Synthesis and Adrenergic β-Blocking Activity of Some 1,3-Benzodioxole Derivatives

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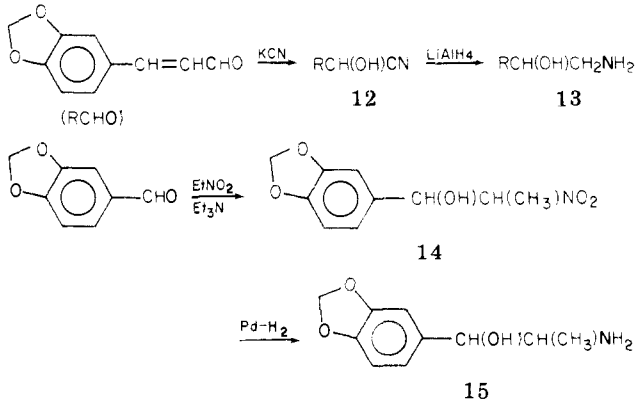
A series of 1,3-benzodioxole derivatives was synthesized. We found four compounds (**2**, **3**, **10**, and **11** in Table IV) to have about the same order of β-blocking activity as that of sotalol. In addition, it is of interest that some of the compounds (**2**–**4**) were found to have hypotensive activities, although they were about one-tenth of that of hydralazine. Sotalol did not produce any change in blood pressure, and propranolol raised the blood pressure.

In an attempt to find new β-adrenoceptor blocking agents, we synthesized various analogues of α-(isopropylaminomethyl)-1,3-benzodioxole-5-methanol (compound **2** in Table IV), whose structure has already been known.[1] In our preliminary experiments, compound **2** was found to have about the same β-blocking activity as sotalol and, also, to have a significant hypotensive effect in anesthetized rats. In this regard, chemical modification of compound **2** was made with substituents other than isopropyl on nitrogen. Moreover, guanidyl substitution at the end of the side chain and introduction of an ester group between the aromatic ring and the side chain were also made, expecting new hypotensives. Among these compounds, compounds **5** and **6** have been briefly reported to inhibit the hypertensive effects of noradrenaline and tyramine.[2] Two of the present authors have already claimed compounds (**9**–**11**) as β-blocking agents in Japanese Patents.[3]

Chemistry. The syntheses of the compounds described in Tables I and III were accomplished by three procedures (Scheme I). Compounds **1** and **4** were prepared by reductive alkylation of amino alcohols **13** and **15**, respectively, with Me_2CO and $NaBH_4$[4] (method A). The amino alcohols **13** and **15** were obtained by the reduction of **12** and **14** with $LiAlH_4$ and Pd–H_2, respectively.



Compound **4** was the pure threo isomer on the basis of the coupling constant (9 Hz) of the benzylic proton.[5] Compound **2** has already been prepared by method A by Heacock et al.[1] We synthesized compounds **2** and **3** by method B. Treatment of **16** with *N*-benzyl-*N*-alkylamines, followed by catalytic reduction, gave **2** and **3** in good yield.

Scheme I

Method A

$$RCH(OH)CH_2NH_2 \xrightarrow[NaBH_4]{Me_2CO} RCH(OH)CH_2NH\text{-}i\text{-}Pr$$

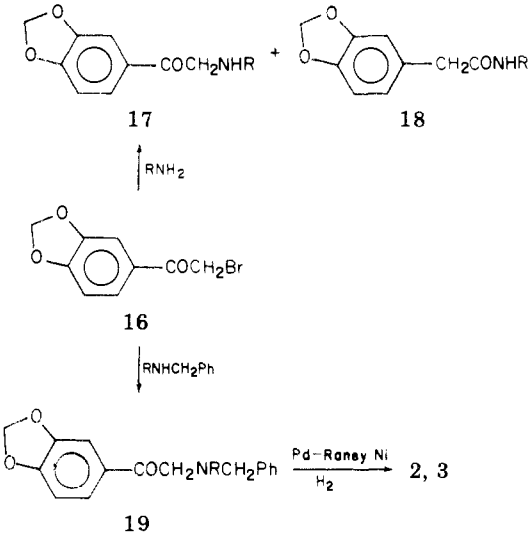
Method B

$$RCOCH_2Br \xrightarrow{R_1NHCH_2Ph} RCOCH_2N(R_1)CH_2Ph \xrightarrow{Pd\text{-}H_2} RCH(OH)CH_2NHR_1$$

Method C

$$RCH(O)CH_2 \xrightarrow{R_1R_2NH} RCH(OH)CH_2NR_1R_2$$

The other process for obtaining **2** and **3** via **17** was unfavorable because a substantial amount of by-product **18** was formed upon treatment of **16** with primary amines.[6]



The guanidine analogues of compound **2** in Table II were prepared by the reaction of the corresponding amines with *S*-methylisothioureas. Compounds **5**–**7** were obtained as

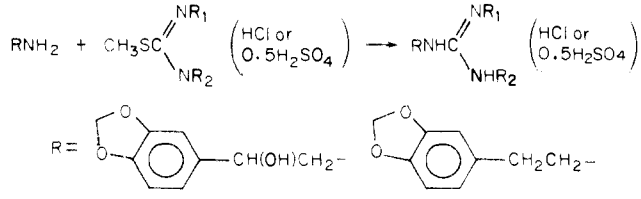
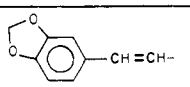
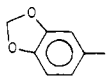
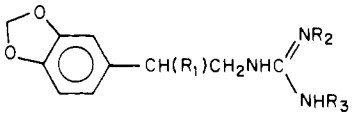


Table I

Compd	R[c]	R_1	R_2	Methods[a]	Form	Crystn solvent	Mp °C	Formula[b]
				$RCH(OH)CHR_1NHR_2$				
1		H	$CH(CH_3)_2$	A[d]	HCl	*i*-PrOH	156-157.5	$C_{14}H_{19}NO_3 \cdot HCl$
2		H	$CH(CH_3)_2$	A,[e] B[g]	HCl	*i*-PrOH	182-183[f]	$C_{12}H_{17}NO_3 \cdot HCl$
3		H	$C(CH_3)_3$	B	HCl	MeOH-EtOH	235-236	$C_{13}H_{19}NO_3 \cdot HCl$
4		CH_3	$CH(CH_3)_2$	A	HCl	*i*-PrOH	167-168	$C_{13}H_{19}NO_3 \cdot HCl$

[a] Methods refer to Experimental Section. [b] All compounds analyzed for C, H, and N. [c] Where there is a blank space in this column, the R group is the preceding structure. [d] Starting material, 3-(1,3-benzodioxol-5-yl)-2-propenal, mp 83-84 °C (lit.[11] mp 83-84 °C). [e] Intermediate, α-aminomethyl-1,3-benzodioxole-5-methanol, mp 183-184 °C (lit.[1] mp 181-182 °C, as HCl). [f] Literature on **2** gives mp 179 °C (see ref 1). [g] Starting material, 1-(1,3-benzodioxol-5-yl)ethanone, was obtained essentially according to the method of Reynolds et al.,[12] mp 86-88 °C (lit.[13] mp 87-88 °C).

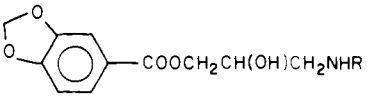
Table II



Compd	R_1	R_2	R_3	Form	Crystn solvent	Mp, °C	Formula[a]
5[b]	H	H	H	$0.5H_2SO_4$	MeOH-EtOH	190-193[f]	$C_{10}H_{13}N_3O_2 \cdot 0.5H_2SO_4$
6[c]	OH	H	H	$0.5H_2SO_4$	MeOH-H_2O	212-214[g]	$C_{10}H_{13}N_3O_3 \cdot 0.5H_2SO_4$
7[d,e]	H	CH_2-CH_2		HCl	*i*-PrOH	153-155	$C_{12}H_{15}N_3O_2 \cdot HCl$
8	OH	CH_2-CH_2		HCl	EtOH-*n*-hexane	182-183	$C_{12}H_{15}N_3O_3 \cdot HCl$

[a] All compounds analyzed for C, H, and N. [b] Starting material, 1,3-benzodioxole-5-ethanamine, mp 210-211 °C (lit.[14] mp 210-212 °C as HCl). [c] Starting material, α-aminomethyl-1,3-benzodioxole-5-methanol, see footnote *e* of Table I. [d] R_f 0.53 (*n*-BuOH-AcOH-H_2O, 12:3:5); IR 1670 cm^{-1}; NMR (D_2O) 2.86-2.88 (m, ArH, 3 H), 7.73 (s, OCH_2O, 2 H), 4.1 (s, NCH_2CH_2N, 4 H), 4.1-4.4 (m, $ArCH_2CH_2N$, 2 H), 4.66-4.70 (m, $ArCH_2CH_2N$, 2 H). [e] *S*-Methylethyleneisothiourea hydrochloride was prepared by the reaction of ethylenethiourea with CH_3I, followed by application to a column of anion-exchange resin (Diaion PA-312, Cl type): mp 166-167 °C (as HCl salt); mp 140-141.5 °C (as HI salt). [f] Lit.[2] 183 °C. [g] Lit.[2] 219 °C.

Table III

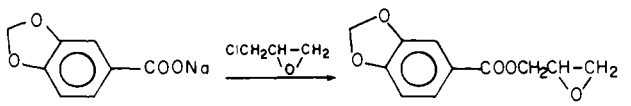


Compd	R	Method[a]	Form	Crystn solvent	Mp, °C	Formula[b]
9[c]	CH_3	C	Oxalate	MeOH-EtOH	179-180	$C_{12}H_{15}NO_5 \cdot C_2H_2O_4$
10	$CH(CH_3)_2$	C	HCl	*n*-BuOH	170-171	$C_{14}H_{19}NO_5 \cdot HCl$
11	$C(CH_3)_3$	C	HCl	*i*-PrOH	171-172	$C_{15}H_{21}NO_5 \cdot HCl$

[a] Methods refer to Experimental Section. [b] All compounds analyzed for C, H, and N. [c] Starting material, piperonylic acid, mp 227-228 °C (lit.[15] mp 225 °C). Intermediate, 3-(*N*-benzyl-*N*-methylamino)-2-hydroxypropyl 3,4-(methylenedioxy)benzoate oxalate (**21**): mp 234-235 °C from EtOH; IR 1710 cm^{-1}.

salt forms in good yield, but compound **8** was accompanied by by-products and had to be purified via the free base.

The compounds containing an ester group (Table III) were prepared from an intermediate glycidyl ester **20**. The reaction of 3,4-methylenedioxybenzoic acid with epichlorohydrin gave **20** in poor yield. To avoid the troublesome problem of secondary reaction of glycidyl ester with hydrogen chloride,[7] a salt of the carboxylic acid was used as starting material. The reaction of the salt of the carboxylic acid with epichlorohydrin was effected by using a quaternary ammonium halide[8] as catalyst.



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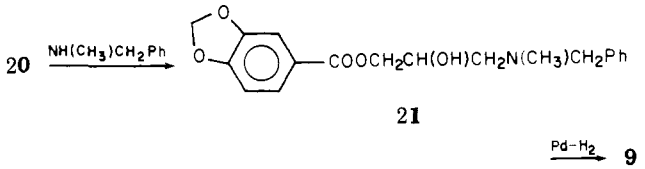
The ring-opening reaction of glycidyl ester **20** by amines (*i*-$PrNH_2$ and *tert*-$BuNH_2$) gave the desired secondary alcohols **10** and **11** selectively as in the propranolol series.[9] However, treatment of **20** with CH_3NH_2 in MeOH gave **9**, accompanied by a small amount of its position isomer. However, treatment of **20** with *N*-benzyl-*N*-methylamine, followed by catalytic debenzylation, gave **9** as the sole product in good yield.



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Biological Results. The compounds were examined for their β-blocking activities and their actions on blood pressure. β-Adrenergic blocking activities of the compounds were determined mainly with guinea-pig atrial preparations. Isolated guinea-pig atria were suspended in physiological salt solution maintained at 37 °C and oxygenated with 95% O_2 and 5% CO_2. Composition of the physiological salt solution used was as follows (in mM): NaCl 135, KCl 5, $CaCl_2$ 2, $MgCl_2$ 1, $NaHCO_3$ 15, and glucose 5.5. Isometric contractions were measured with

Table IV. Summary of the Pharmacological Results

Compd	Guinea-pig atria β-blockade		Unanesthetized rats blood pressure, mmHg[a]				
	pA_2	N	0 h[b]	1 h	3 h	5 h	N
1	[c]						
2	6.2 ± 0.2[d]	4	113 ± 2.9	97 ± 3.2	84 ± 5.0	87 ± 2.8	8
3	6.5 ± 0.1	5	112 ± 2.6	83 ± 3.8	77 ± 1.4	77 ± 2.1	8
4			114 ± 3.2	92 ± 3.4	91 ± 5.1	94 ± 4.7	4
5							
6							
7							
8							
9	5.3 ± 0.2	3					
10	6.9 ± 0.1	4					
11	6.9 ± 0.2	3					
Propranolol	8.2 ± 0.1	5	118 ± 3.5	141 ± 7.0	119 ± 3.0	117 ± 6.4	4
Sotalol	6.8 ± 0.1	4	114 ± 3.0	112 ± 4.8	108 ± 7.6	107 ± 7.4	4
Hydralazine[e]			122 ± 2.7	83 ± 1.6	89 ± 2.3	94 ± 1.7	16

[a] Values obtained 1, 3, and 5 h after oral administration of 50 mg/kg. [b] Values obtained before the administration of the drugs. [c] Compounds were substantially inactive. The highest doses tested were 5×10^{-5} M and 100 mg po which did not produce significant β-blocking action and changes in blood pressure, respectively. [d] Values are mean ± SE. [e] Dose of hydralazine was 5 mg/kg po.

a force displacement transducer (Nihon Kohden, Model SB 1T) and recorded on an ink-writing oscillograph (Nihon Kohden, Model RM-150); rate of spontaneous contraction was electronically measured (Nihon Kohden, RT-2).

As the first screening, the compounds were tested for their inhibiting activities on the increases in rate and force of contractions produced by a single dose of isoproterenol (3×10^{-8} M, a dose producing approximately 80% of the maximum effect); two atria were used for each compound. As a result, five of the compounds (**2**, **3**, **9**–**11**) were found to be considerably potent, while the rest of the compounds were substantially free from β-blocking activity. Therefore, pA_2 values for these five compounds were determined on the basis of the shift of dose–response curves. As shown in Table IV, pA_2 values for most of these compounds were higher than 6: 6.2 for compound **2**, 6.5 for compound **3**, 6.9 for compound **10**, and 6.9 for compound **11**. Since the pA_2 value for sotalol determined in the present series of experiments was 6.8, compounds **2**, **3**, **10**, and **11** were as potent β-blockers as sotalol.

Most of the compounds were free from direct cardiac action with three exceptions. Compound **2** produced an increase in beating rate by about 25%. Only a slight depression in rate of beating was produced by compounds **4** and **9** (less than 10% of the control rate).

For the blood pressure measurements, male rats (150–180 g) were anesthetized and a cannula was fixed in the carotid artery of each rat. After the operation (3–4 days), blood pressure was led to the pressure transducer through the cannula and recorded on an ink-writing oscillograph. Animals were unanesthetized and freely movable during the blood pressure measurement. Three of the compounds tested (**2**–**4**) were found to be hypotensive and the rest of the compounds were substantially ineffective, as shown in Table IV. Among these three compounds, compound **3** was the most potent in lowering blood pressure. Percent decreases in blood pressure produced 1, 3, and 5 h after the oral administration of 50 mg/kg of the compounds were as follows: 14, 26, and 23 for compound **2**, 26, 31, and 31 for compound **3**, and 19, 20, and 18 for compound **4**. The values obtained from exactly the same experiments using hydralazine (5 mg/kg po) were 32, 27, and 23. Therefore, the hypotensive activity of compound **3** was about one-tenth of that of hydralazine. Sotalol did not produce significant changes in blood pressure at the same dose (oral 50 mg/kg) and propranolol showed a hypertensive effect. Thus compounds **2** and **3** may be unique compounds in the sense that they have both β-blocking and hypotensive activities.

Discussion

Since only a limited number of the compounds were studied in the present study, detailed discussions on the structure–activity relationships are impossible. However, the following might be pointed out. Guanidyl substitution at the end of the side chain (compounds **5**–**8**) resulted in the elimination of both β-blocking and hypotensive activities of the mother compounds. Introduction of the ester structure between the aromatic ring and side chain (compounds **9**–**11**) did not significantly influence the β-blocking potency of the mother compounds (**2**, **3**), while their hypotensive actions were almost totally abolished by this modification.

Experimental Section

Methods A–C are representatives for compounds reported in the tables. Melting points and recrystallizing solvents given in the tables are usually not reported in the text. Hydrogenations were carried out at room temperature and atmospheric pressure unless stated otherwise. The melting points for the samples were determined with a Mitamura hot-stage apparatus and were not corrected. The NMR data are given in the order of multiplicity, assignment, coupling constant, and integration. Chemical shifts were reported in τ values relative to Me_4Si as external standard (in D_2O) and as internal standard (in $CDCl_3$).

A. 4-(1,3-Benzodioxol-5-yl)-1-isopropylamino-3-buten-2-ol (1). The reaction of 3-(1,3-benzodioxol-5-yl)-2-propenal sodium bisulfite addition product (56 g) with KCN (8 g) in Et_2O–H_2O at 0–3 °C yielded cyanohydrin **12** as an oil: yield 23 g; IR (film) 3400 (br), 2230 cm^{-1}.

The solution of crude **12** (22.5 g) in dry Et_2O (0.5 l.) was added to a suspension of $LiAlH_4$ (25 g) in Et_2O (0.5 l.) over 0.5 h and the reaction mixture was stirred for 5 h at room temperature. Excess $LiAlH_4$ was destroyed; the metal salts were removed by filtration and washed with several 50-ml portions of Et_2O. The combined filtrate and washings were evaporated to a crude crystal **13** which was recrystallized from benzene–ligroine: yield 4.3 g; mp 104–106 °C; IR 1640 cm^{-1}; NMR ($CDCl_3$) 3.45 (d, ArC*H*=CH–, $J_{3,2}$ = 15 Hz, 1 H), 4.05 (q, ArCH=C*H*–, J = 15, 6 Hz, 1 H), 4.06 (s, OCH_2O, 2 H), 5.8 (m, C*H*OH, 1 H), 7.05–7.4 (m, CH_2NH_2, 2 H), 7.75 (br singlet, OH, NH_2, 3 H).

Methanolic HCl (3.8 N, 0.16 ml) was added to a stirred solution of **13** (4.3 g) and Me_2CO (3 ml) in MeOH (70 ml). The mixture was stirred at 20 °C for 0.5 h and the $NaBH_4$ was added during 15 min to the stirred solution. The solution was heated to reflux for 1 h and cooled. The MeOH was evaporated in vacuo. H_2O (20 ml) was added and the mixture was extracted with Et_2O. The extract gave **1**: mp 81–82.5 °C from ligroine; NMR ($CDCl_3$) 3.1–3.3 (m, ArH, 3 H), 3.45 (d, ArC*H*=CH, $J_{3,2}$ = 15 Hz, 1 H), 3.97 (q, ArCH=C*H*, J = 15, 6 Hz, 1 H), 5.5–5.9 [m, C*H*$(CH_3)_2$, 1 H].

6.9–7.1 (br singlet, OH, NH, 2 H), 7.05 (m, CHOH, 1 H), 7.15–7.5 (m, CH_2N, 2 H), 8.93 [d, $CH(CH_3)_2$, 6 H]. Treatment with Et_2O–HCl gave 1·HCl: yield 2.2 g; IR 1255 cm^{-1}.

1-(1,3-Benzodioxol-5-yl)-2-isopropylamino-1-propanol (4). A solution of 3,4-methylenedioxybenzaldehyde (100 g), nitroethane (134 g), and triethylamine (3 g) in MeOH (100 ml) and H_2O (50 ml) was stirred at 40 °C for 10 h. AcOH (1.8 g) was added to the cooled reaction mixture. The MeOH and excess $EtNO_2$ were evaporated under reduced pressure. H_2O (50 ml) was added and the product (14) was obtained by extraction with AcOEt as an viscous oil which was not further purified due to its instability: yield 72.5 g; R_f 0.88 (MeOH–$CHCl_3$, 1:1); IR (film) 3350 (br), 1560 cm^{-1}.

A solution of 14 (30 g) in MeOH (0.3 l.) was hydrogenated in the presence of Pd/C (5%, 7 g) at 30–40 kg/cm^2 in an autoclave. The mixture was filtered and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in dioxane and dioxane–HCl was added to the solution. The precipitate was filtered, washed with dioxane, and dried. 15·HCl was converted to its free base in the usual manner. The base 15 was recrystallized from benzene–*n*-hexane: yield 9.1 g; mp 85–87 °C; R_f 0.17 (MeOH–$CHCl_3$, 1:1). Using the procedure for 1, 15 (3 g), Me_2CO (2.3 ml), and $NaBH_4$ (0.92 g) yielded 2.5 g of 4: mp 92–93 °C (*i*-PrOH–*n*-hexane); R_f 0.41 (MeOH–$CHCl_3$, 1:1). Treatment of AcOEt–HCl gave 4·HCl: yield 2.8 g; R_f 0.70 (*n*-BuOH–AcOH–H_2O, 4:1:1).

B. α-(*tert*-Butylaminomethyl)-1,3-benzodioxole-5-methanol (3). The solution of Br_2 (11.6 g) in $CHCl_3$ (30 ml) was added to the solution of 1-(1,3-benzodioxol-5-yl)ethanone (11.8 g) in $CHCl_3$ (150 ml) at 0–5 °C. The reaction mixture was stirred for 3 h at room temperature. The $CHCl_3$ was evaporated and the residue was recrystallized from *i*-PrOH and ligroine. 16 (12.5 g) was yielded: mp 91–92 °C; IR 1680 cm^{-1}.

A solution of 16 (76 g) and *t*-$BuNHCH_2Ph$ (102.1 g)[10] in EtOAc (100 ml) was stirred at 50 °C for 24 h. The precipitate (*t*-$BuNHCH_2Ph$·HBr) was removed by filtration and the filtrate was evaporated to dryness. The residual solid was recrystallized from *n*-hexane. The base was treated with EtOAc–HCl and 19·HCl separated out: yield 63 g; mp 196–198 °C from EtOH; IR 1670 cm^{-1}.

A solution of 19·HCl (40 g) in MeOH (0.9 l.) was hydrogenated in the presence of Pd/C (3%, 2 g) and Raney nickel (10 g). The mixture was filtered and the filtrate was evaporated to dryness. The residue was recrystallized to give 3·HCl: yield 31.7 g; NMR (D_2O) 2.5–2.7 (m, ArH, 3 H), 3.6 (s, OCH_2O, 2 H), 4.5–4.9 (m, CHOH, 1 H), 6.23–6.43 (m, CH_2N, 2 H), 8.17 [s, $C(CH_3)_3$, 9 H].

C. 3-*tert*-Butylamino-2-hydroxypropyl 3,4-(Methylenedioxy)benzoate (11). To a vigorously agitated suspension of sodium 3,4-(methylenedioxy)benzoate (48 g) in epichlorohydrin (37 g) and toluene (220 ml) at reflux was added crystalline benzyltrimethylammonium chloride (4.8 g) and agitation and heating at reflux were continued for 15 min. The suspension was then cooled and H_2O (200 ml) was added. The two layers were separated and the epichlorohydrin phase was washed with aqueous $NaHCO_3$ and H_2O successively. Evaporation of unchanged epichlorohydrin and toluene gave crude glycidyl ester 20. Distillation of the crude product gave 34 g of colorless oil: bp 182 °C (2.8 mm). The distillate showed one component on GLC analysis on a shimalite W column (AW-DMCS coating, 200 °C): IR (neat) 1720, 1280, 1260 cm^{-1}; NMR ($CDCl_3$) 2.3–3.4 (m, ArH, 3 H), 3.97 (s, OCH_2O, 2 H), 5.45 (q, $COOCH_2$, 12, 4, 1 H), 5.96 (q, $COOCH_2$, 12, 6, 1 H), 6.80 (m, CH-CH_2O, 1 H), 7.20 (q, CH-CH_2-O, 5.5, 4.5, 1 H), 7.38 (q, CH-CH_2-O, 5.5, 3, 1 H).

A solution of 20 (7 g) and *t*-$BuNH_2$ (7.3 g) in EtOH (30 ml) was heated under reflux for 1 h and then EtOH and excess *t*-$BuNH_2$ were evaporated. HCl (1 N, 20 ml) was added to the oily residue, and the mixture was washed with Et_2O (50 ml × 2). The aqueous acidic solution was made alkaline with 3 N NaOH and extracted with EtOAc. The extract gave an oil which was converted to its hydrochloride in Me_2CO: yield 4.7 g; IR 3200, 1710, 1275 cm^{-1}; NMR (D_2O) 1.95–2.9 (m, ArH, 3 H), 3.57 (s, OCH_2O, 2 H), 5.2–5.35 [m, $COOCH_2CH(OH)$, 3 H], 6.25–6.5 (m, CH_2N, 2 H), 8.15 [s, $C(CH_3)_3$, 9 H].

1-(1,3-Benzodioxol-5-yl)-2-guanidylethanol (6). A solution of *S*-methylisothiourea·$0.5H_2SO_4$ (6.5 g) in H_2O (50 ml) was added to a stirred solution of 1-(1,3-benzodioxol-5-yl)-2-aminoethanol (9.1 g) in MeOH (80 ml) at 40 °C. The mixture was stirred at 50 °C for 2 h and then cooled. The MeOH–H_2O was evaporated. The oily residue was stirred with EtOH and the solid 6·$0.5H_2SO_4$ separated: yield 10 g; R_f 0.65 (*n*-BuOH–AcOH–H_2O, 12:3:5); IR 1665, 1640 cm^{-1}; NMR (D_2O) 1.3–1.5 (m, ArH, 3 H), 2.44 (s, OCH_2O, 2 H), 3.27–3.5 (m, CHOH, 1 H), 5.6–6.0 (m, CH_2N, 2 H).

1-(1,3-Benzodioxol-5-yl)-2-(imidazolin-2-yl)aminoethanol (8). A solution of *S*-methylethyleneisothiourea hydrochloride (16 g) in MeOH (100 ml) was added to a stirred solution of 1-(1,3-benzodioxol-5-yl)-2-aminoethanol (12.8 g) in MeOH (50 ml) at 40 °C. The mixture was stirred at 40 °C for 2 h and then cooled. The MeOH–H_2O was evaporated in vacuo. The residue was suspended with *i*-PrOH and filtered. Evaporation of the filtrate left an oily residue which was dissolved in 30 ml of MeOH–H_2O (1:1) and applied to a 2 × 90 cm column of anion-exchange resin (Diaion PA-312, OH type). Elution was continued with MeOH–H_2O (1:1, 900 ml). Evaporation of the last 700 ml of mixed solvent gave crystals which were suspended Me_2CO and filtered: R_f 0.55 (*n*-BuOH–AcOH–H_2O, 12:3:5). Treatment of the crystals with MeOH–HCl gave 8·HCl: yield 9.2 g; IR 1660 cm^{-1}; NMR (CD_3OD) 1.17–2.83 (m, ArH, 3 H), 2.04 (s, OCH_2O, 2 H), 4.67–5.0 (m, CHOH, 1 H), 5.77 (s, NCH_2CH_2N, 4 H), 5.17–5.7 (m, CH_2N, 2 H).

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