_2\text{O}$  (1 g). The mixt was filtered, and the filtrate was evapd to dryness to give **6  $\cdot \text{HBr}$ .**

1-(1,4-Benzodioxan-6-yl)-2-(1-methyl-3-phenylpropylamino)ethanol (**43**). A soln of  $41 \cdot \text{H}_2\text{O}$  (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  $\text{Pt}_2\text{O}$  (0.3 g). The mixt was filtered, and the filtrate was evapd to dryness. The residual gum was stirred with  $\text{Et}_2\text{O}$  and solid **43**  $\cdot \text{HCl}$  sepd.

Ethyl *N*-*p*-Toluenesulfonylbenzomorpholine-2-carboxylate (**74**). Ethyl  $\alpha, \beta$ -dibromopropionate (15 g, 0.0057 mole) was added to a stirred mixt of 2-*p*-toluenesulfonylaminophenol<sup>14</sup> (50 g, 0.19 mole), anhyd  $\text{K}_2\text{CO}_3$  (25 g), and  $\text{Me}_2\text{CO}$  (700 ml) which was being heated under reflux. After 30 min, more  $\text{K}_2\text{CO}_3$  (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  $\text{Me}_2\text{CO}$ . **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  $\text{Et}_2\text{O}$ . The ext gave **75**:  $\tau$  (TFA) 2.1–3.0 (multiplet, Ar H, 8), 5.3 ( $\text{H}_A = \text{H at C}_2$ ), 5.6 ( $\text{H}_B = \text{H at C}_3$ ), 6.25 ( $\text{H}_X = \text{H at C}_5$ ) (ABX system,  $\text{OCH}_2\text{CH}(\text{CO}_2\text{H})\text{N}$ ,  $J_{AB} = 3$ ,  $J_{AX} = 12$ ,  $J_{BX} = 8$  cps, 3), 7.54 (singlet, Ar $\text{CH}_3$ , 3).

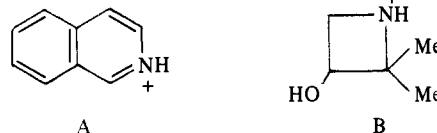
*N*-*p*-Toluenesulfonylbenzomorpholine-2-carbonyl Chloride (**76**). **75** (15 g),  $\text{SOCl}_2$  (150 ml), and  $\text{CHCl}_3$  (450 ml) were heated under reflux for 16 hr.  $\text{CHCl}_3$  and excess of  $\text{SOCl}_2$  were evapd to leave **76** as a solid.

Diazomethyl *N*-*p*-Toluenesulfonylbenzomorpholin-3-yl Ketone (**77**). A slight excess of ethereal  $\text{CH}_2\text{N}_2$  was added to a soln of **76** (13.5 g) in  $\text{Et}_2\text{O}$  (350 ml) and after 16 hr the  $\text{Et}_2\text{O}$  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  $\text{Me}_2\text{CO}$  (8 g) and EtOH (20 ml) was hydrogenated in the presence of  $\text{Pt}_2\text{O}$  (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  $\text{Et}_2\text{O}$  (50 ml). The acidic aq soln was made alk with NaOH (2 *N*) and then extd with  $\text{Et}_2\text{O}$ . The ext gave **34**.

Attempted Detosylation of **74**. Small pieces of Na were added to a soln of **74** (3 g) in liq  $\text{NH}_3$  until a blue color persisted for 3 min. Excess Na was destroyed with  $\text{AcONH}_4$ , and then the  $\text{NH}_3$  was allowed to evap.  $\text{H}_2\text{O}$  was added, and the mixt was extd with  $\text{EtOAc}$ . 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-2,3,4,6,11,11 $\alpha$ -hexahydro-1*H*-pyrimido[1,6-*b*]isoquinoline (**80**). A soln of 1-(isoquinol-3-yl)-2-nitroethanol (**79**)<sup>#</sup> (1 g) in HCl (2 *N*, 5 ml),  $\text{H}_2\text{O}$  (40 ml), and  $\text{Me}_2\text{CO}$  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  $\text{Et}_2\text{O}$ . Fractional crystn from  $\text{EtOAc}$  gave **80**: mp 188–190°;  $\tau$  ( $\text{D}_2\text{O}$ ) 2.51 (singlet, Ar H, 4) 8.32 and 8.75 (singlets,  $\text{CH}_3$ , 3 each); *m/e* 232 ( $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$ ), 130 ( $\text{C}_8\text{H}_8\text{N(A)}$ , 72.8\*), 101 ( $\text{C}_5\text{H}_{11}\text{NO}$  (B), 43.9\*), 58,  $\text{Me}_2\text{C}=\text{NH}_2^+$ , 33.3\*). *Anal.* ( $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}$ ) C, H, N.



The mother liquors from the above crystn were evapd and the gum (in  $\text{Et}_2\text{O}$ ) was treated with  $\text{Et}_2\text{O}$ –HCl. The hydrochloride was fractionally crystd to give **31**  $\cdot 2\text{HCl}$ .

E. 2-Isopropylamino-1-(2-phenothiazinyl)ethanol (**14**). A soln of 2-chloro-1-(2-phenothiazinyl)ethanol<sup>15</sup> (5 g, 0.018 mole) and *i*-Pr $\text{NH}_2$  (10 ml, 0.12 mole) in MeOH (250 ml) was heated under reflux for 66 hr and then the MeOH and excess *i*-Pr $\text{NH}_2$  were evapd. The residue was dissolved in dil HCl, and the soln was washed with  $\text{Et}_2\text{O}$ . The aq acid soln was made alk and extd with  $\text{Et}_2\text{O}$ . The ext gave **14**.

1-(1,2-Dihydro-1-methyl-2-oxo-4-quinolyl)-2-isopropylaminoethanol (**30**). A soln of trimethylloxosulfonium iodide<sup>7</sup> (2.4 g, 0.011 mole) in DMSO (50 ml) was stirred under  $\text{N}_2$  while a 50% mineral oil dispersion of NaH (0.52 g, 0.011 mole) was added in small portions. The mixt was stirred under  $\text{N}_2$  at 50–60° for 30 min and then a soln of 1,2-dihydro-1-methyl-2-oxoquinoline-4-carbaldehyde<sup>16</sup> (1.87 g, 0.01 mole) in DMSO (30 ml) was added. The mixt was stirred at 50–60° for 2 hr, cooled, didd with  $\text{H}_2\text{O}$  (200 ml), and extd with  $\text{CHCl}_3$ . The ext gave the intermediate oxirane as a gum. This was dissolved in EtOH (80 ml) and *i*-Pr $\text{NH}_2$  (8 ml), and the mixt was refluxed for 3 hr. EtOH and excess *i*-Pr $\text{NH}_2$  were evapd and then **30** was isolated in the same way as **14**.

<sup>#</sup>Kindly donated by Dr. T. R. Gormley, Department of Chemistry, University College, Dublin.



2-( $\alpha,\beta$ -Diacetoxyvinyl)quinoxaline (83) and 2-Acetoxyacetyl-quinoxaline (82). A suspension of 2-(D-*arabino*-tetrahydroxybutylquinoxaline<sup>8</sup> (15 g) in dry C<sub>5</sub>H<sub>5</sub>N (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<sub>2</sub>O (100 ml), and the soln was acidified with H<sub>2</sub>SO<sub>4</sub> (6 N, 20 ml). The red solid (84) which sepd was isolated and dried. A soln of this solid (5.9 g) in C<sub>5</sub>H<sub>5</sub>N (18 ml) and Ac<sub>2</sub>O (18 ml) was kept at room temp for 18 hr, poured into H<sub>2</sub>O (200 ml), and extd 5 times with Et<sub>2</sub>O (100 ml each time). The combined Et<sub>2</sub>O exts were washed successively with HCl (1 N, 100 ml), satd NaHCO<sub>3</sub> soln (100 ml), and then H<sub>2</sub>O (100 ml). The ext gave 83, mp 117°, and 82, mp 113–114°, by fractional crystn from petr ether, bp 60–80°: 83, nmr  $\tau$  (CDCl<sub>3</sub>) 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<sub>3</sub>)=CHOCOCH<sub>3</sub>, 3 and 3); *Anal.* (C<sub>14</sub>H<sub>12</sub>N<sub>2</sub>O<sub>4</sub>) C, H, N; 82, nmr  $\tau$  (CDCl<sub>3</sub>) 0.50 (singlet, N=CCH=N, 1), 1.65–2.25 (multiplet, Ar H, 4), 4.25 (singlet, COCH<sub>2</sub>OAc, 2), 7.62 (singlet, OCOCH<sub>3</sub>, 3); *Anal.* (C<sub>12</sub>H<sub>10</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

2-Isopropylamino-1-(2-quinoxaly)ethanol (32). *i*-PrNH<sub>2</sub> (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<sub>4</sub> (1 g, 0.027 mole) in EtOH (10 ml) was added. After 1 hr glac AcOH (15 ml) was added slowly, followed by H<sub>2</sub>O (100 ml) and HCl (6 N, 5 ml). The EtOH was evapd, and the residual aq soln was washed 3 times with Et<sub>2</sub>O. The aq soln was made alk with NaOH (6 N, 20 ml) and extd with Et<sub>2</sub>O. 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<sup>17</sup> (3.4 g, 0.02 mole), SeO<sub>2</sub> (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<sub>3</sub> (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<sub>2</sub>O extn.

H. *N*-Isopropyl-1-benzylindole-3-ylglyoxylamide (68). A soln of 1-benzylindole (26 g, 0.125 mole) in Et<sub>2</sub>O (200 ml) was added during 1 hr to a stirred soln of (COCl)<sub>2</sub> (9 ml, 0.105 mole) in Et<sub>2</sub>O (100 ml) at 5°. After 30 min a soln of *i*-PrNH<sub>2</sub> (31 ml, 0.37 mole) in Et<sub>2</sub>O (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<sup>18</sup> (20 g, 0.133 mole) and AcCl (11 g, 0.14 mole) in CS<sub>2</sub> (60 g) was added during 1 hr to a stirred mixt of AlCl<sub>3</sub> (26 g, 0.2 mole) and CS<sub>2</sub> (80 g) at 10–15°. After 2 days the mixt was poured onto ice. The CS<sub>2</sub> phase was sepd, and the aq phase was extd with Et<sub>2</sub>O. The combined CS<sub>2</sub>-Et<sub>2</sub>O solns were washed with NaOH (2 N, 50 ml), dried (MgSO<sub>4</sub>), and distd to give 63, bp 120° (0.5 mm).

I. Bromomethyl 3,4-Dihydro-1,5-benzodioxepin-7-yl Ketone (62). Br<sub>2</sub> (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<sub>2</sub> (135 ml) at 0°. After 2 hr the CS<sub>2</sub> was evapd and the residual 62 recrystd.

J. 3,4-Dihydro-1,5-benzodioxepin-7-yl Isopropylaminomethyl Ketone (61). *i*-PrNH<sub>2</sub> (4 g, 0.068 mole) was added to a soln of 62 (7.6 g, 0.028 mole) in Et<sub>2</sub>O (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<sub>2</sub>O (100 ml). NaOH (8 N, 20 ml) was added to the aq acid soln. The product (61) was isolated by Et<sub>2</sub>O extn and converted to 61·HCl with Et<sub>2</sub>O-HCl.

K. Aminomethyl 1,4-Benzodioxan-6-yl Ketone (58). A soln of hexamine (6 g, 0.043 mole) in CHCl<sub>3</sub> (100 ml) was added to a soln of 60 (10 g, 0.039 mole) in CHCl<sub>3</sub> (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<sub>2</sub>O (400 ml) were stirred vigorously while Me<sub>2</sub>SO<sub>4</sub> (40 ml) was added. The mixt was stirred for 2 hr and then extd with CHCl<sub>3</sub> (4 times, 100 ml each time). The ext was washed with H<sub>2</sub>O, dried (MgSO<sub>4</sub>), and then evapd to give 49.

M. 1-Allylquinol-4-on-6-yl Methyl Ketone (51). 4-Hydroxyquinol-6-yl methyl ketone<sup>19</sup> (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<sub>6</sub>H<sub>5</sub>Cl. Petr ether (bp 40–60°) was added to the ext to ppt 51, which was then recrystd from H<sub>2</sub>O.

1-(1,3-Benzodioxol-2-yl)-2-bromoethanol. A soln of 1,3-benzodioxol-2-carbonyl chloride<sup>20</sup> (5 g) in Et<sub>2</sub>O (50 ml) was added to a soln of CH<sub>2</sub>N<sub>2</sub> (6.5 g) in Et<sub>2</sub>O (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<sub>2</sub>O (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<sub>4</sub> (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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