3,4-Dihydro-*2H*-1,5-benzodioxepins. A Novel Class of β-Adrenergic Stimulants

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A series of 3-substituted-aminomethyl-3-hydroxy-3,4-dihydro-*2H*-1,5-benzodioxepins is described. Members of the series constitute a unique class of β-adrenergic stimulants and possess interesting bronchial dilator activity.

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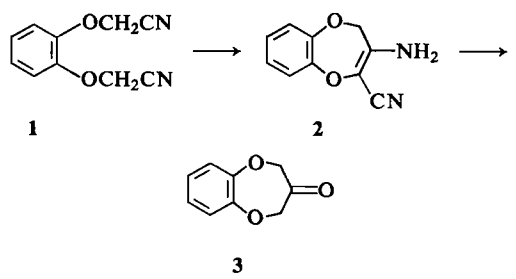
On a préparé une série d'aminométhyl-3 hydroxy-3-dihydro-3,4 (*2H*)-benzodioxepines-1,5 substitué sur l'azote. Les membres de cette série constituent une classe unique de stimulants β-adrénergiques et possèdent une activité broncho-dilatatrice intéressante.

As an extension of an interest in 1-phenoxy-3-amino-2-propanols with β-adrenergic blocking activity, it was decided to prepare as analogs 3,4-dihydro-*2H*-1,5-benzodioxepins (**A**) containing hydroxyl and amino functions in a similar vicinal relationship. Instead of the expected β-adrenergic blocking properties, a number of the compounds displayed β-adrenergic stimulant activity.

A practical preparative method was devised for the key intermediate, 3-oxo-3,4-dihydro-*2H*-1,5-benzodioxepin (**3**) (1), in the syntheses of the desired amino derivatives. Thorpe cyclization of 1,2-di(cyanomethoxy)benzene (**1**) afforded an enamino nitrile (**2**) which was hydrolyzed to the ketone (**3**) in acceptable overall yield. Three similar syntheses have been published recently (2).

From the ketone (**3**), two routes to the final products were developed. The ketone (**3**) was converted to the cyanohydrin (**4**) which, upon reduction, either catalytically or with lithium aluminum hydride, gave the amino alcohol (**5**). Various *N*-alkyl and *N*-aralkyl derivatives of this amine were obtained by reductive alkylations in the presence of aldehydes or ketones and by amide formation followed by lithium aluminum hydride reduction. Alternatively, conversion of the ketone (**3**) to the epoxide (**6**) by treatment with dimethyl sulfoxonium methylide and then reaction of the epoxide with a primary amine afforded an *N*-substituted amino alcohol (**A**). The latter route is more versatile in that the products are not limited to those bearing a primary or secondary alkyl group on the nitrogen atom. Treatment of the amino alcohol (**5**) with nitrous acid provided a convenient method for the large scale preparation of the epoxide (**6**). A small amount of the glycol (**7**) was obtained along with the epoxide but the Tiffeneau–Demjanov ring-expanded product (**8**) was not observed.

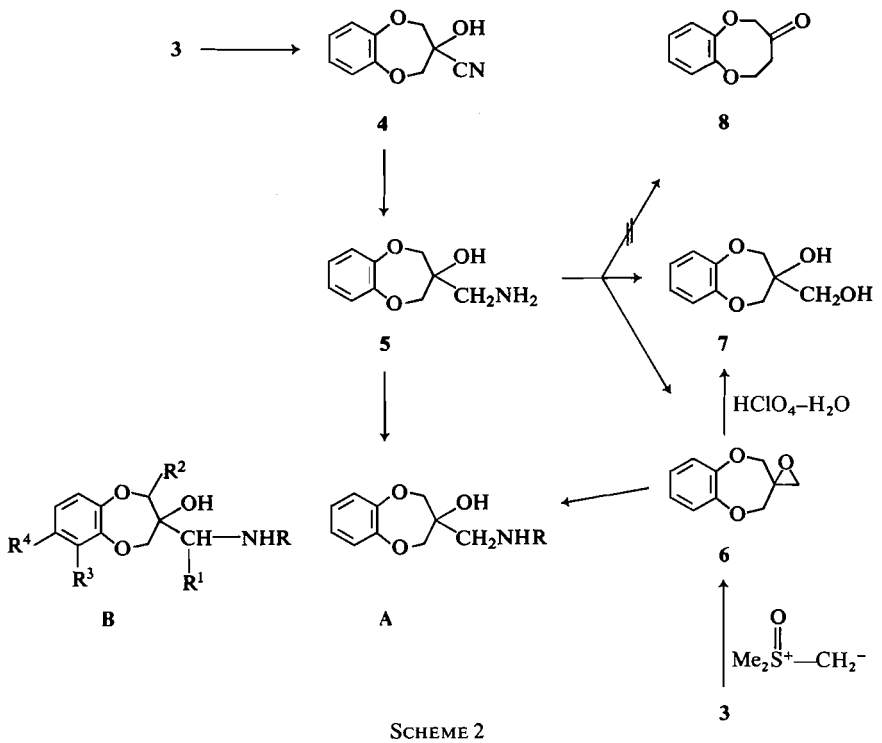


1 **2** **3**

SCHEME 1

Interesting pharmacological activity shown by some of the initial compounds of formula **A** that were made, especially R = *i*-Pr, necessitated the preparation of more highly substituted derivatives (**B**).

A number of readily available substituted catechols served as starting materials for syntheses based on the routes in Schemes 1 and 2. Although cyclization of a 1,2-di(cyanomethoxy)-benzene derived from a mono-substituted catechol could give rise to two isomeric enamino nitriles, in no case were two isolated, neither did



SCHEME 2

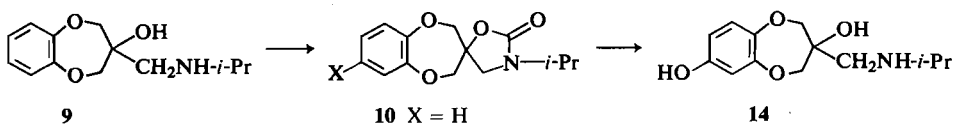
thin-layer chromatography nor n.m.r. spectrum suggest the presence of two products. The direction of cyclization of these compounds would be difficult to establish but structural ambiguity disappears when they are hydrolyzed to the ketones. Examples of substituted derivatives of **1–5** are given in Tables 1–5, respectively, and compounds of general formula **B** in Table 6.

Compound **B** (R = *t*-Bu; R^3 = OH; R^1 = R^2 = R^4 = H) was made by demethylating the corresponding 6-methoxy compound with boiling 48% HBr. The stability of the dioxepin system under these conditions is noteworthy, as also is the survival of the 3-hydroxyl group.

Compound **B** (R = *i*-Pr; R^4 = OH; R^1 = R^2 = R^3 = H) was made from **9** (**A**; R = *i*-Pr) as follows. The amino and hydroxyl functions were protected by incorporation into an oxazolidone ring; this derivative (**10**) was nitrated under mild conditions to give **11**, which was converted by conventional reactions to the required hydroxy derivative (**14**). Cleavage of the oxazolidone ring in either **11** or **13** required unusually vigorous conditions.

Access to compounds with a branched side chain (*e.g.* **B**, R^1 = Me—) was achieved by condensation of the ketone (**3**) with a nitro alkane followed by reduction of the nitro group and reductive alkylation.

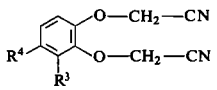
Introduction of a methyl group into the dioxepin ring (**B**, R^2 = Me—) was effected by partial hydrolysis if the enamino nitrile (**2**) to the keto nitrile (**15**) which was methylated via its thallium salt. This latter procedure did not show its usual



10 X = H
11 X = NO_2
12 X = NH_2
13 X = OH

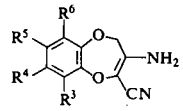
SCHEME 3

TABLE 1. Analyses of compound **1** and its derivatives



Compound	R^3	R^4	Crystallization solvent	Yield (%)	Melting point (°C)	Formula	Analyses
1	H	H	MeOH	73	85–85.5	$C_{10}H_8N_2O_2$	C, H, N
26	H	Cl	C_6H_6	13	125–127	$C_{10}H_7ClN_2O_2$	C, H, Cl, N
27	H	CH_3	MeOH	64	85–86.5	$C_{11}H_{10}N_2O_2$	C, H, N
28	CH_3O	H	MeOH	72	70–72	$C_{11}H_{10}N_2O_3$	C, H, N

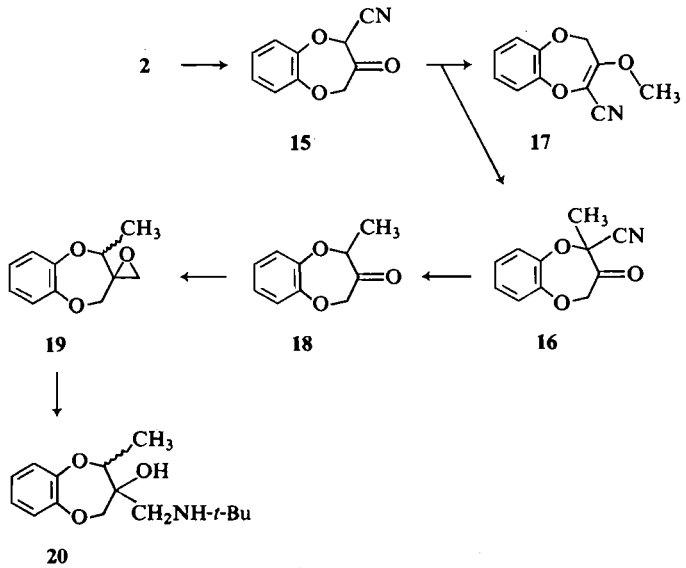
TABLE 2. Analyses of compound **2** and its derivatives



Compound	R^3 or R^6	R^4 or R^5	Crystallization solvent	Yield (%)	Melting point (°C)	Formula	Analyses
2	H	H	$CHCl_3$	62	168–169	$C_{10}H_8N_2O_2$	C, H, N
29	H	Cl	Glyme–$CHCl_3$	56	218.5–219.5	$C_{10}H_7ClN_2O_2$	C, H, Cl, N
30	H	CH_3	$CHCl_3$	52	170.5–172	$C_{11}H_{10}N_2O_2$	C, H, N
31	CH_3O	H	MeCN	78	216–218	$C_{11}H_{10}N_2O_3$	C, H, N

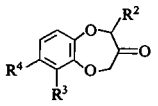
high degree of regiospecificity (3) and gave a significant amount of the enol ether (**17**) in addition to the desired keto nitrile (**16**). Hydrolysis and decarboxylation of **16** afforded **18**, which was converted to the oxirane (**19**) by the sulfoxonium methylide procedure. The yield and quality of the oxirane were poor but treatment of the crude product with *t*-butylamine afforded **20** in low yield.

The unusual stability of the oxazolidone system



SCHEME 4

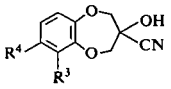
TABLE 3. Analyses of compound **3** and its derivatives



Compound	R^2	R^3	R^4	Method	Yield (%)	Crystallization solvent	Boiling or melting point (°C)	Formula	Analyses
3	H	H	H	*A*	51	—	64–68/0.35 Torr	$C_9H_8O_3$	
18	CH_3	H	H	*B*	67	—	100–105/0.15 Torr (46.5–48)	$C_{10}H_{10}O_3$	C, H[a]
32	H	H	Cl	*A*	50	Hexane	97/0.15 Torr (54–56)	$C_9H_7ClO_3$	C, H, Cl
33	H	H	CH_3	*A*	43	—	71–82/0.01 Torr	$C_{10}H_{10}O_3$	C, H
34	H	CH_3O	H	*A*	25	Et_2O	(101–102)	$C_{10}H_{10}O_4$	C, H
				B	83				

[a]H: calcd.: 5.66; found: 6.09.

TABLE 4. Analyses of compound **4** and its derivatives



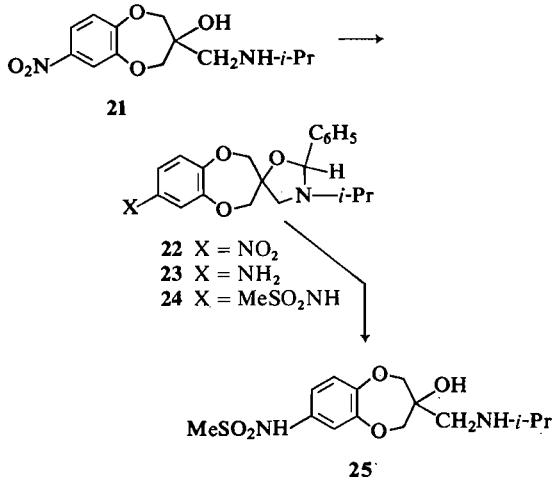
Compound	R^3	R^4	Crystallization solvent	Yield[a] (%)	Melting point (°C)	Formula	Analyses
4	H	H	CCl_4	43.5	108.5–110	$C_{10}H_9NO_3$	C, H, N
35	H	Cl	CH_2Cl_2–CCl_4	68	117–118.5	$C_{10}H_8ClNO_3$	C, H, Cl, N
36	H	CH_3	CCl_4	47	127–129	$C_{11}H_{11}NO_3$	C, H, N
37	CH_3O	H	CCl_4	39	115–117	$C_{11}H_{11}NO_4$	C, H, N

[a]Yield of recrystallized product. However, crude product was usually used in the next step.

precluded its use as a protective group during synthesis of aryl acyl amido derivatives of **B**. For the synthesis of the methanesulfonamido derivative **25**, the more readily hydrolyzable oxazolidine ring derived from benzaldehyde was employed. A few tertiary amines are described in Table 7.

Biological Activity

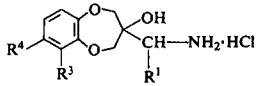
In recent years there has been a search for β-adrenergic stimulants showing selective action on the β_2-adrenergic receptors which mediate relaxation of bronchial muscle, rather than action on the β_1-adrenergic receptors which mediate responses of heart muscle.[1] The structures of most of the new β-stimulants described, have been based upon the observation that the 3-phenolic group of the catecholamine molecule can be replaced by a variety of other substituents with retention of pharmacological activity and improved selectivity. In addition, because the modified molecules are not substrates for catechol-*O*-methyltransferase, they exhibit longer duration



SCHEME 5

[1]For more detailed information about the classification of adrenergic receptors see the publication of Lands and Brown (4).

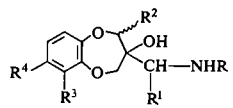
TABLE 5. Analyses of compound **5** and its derivatives



Compound	R^1	R^3	R^4	Method	Crystallization solvent	Yield[a] (%)	Melting point (°C)	Formula	Analyses
5	H	H	H	*C*	EtOH	79	235–240	$C_{10}H_{13}NO_3 \cdot HCl$	C, H, N
38	CH_3	H	H	*D*	*i*-PrOH–Et_2O EtOH	36	204–206	$C_{11}H_{15}NO_3 \cdot HCl$	C, H, Cl, N
39	C_2H_5	H	H	*D*	*i*-PrOH	31	197–198	$C_{12}H_{17}NO_3 \cdot HCl$	C, H, Cl, N
40	H	CH_3O	H	*C*	MeOH	62	227–229.5	$C_{11}H_{15}NO_4 \cdot HCl$	C, H, Cl, N
41	H	H	Cl	*C*	*i*-PrOH	40	Sinters at *ca.* 198, dec. > 240	$C_{10}H_{12}ClNO_3 \cdot HCl$	C, H, Cl, N
42	H	H	CH_3	*C*	*i*-PrOH	24	Sinters at *ca.* 217	$C_{11}H_{15}NO_3 \cdot HCl$	C, H, Cl, N

[a]Yields of **5**, **40**, **41**, and **42** are overall yields from the ketone of recrystallized product, obtained by reduction of crude cyanohydrin. Yields of **38** and **39** are based on crude nitro compound.

TABLE 6. Analyses of compounds of general formula **B**



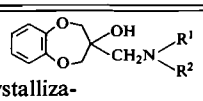
Compound	R	R^1	R^2	R^3	R^4	Method	Crystallization solvent	Yield (%)	Melting point (°C)	Formula	Analyses
43	CH_3	H	H	H	H		EtOH	33	217–219	$C_{11}H_{15}NO_3 \cdot HCl$	C, H, Cl, N
44	C_2H_5	H	H	H	H		EtOH	47	181.5–183	$C_{12}H_{17}NO_3 \cdot HCl$	C, H, Cl, N
45	$(CH_3)_2N$	H	H	H	H	*F*	*i*-PrOH	50	186–188	$C_{12}H_{18}N_2O_3 \cdot HCl$	C, H, N, Cl[a]
9	$(CH_3)_2CH$	H	H	H	H	*E*	*i*-PrOH	83	174.5–175.5	$C_{13}H_{19}NO_3 \cdot HCl$	C, H, N
46	$(CH_3)_2CH$	CH_3	H	H	H		EtOH–Et_2O	76	215–217	$C_{14}H_{21}NO_3 \cdot HCl$	C, H, Cl, N
47	$(CH_3)_2CH$	H	H	H	Cl	*E*	*i*-PrOH	70	171–172.5	$C_{13}H_{18}ClNO_3 \cdot HCl$	C, H, Cl, N
48	$(CH_3)_2CH$	H	H	H	CH_3	*E*	EtOH	76	175–177	$C_{14}H_{21}NO_3 \cdot HCl$	C, H, Cl, N
21	$(CH_3)_2CH$	H	H	H	NO_2		*i*-Pr_2O	62	97.5–98.5	$C_{13}H_{18}N_2O_5$	C, H, N
							EtOH		195–196dec.	$C_{13}H_{18}N_2O_5 \cdot (COOH)_2$	C, H, N
49	$(CH_3)_2CH$	H	H	H	NH_2		C_6H_6	74	95.5–97.5	$C_{13}H_{20}N_2O_3$	C, H, N
14	$(CH_3)_2CH$	H	H	H	HO		C_6H_6	39	133.5–134	$C_{13}H_{19}NO_4$	C, H, N

TABLE 6. (*Concluded*)

Compound	R	R¹	R²	R³	R⁴	Method	Crystallization solvent	Yield (%)	Melting point (°C)	Formula	Analyses
25	$(CH_3)_2CH$	H	H	H	CH_3SO_2NH			47	214–215dec.	$C_{14}H_{22}N_2O_5S\cdot(COOH)_2$	H, N, S, C[b]
50	$(CH_3)_2CH$	H	H	CH_3O	H	*E*	EtOH–Et_2O	56	155–157	$C_{14}H_{21}NO_4\cdot C_4H_4O_4$[c]	C, H, N
51	$(CH_3)_2CH$	H	H	HO	H		MeOH–EtOAc	80	196–197	$C_{13}H_{19}NO_4\cdot HBr$	C, H, Br, N
52		H	H	H	H	*F*	EtOH	55	187–189	$C_{13}H_{17}NO_3\cdot HCl$	C, H, Cl, N
53		H	H	H	H	*E*	*i*-PrOH	74	183–184	$C_{14}H_{21}NO_3\cdot HCl$	C, H, Cl, N
54	$(CH_3)_3C$	H	H	H	H	*F*	*i*-PrOH	75	186.5–188	$C_{14}H_{21}NO_3\cdot HCl$	C, H, Cl, N
20	$(CH_3)_3C$	H	CH_3	H	H	*F*	EtOH–*i*-PrOH	3	229–230dec.	$C_{15}H_{23}NO_3\cdot(COOH)_2$	C, H, N
55	$(CH_3)_3C$	H	H	CH_3O	H	*F*	EtOH	81	193–195dec.	$C_{15}H_{23}NO_4\cdot C_4H_4O_4$	C, H, N
56		H	H	H	H	*F*	*i*-PrOH	62	192–193	$C_{14}H_{19}NO_3\cdot HCl$	C, H, Cl, N
57		H	H	H	H	*F*	EtOH	66	190.5–192.5	$C_{15}H_{19}NO_3\cdot HCl$	C, H, Cl, N
58		H	H	H	H	*F*	*i*-PrOH	55	138.5–140	$C_{14}H_{21}NO_4\cdot C_4H_4O_4$[c]	C, H, N
59		H	H	H	H	*F*	*i*-Pr_2O MeOH	40	122–124 267–276	$C_{20}H_{27}NO_3$ $C_{20}H_{27}NO_3\cdot HCl$	 C, H, Cl, N
60	$HO(CH_2)_2O(CH_2)_2$	H	H	H	H	*F*	EtOH–Et_2O	63	155–158	$C_{14}H_{21}NO_5\cdot HCl$	C, H, Cl, N
61	$-(CH_2)_6-$[d]	H	H	H	H	*F*	MeOH	44	274–277	$C_{26}H_{36}N_2O_6\cdot 2HCl$	C, H, Cl, N
62	$C_6H_5CH_2$	H	H	H	H	*E*	EtOH	46	214–216	$C_{17}H_{19}NO_3\cdot HCl$	C, H, Cl, N
63	$C_6H_5CH_2CH_2$	H	H	H	H	*E*	EtOH	11	229–231	$C_{18}H_{21}NO_3\cdot HCl$	C, H, Cl, N
64	$C_6H_5CH(OH)CH_2$	H	H	H	H	*F*	EtOH	44	200–202	$C_{18}H_{21}NO_4\cdot HCl$	C, H, Cl, N
65	$C_6H_5CH_2CH(CH_3)$	H	H	H	H	*E*	EtOH	49	170–174	$C_{19}H_{23}NO_3\cdot HCl$	C, H, Cl, N
66	$C_6H_5CH_2CH_2CH(CH_3)$[e]	H	H	H	H	*E*	*i*-PrOH	26	180–183	$C_{20}H_{25}NO_3\cdot HCl$	C, H, Cl, N
67	$4\text{-}ClC_6H_4CH_2CH(CH_3)$	H	H	H	H	*E*	EtOH	52	163–165	$C_{19}H_{22}ClNO_3\cdot HCl$	C, H, Cl, N
68	$4\text{-}HOC_6H_4CH_2CH(CH_3)$	H	H	H	H	*E*	$CHCl_3$	50	129.5–130.5	$C_{19}H_{23}NO_4$	C, H, N
69	$3,4\text{-}(CH_2O_2)C_6H_3CH_2CH(CH_3)$	H	H	H	H	*E*	EtOH MeOH	64 62	127–129dec. 188–189.5	$C_{19}H_{23}NO_4\cdot H_3PO_4\cdot H_2O$ $C_{20}H_{23}NO_5\cdot HCl$	C, H, N, P[f] C, H, Cl, N
70	$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2CH(CH_3$	H	H	H	H	*E*	MeOH	72	220–221.5	$C_{22}H_{29}NO_6\cdot HCl$	C, H, Cl, N
71	$3\text{-Indolyl-}CH_2CH(CH_3)$	H	H	H	H	*E*	EtOH–Et_2O	60	190–191dec.	$C_{21}H_{24}N_2O_3\cdot HCl$	C, H, Cl, N
72	$4\text{-}(CH_3)_2NC_6H_4CH_2CH(CH_3)$	H	H	H	H	*F*	*i*-PrOH	50	226–228	$C_{21}H_{28}N_2O_3\cdot 2HCl$	C, H, Cl, N
73	$2\text{-Furyl-}CH_2CH(CH_3)$	H	H	H	H	*F*	EtOH	66	166.5–168	$C_{17}H_{21}NO_4\cdot HCl$	C, H, N

[a]Cl: calcd.: 12.90; found: 13.35.
[b]C: calcd.: 45.70; found: 45.08.
[c]Maleate.
[d]A bis-compound.
[e]The ketone reactant was benzalacetone.
[f]P: calcd.: 6.95; found: 7.38

TABLE 7. Analyses of some tertiary amines



Compound	R^1	R^2	Method	Crystallization solvent	Yield (%)	Melting point (°C)	Formula	Analyses
74	CH_2—CH_2		*F*	*i*-Pr_2O	71	98–99.5	$C_{12}H_{15}NO_3$	C, H, N[a]
75	CH_3	CH_3		*i*-PrOH	38	118–120	$C_{12}H_{17}NO_3$·HCl	C, H, Cl, N
76	$CH_2CH_2OCH_2CH_2$		*F*	EtOH	72	173–176	$C_{14}H_{19}NO_4$·HCl	C, H, Cl, N

[a]N: calcd.: 6.33; found: 6.81.

TABLE 8. Adenyl cyclase assay[a]

Activity	Compound
Active (40% increase in glycerol release)	**44, 9, 49, 14[b], 52, 53, 54, 58, 60, 62, 63, 65, 66, 67, 68, 71**
Moderately active (25% increase in glycerol release)	**43, 47, 50, 55, 56, 57, 59, 61, 64, 69, 70, 72, 74, 75**
Inactive	**20[c], 45, 46, 48, 21, 25, 51, 73, 76**

[a]Based upon the procedures of Rodbell (12) and Korn (13).
[b]Subsequently found to be not very active in the *in vivo* assays.
[c]However, the compound showed activity *in vivo*.

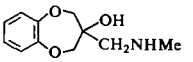
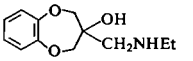
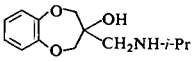
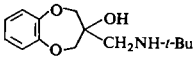
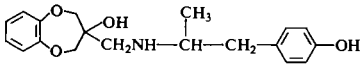
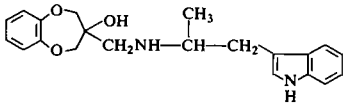
of action. The active compounds described in this paper constitute a novel class of β-stimulants in that there is no functionality present to mimic the phenolic groups of the catecholamines.

The compounds were tested for their ability to stimulate the enzyme adenyl cyclase as evinced by enhanced release of glycerol from rat epididymal adipose tissue (Table 8) and as inhibitors of histamine-induced bronchial constriction in the dog. Bronchial dilator data for some of the more interesting compounds are given in Table 9. As far as the substituent (R) on the nitrogen atom is concerned, the structure activity relationship in this series parallels that observed in other classes of β-stimulants (and in β-adrenergic blocking agents). The most active members of the series are secondary amines (**B**, $R^1 = R^2 = R^3 = R^4 =$ H) in which R is an alkyl or aralkyl group of the type that confers greatest activity on compounds of the catecholamine series (4). Primary or tertiary amines are generally inactive.

Comparison of the dihydrobenzodioxepin compounds with the isomeric benzodioxan derivatives indicates marked differences in pharmacological behavior because the latter are claimed to be β-adrenergic blocking agents (5).

There have been speculations about the molecular mechanism for β-stimulant activity which suggest that the two hydroxyl groups in the catechol nucleus are involved in chelation with a divalent metal ion (*6a*) or that the agonist molecule may bring about a conformational change in the enzymic (or receptor) protein and its associated shell of water molecules by hydrogen bonding at a specific site adjacent to an aromatic binding site (*6b*). While these possibilities could apply to the benzodioxepins also, the different location of the two ether oxygen atoms relative to the side chain, plus their lack of acidity means that significant differences must exist in their interactions at the receptor level. Introduction of acidic substituents on the aromatic ring of the dihydrobenzodioxepins (**14, 25, 51**), in order to increase their resemblance to the catecholamines, resulted in a reduction in biological activity. This was particularly surprising in the case of **51** which, on the basis of a comparison of molecular models, seemed most likely to be capable of interacting like a catecholamine at a receptor site. In view of the difficulty of displacing the 3-hydroxyl group in these compounds, the β-adrenergic agonist theory of Larsen (7) does not seem applicable to this series of β-stimulants.

TABLE 9. Inhibition of histamine-induced bronchial constriction in the anesthetized dog

Compound	Structure	Route of administration[a]	ED_{50}[b] (μg/kg)	No. of animals	ΔHR[c] (b.p.m.)	ΔBP[d] (Torr)
43		i.v.	650	1	+30	−20
44		i.v.	220	1	+38	−40
9		i.v.	29	1	+75	−50
54		i.v. i.d.	14 66	3 5	+22 +41	−25 −34
68		i.v.	37	1	+27	−45
71		i.v.	58	1	+39	−39
Salbutamol (11)		i.v. i.d.	4 29	3 5	+68 +67	−70 −55
Isoproterenol		i.v. i.d.	0.08 240	8 5	+76 +37	−57 −35

NOTE: Mongrel dogs were anaesthetized with vinbarbital (60 mg/kg i.v., supplemented by 20 mg/kg intramuscularly). Bronchoconstriction was induced at 15-min intervals by intravenous injection of 20 μg of histamine acid phosphate. Following stabilization of the bronchoconstrictor responses, test substances were injected i.v. cumulatively in threefold increments either 1- (isoproterenol) or 2 min (other compounds) before challenge until a greater than 50% inhibition of bronchoconstriction was observed. In the case of i.d. administration, three dose levels (*e.g.* 10, 30, and 100 μg/kg) calculated to produce 16–84% inhibition of the induced bronchoconstrictor response were used for each compound and five dogs were used at each dose level.

[a]Intravenous (i.v.) or intraduodenal (i.d.).
[b]Effective dose (50).
[c]Change in heart rate (beats per minute).
[d]Change in blood pressure. Results for heart rate and blood pressure are the maximal changes seen over the dose range.

Compound **54**, like salbutamol,[2] shows good absorption from the duodenum (indicated by a low ratio of i.d.[3] activity/i.v. activity in Table 9) and thereby makes up for its lack of intrinsic activity relative to isoproterenol which is very poorly absorbed. Duration of action is good and the moderate chronotropic activity at bronchial dilator dose levels is indicative of a degree of specificity for β_2-receptors.

Experimental

Melting points (uncorrected) up to 220° were taken in a Thomas Hoover capillary melting point apparatus and those above 220° were taken in an Electrothermal apparatus. The i.r. spectra were recorded with a Perkin Elmer 157 spectrometer and n.m.r. spectra with a Varian A60A spectrometer with TMS as internal reference. Mass spectra were provided by Morgan Schaffer Corporation, and microanalyses by Organic Microanalyses Laboratories (Dr. C. Daesslé), both of Montreal. Analyses are within 0.4% of theory unless otherwise stated. A table of analytical data is provided as supplementary material.[4]

1,2-Di-(cyanomethoxy)benzene (1)

To a stirred mixture of catechol (99 g, 0.9 mol), finely powdered K_2CO_3 (168 g, 1.22 mol), and acetone (600 ml) was added chloroacetonitrile (90.6 g, 1.2 mol) over 5 min. The mixture was heated slowly to reflux, then after 1½ h under reflux, the mixture was treated with more K_2CO_3

[2]2-*t*-Butylamino-1-(4-hydroxy-3-hydroxymethylphenyl) ethanol, a selective β-stimulant (11).

[3]Note, i.d. is used as an abbreviation for intraduodenal in this paper, not intradermal.

[4]A complete set of tabular data is available, at a nominal charge, from the Depository of Unpublished Data, CISTI, National Research Council of Canada, Ottawa, Canada K1A 0S2.

(84 g, 0.61 mol) and chloroacetonitrile (45.3 g, 0.6 mol). After a further 3½ h under reflux the mixture was filtered, the inorganic solid was washed with acetone (150 ml), and the combined filtrate evaporated to an oil that crystallized and was recrystallized from MeOH–H_2O (400 ml : 50 ml) giving 138 g (73%) of **1**, m.p. 85–85.5°; ν_{max} (KBr) 1500, 1080, 680, no ν CN; δ (CD_3CN) 7.20 (4H, s, aryl H), 4.98 (4H, s, OCH_2); analyzed (C, H, N) for $C_{10}H_8N_2O_2$.

3-Amino-4-cyano-2H-1,5-benzodioxepin (2)

A solution of **1** (9.4 g, 0.05 mol) in dry DMSO (20 ml) was added dropwise to potassium *t*-butoxide (12.3 g, 0.11 mol) in dry DMSO (30 ml) under dry N_2, with external cooling (water bath at room temperature). The mixture was stirred for 2 h and then poured into dilute acetic acid (6.6 ml AcOH in 20 ml H_2O). The crude product was collected, washed with water, dried, and recrystallized from chloroform giving 5.8 g (62%) of **2**, m.p. 162–164°. Pure **2** has m.p. 168–169°; ν_{max} (KBr) 3463, 3360, 2192, 1656, 747, (*cf.* ref. 8); δ (DMSO-d_6) 6.97–6.93 (4H, m, aryl H), 6.58 (2H, bs, NH_2), 4.93 (2H, s, OCH_2). Analyzed (C, H, N) for: $C_{10}H_8N_2O_2$.

3-Oxo-3,4-dihydro-2H-1,5-benzodioxepin (3)

Method A, Table 3

A mixture of **2** (29.75 g, 0.158 mol), water (20 ml), and acetic acid (300 ml) was heated under reflux for ½ h. Phosphoric acid (85%; 120 ml) was added slowly and the mixture refluxed overnight. The solution was cooled to room temperature, poured into ice water (250 ml) and saturated with ammonium sulfate, before continuously extracting with ether for 48 h. The ethereal solution was evaporated, the oily residue dissolved in ether, and the solution treated with charcoal, filtered, extracted with 10% Na_2CO_3 solution, dried ($MgSO_4$), and distilled to give **3** as a colorless oil, 13.15 g (51%), b.p. 64–68°/0.35 Torr, that crystallized on standing, m.p. 33–36°; ν_{max} (CCl_4) 1745, 1490, 1257, 1049 (l); δ ($CDCl_3$) 6.98 (4H, s, aryl H), 4.68 (4H, s, OCH_2).

6-Methoxy-3-oxo-3,4-dihydro-2H-1,5-benzodioxepin (34)

Method B, Table 3

To methanol (450 ml) saturated with HCl was added **31** (61.3 g, 0.28 mol) and the suspension was stirred until solution occurred. The solution was allowed to stand at room temperature for 6 days, then methanol (450 ml) and water (900 ml) were added, and the mixture was heated under reflux for 10 h. Evaporation of the mixture gave 19.1 g (83%) of **34**, m.p. 101–102°; ν_{max} (KBr) 1743, 1500, 1105; δ ($CDCl_3$) 7.07–6.55 (3H, m, aryl H), 4.78, 4.72 (2H and 2H, 2s, OCH_2), 3.87 (3H, s, OCH_3). Analyzed (C, H) for $C_{10}H_{10}O_4$.

3-Cyano-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (4)

A solution of KCN (13.5 g, 0.208 mol) in water (27 ml) was added dropwise to a solution of **3** (18.7 g, 0.114 mol) in acetic anhydride (19.6 ml) with stirring and cooling (ice bath). The mixture was stirred at room temperature overnight and then basified with 10% Na_2CO_3 solution. Ether extraction of the basified mixture gave **4** as a pale yellow oily solid, 24.3 g (> 100%). This crude material was used in the next step because recrystallization of the solid gave a poor recovery. Crude **4** on recrystallization from CCl_4 (4 parts v/w) afforded a 43% yield of colorless platelets, m.p. 108.5–110°; ν_{max} (KBr) 1505, 1255, 1126, no ν CN. Analyzed (C, H, N) for $C_{10}H_9NO_3$.

3-Aminomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin Hydrochloride (5)

Method C, Table 5

A solution of crude **4** (4.92 g, 30 mmol) in dry ether (100 ml) was added dropwise with stirring to a slurry of lithium aluminum hydride (3.8 g, 100 mmol) in ether (100 ml) under N_2 during ¾ h. Then the mixture was stirred under reflux for 2¾ h before quenching with water (3.8 ml), followed by 10% NaOH solution (5.7 ml) and more water (11.4 ml). The inorganic solid was filtered off, washed with ether (50 ml), and the combined filtrate was dried ($MgSO_4$) and evaporated to afford crude base **5**, 5.13 g (87%), m.p. 60–63°. This can be recrystallized from benzene to afford platelets, m.p. 66–68°, but the solid appears to absorb water and CO_2 from the air. Accordingly a solution of the base in ether was treated with ethanolic HCl solution to give the hydrochloride, m.p. 235–240° (*i*-PrOH); ν_{max} (KBr) 1499, 1300, 1099, 750. Analyzed (C, H, N) for $C_{10}H_{13}NO_3 \cdot HCl$)

3-Hydroxy-3-isopropylaminomethyl-3,4-dihydro-2H-1,5-benzodioxepin Hydrochloride (9)

Method E, Table 6

A mixture of **5** (3.47 g, 15 mmol), anhydrous sodium acetate (1.23 g, 15 mmol), and ethanol (40 ml) was stirred under N_2 for 10 min. Acetone (960 mg, 16.5 mmol) was added and stirring was continued for 20 min. Hydrogenation of the mixture at 26° and atmospheric pressure in the presence of platinium oxide was carried out until uptake of H_2 was complete. The catalyst was filtered off and the filtrate evaporated to a syrup. Dry ether (60 ml) was added, followed by a slight excess of ethanolic HCl to afford **9**, 3.91 g (95%), m.p. 173–175°. Recrystallization of the solid from isopropanol (75 ml) gave pure **9**, 3.43 g (83%), m.p. 174.5–175.5°; ν_{max} (KBr) 3340, 3295, 1497, 1253, 1055. Analyzed (C, H, N) for $C_{13}H_{19}NO_3 \cdot HCl$.

3,4-Dihydro-2H-1,5-benzodioxepin-3-spirooxirane (6)

Procedure a

Sodium hydride (132 mg, 5.5 mmol) was suspended in dry DMSO (2 ml) and trimethyl sulfoxonium iodide (1.25 g; 5.68 mmol) was added. When H_2 evolution had abated (*ca.* 30 min), a solution of **3** (820 mg, 5 mmol) in DMSO (1.2 ml) was added dropwise and with stirring at room temperature. Stirring was continued for 2 h at 26° and then for 1 h at 50°. The mixture was poured into water (30 ml) and **6** was isolated by extraction with CH_2Cl_2 (2 × 20 ml), 456 mg (51%), m.p. 147–149° (MeOH).

Procedure b

A solution of $NaNO_2$ (6.9 g, 0.1 mol) in water (50 ml) was added slowly with stirring during ½ h to a solution of **5**·HCl (23.17 g, 0.1 mol) in water (200 ml) containing acetic acid (0.1 ml) at −4 to 0°. Then the solution was stirred at room temperature for ½ h and the crude **6** was collected, 14.84 g, m.p. 132–144°. Recrystallization of the solid from MeOH (*ca.* 450 ml) gave 11.65 g (65%) of **6**, m.p. 147–149°; ν_{max} (KBr) 1494, 1242, 1006; δ (DMSO-d_6) 6.98 (4H, s, aryl H), 4.35 and 3.99 (2H and 2H, 2d, OCH_2, J = 13 Hz), 2.89 (2H, s, oxirane H). Analyzed (C, H) for $C_{10}H_{10}O_3$.

Extraction of the aqueous filtrate with ether afforded an oil (1.3 g) that crystallized from $CHCl_3$ and was recrystallized from water to give 254 mg of **7**, m.p. 124.5–125.5°. This glycol can be obtained by hydrolyzing **6** with dilute $HClO_4$; ν_{max} (KBr) 3420, 1499, 1048; *m/e* 196 (M^+). Analyzed (C, H) for $C_{10}H_{12}O_4$.

6-Methoxy-3,4-dihydro-2H-1,5-benzodioxepin-3-spirooxirane (79)

This was prepared in 28% yield by procedure *a* above, m.p. 106–110° (MeOH) (pure **79** has m.p. 110.5–111.5°); ν_{max} (KBr) 1489, 1472, 1092, 1079; δ (DMSO-d_6) ~7.1–6.5 (3H, m, aryl H), 4.35 and 3.98 (1H and 1H, 2d, OCH_2, J = 13½ Hz), 4.30 and 3.98 (1H and 1H, 2d, OCH_2, J = 13½ Hz), 3.75 (3H, s, OCH_3), 2.89 (2H, s, oxirane H). Analyzed (C, H) for $C_{11}H_{12}O_4$.

3-t-Butylaminomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin Hydrochloride (54)

Method F, Table 6

A mixture of **6** (1.78 g, 10 mmol), *t*-butylamine (3.2 ml, ~30 mmol), and methanol (25 ml) was stirred at room temperature for 42 h. Evaporation of the solvent, dissolution of the oily residue in ether, and treatment with excess ethanolic HCl solution afforded 3.0 g of **54**, m.p. 169–177°. Recrystallization of the crude product from isopropanol gave 2.15 g (75%) of **54**, m.p. 186.5–188°; ν_{max} (KBr) 3265, 1491, 1253, 1050; δ (DMSO-d_6) ~9.0 (2H, bs, NH_2^+), 7.03 (4H, s, aryl H), 6.37 (1H, bs, OH), 4.46 and 4.12 (2H and 2H, 2d, OCH_2, J = 6 Hz), 3.45 (2H, s, CH_2N), 1.36 (9H, s, *t*-Bu). Analyzed (C, H, Cl, N) for $C_{14}H_{21}NO_3 \cdot HCl$.

3-Formamidomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (77)

To a solution of **5** (5.86 g, 30 mmol) in dry ether (60 ml) was added formic acetic anhydride (9) (31.5 mmol) dropwise and the mixture was stirred overnight. The solution was washed successively with water, 10% Na_2CO_3 solution, and water. The product was not completely soluble in ether at this point: after separating the ether layer, an extraction with chloroform was performed. The combined extract yielded 6.1 g (91%) of waxy solid, used without purification in the next step.

3-Methylaminomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin Hydrochloride (43)

Reduction of **77** (5.80 g, 26 mmol) with lithium aluminum hydride (2.0 g, 52 mmol) in dry ether (110 ml), followed by isolation of the product as the hydrochloride, gave 2.14 g (33%) of **43**, m.p. 217–219° (EtOH); ν_{max} (KBr) 3259, 1500, 1259. Analyzed (C, H, Cl, N) for $C_{11}H_{15}NO_3 \cdot HCl$.

3-Acetamidomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (78)

To a solution of **5** (3.20 g, 15.9 mmol) and triethylamine (1.68 g, 16.7 mmol) in dry chloroform was added dropwise acetic anhydride (1.70 g, 16.7 mmol) in dry chloroform. After 1 h at room temperature, the reaction mixture was washed with water, 3.6 *N* sulfuric acid, water, 10% Na_2CO_3 solution, and water. Evaporation of the organic layer yielded 3.41 g (89%) of **78**, m.p. 98–100° ($CHCl_3$); ν_{max} (KBr) 3312, 1635 (br), 1497. Analyzed (C, H, N) for $C_{12}H_{15}NO_4$.

3-Ethylaminomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin Hydrochloride (44)

Reduction of **78** with lithium aluminum hydride in ether gave 47% of **44**, m.p. 181.5–183° (EtOH); ν_{max} (KBr) 3235, 1497, 1055. Analyzed (C, H, Cl, N) for $C_{12}H_{17}NO_3 \cdot HCl$.

2-Cyano-3-oxo-3,4-dihydro-2H-1,5-benzodioxepin (15)

A mixture of **2** (30.0 g, 0.16 mol), concentrated HCl (90 ml), water (90 ml), and ethanol (450 ml) was heated under reflux for 1¾ h. After evaporation of the mixture, water was added to dissolve NH_4Cl, and the product was extracted with ether (4 × 200 ml). The dried ethereal solution (Na_2SO_4 followed by $CaSO_4$) was evaporated to an oil at 50°/15 Torr and further stripping at 50°/0.1 Torr induced crystallization; 29.2 g (96%) of slightly waxy solid, m.p. 134–136° was obtained. Recrystallization of the crude material either from benzene or from diisopropyl ether containing 5% ethyl acetate gave pure **15**, m.p. 135–136°, but recovery was low; ν_{max} (KBr) 1752, 1489, 1260; no ν CN. Analyzed (C, H, N) for $C_{10}H_7NO_3$.

2-Cyano-2-methyl-3-oxo-3,4-dihydro-2H-1,5-benzodioxepin (16)

To a warm, stirred, solution of **15** (7.95 g, 42 mmol) in benzene (80 ml) was added a solution of thallous ethoxide (10.0 g, 40 mmol) in benzene (40 ml). After 30 min, the solid was collected, washed with benzene, and added to methyl iodide (60 ml). The suspension was heated under reflux for 6 h, filtered, and evaporated to an oil (8.2 g). Chromatography of the oil on 480 g of Baker 3405 silica gel by the dry column technique (10) gave 1.07 g (12%) of enol ether (**17**) as an oil; ν_{max} (neat) 2208 (medium intensity), 1650, 1495, 1240; δ (CCl_4), ~7.1–6.75 (4H, m, aryl H), 4.77 (2H, s, CH_2), 3.97 (3H, s, OCH_3).

The cyano ketone **16** was obtained as a low-melting solid, 5.71 g (67%), m.p. 71–72° ($CHCl_3$–CCl_4); ν_{max} (KBr) 2245 (very small), 1760, 1495, 1251; δ (CCl_4) 6.98 (4H, s, aryl H), 4.70 and 4.65 (2H, 2s, OCH_2), 1.86 (3H, s, CH_3). Analyzed (C, H, N) for $C_{11}H_9NO_3$.

2-Methyl-3-oxo-3,4-dihydro-2H-1,5-benzodioxepin (18)

Hydrolysis of **16** by method *B*, Table 3, gave **18** in 67% yield; ν_{max} (KBr) 1750, 1495, 1265; δ (CCl_4) 6.89 (4H, s, aryl H), 4.95 (1H, quartet, OCH, J = 6½ Hz), 4.76 and 4.40 (2H, 2d, OCH_2, J = 15 Hz), 1.43 (3H, d, CH_3, J = 6½ Hz).

Anal. Calcd. for $C_{10}H_{10}O_3$: H, 5.66. Found: H, 6.09.

3-t-Butylaminomethyl-3-hydroxy-2-methyl-3,4-dihydro-2H-1,5-benzodioxepin Oxalate (20)

On treating **18** (891 mg, 5 mmol) with dimethyl sulfoxonium methylide as described in procedure *a*, there was obtained a very crude product from which **19** could not be isolated. The crude product (672 mg) in methanol (10 ml) was treated with *t*-butylamine (1 ml) and the mixture was allowed to stand for 5 days, then evaporated to dryness. The residue was treated with CH_2Cl_2 (25 ml) and extracted with *N* HCl (10 ml + 5 ml). The acid extract was washed with CH_2Cl_2 (10 ml) and with ether (20 ml); then it was basified with 5 *N* NaOH solution (5 ml) and extracted with ether (2 × 20 ml), giving **20** (free base) as a colorless gum, 119 mg (9%). This material appeared to be homogeneous by t.l.c. but some impurity was evident in the n.m.r. spectrum; δ ($CDCl_3$) ~7.0–6.95 (4H, m,

aryl H), 4.32–3.97 (3H, m, OCH and OCH_2), 1.33 (3H, d, CH_3, J = 6 Hz), 1.10 (9H, s, *t*-Bu). The CH_2N signal was obscured by impurity. The base was treated with oxalic acid to give **20**, m.p. 229–230° dec. (*i*-PrOH). Analyzed (C, H, N) for $C_{15}H_{23}NO_3 \cdot (COOH)_2$.

*3'-Isopropyl-3,4-dihydro-2H-1,5-benzodioxepin-3-spiro-5'-oxazolidin-2'-one (**10**)*

To a stirred solution of phosgene (15.5 g, 0.157 mol) in chloroform (100 ml) cooled to 5–8° was added dropwise a solution of **9** (24.8 g, 0.105 mol) in chloroform (100 ml). The resulting suspension was treated dropwise with triethylamine (44.7 ml, *ca.* 0.32 mol) at 5–8° and then the reaction mixture was stirred for 1 h at room temperature before being poured into water (200 ml). The chloroform layer was separated and washed in succession with 10% HCl (25 ml), water (25 ml), 5% NaOH solution (25 ml), and water (2 × 25 ml). The solution was dried ($MgSO_4$) and evaporated to give a solid, which was recrystallized from carbon tetrachloride (90 ml) to yield 23.1 g (84%) of **10**, m.p. 118–120° (pure **10** has m.p. 121–122° (*i*-Pr_2O)); ν_{max} (KBr) 1721, 1263, 1051; δ (DMSO-d_6) 6.98 (4H, s, aryl H), 4.25 (4H, s, OCH_2), 3.90 (1H, septet, methine, J = 6½ Hz), 3.43 (2H, s, CH_2N), 1.13 (6H, d, CH_3, J = 6½ Hz). Analyzed (C, H, N) for $C_{14}H_{17}NO_4$.

*3'-Isopropyl-7-nitro-3,4-dihydro-2H-1,5-benzodioxepin-3-spiro-5'-oxazolidin-2'-one (**11**)*

A solution of **10** (24.8 g, 94.2 mmol) in acetic acid (100 ml) was cooled to the freezing point in an ice bath and a mixture of 90% HNO_3 and concentrated H_2SO_4 (54 ml containing 1.2 ml of HNO_3 (*d* 1.5) to each 10 ml of H_2SO_4) was added dropwise with stirring over 10 min. The mixture was stirred for 2 h at 26° and poured into water (400 ml). The crude product was taken up in methylene chloride (3 × 100 ml) and the extract was washed with water (100 ml), 10% Na_2CO_3 (75 ml), water (100 ml), and dried ($MgSO_4$). Evaporation of the solvent and recrystallization of the residue twice from alcohol afforded 16.4 g (56%) of **11** which was used in the next stage (pure **11** has m.p. 148–148.5° (alcohol)); ν_{max} (KBr) 1746, 1357, 1040; δ (DMSO-d_6) ~7.97–7.78 and 7.25–7.11 (2H and 1H, 2m, aryl H), 4.42 and 4.38 (2H and 2H, 2s, OCH_2), 3.89 (1H, septet, methine, J = 6½ Hz), 3.46 (2H, s, CH_2N), 1.12 (6H, d, CH_3, J = 6½ Hz). Analyzed (C, H, N) for $C_{14}H_{16}N_2O_6$.

*7-Amino-3'-isopropyl-3,4-dihydro-2H-1,5-benzodioxepin-3-spiro-5'-oxazolidin-2'-one (**12**)*

A mixture of **11** (960 mg, 3.12 mmol), ethanol (30 ml), and 5% palladium-on-charcoal was hydrogenated at 50 p.s.i. and 26° in a Parr apparatus. Work-up of the reaction mixture afforded 445 mg (51%) of **12**, m.p. 163–164° (alcohol); ν_{max} (KBr) 3450, 3360, 1745, 1510; δ (DMSO-d_6) ~6.78–6.60 and 6.25–6.07 (1H and 2H, 2m, aryl H), 4.79 (2H, s, NH_2), 4.13 and 4.05 (2H and 2H, 2s, OCH_2), 3.88 (1H, septet, methine, J = 6½ Hz), 3.36 (2H, s, CH_2N), 1.10 (6H, d, CH_3, J = 6½ Hz). Analyzed (C, H, N) for $C_{14}H_{18}N_2O_4$.

*7-Hydroxy-3'-isopropyl-3,4-dihydro-2H-1,5-benzodioxepin-3-spiro-5'-oxazolidin-2'-one (**13**)*

A solution of **12** (3.27 g, 11.75 mmol) in 10% H_2SO_4 (65 ml) was diazotized at 0–5° with 20% $NaNO_2$ solution (4.05 ml, 11.75 mmol). After stirring the mixture for 30 min at room temperature, a little urea was added to destroy excess HNO_2 (starch iodide paper as indicator) and the solution was poured into a well-stirred suspension of Baker 3405 silica gel (15 g) in boiling 10% H_2SO_4 (130 ml) during a period of 10 min. The mixture was stirred at the b.p. until a negative alkaline β-naphthol test was obtained (*ca.* 30 min). When cool, the solid was collected, washed with a little water, and dried. The solid was suspended in boiling alcohol (100 ml) and then evaporated to dryness in a rotary evaporator. It was placed on top of a column (18 × 1¼ in.) of Baker silica gel and chromatography was carried out by the dry column technique using 1:1 ether–chloroform. The first 300 ml of eluate contained 1.62 g of crude **13**, which on recrystallization from alcohol (20 ml) afforded 1.41 g of **13** of m.p. 215–217° (pure **13** separates from alcohol in prisms, m.p. 216.5–217.5°); ν_{max} (KBr) 3260 (br), 1710, 1507, 1060, 1051; δ (DMSO-d_6) ~7.02–6.75 and 6.52–6.3 (1H and 2H, 2m, aryl H), 4.17 and 4.13 (2H and 2H, 2s, OCH_2), 3.91 (1H, septet, methine, J = 6½ Hz), 3.39 (2H, s, CH_2N), 1.12 (6H, d, CH_3, J = 6½ Hz). Analyzed (C, H, N) for $C_{14}H_{17}NO_5$.

*3-Hydroxy-3-isopropylaminomethyl-7-nitro-3,4-dihydro-2H-1,5-benzodioxepin (**21**)*

A mixture of **11** (7.98 g, 25.9 mmol), dioxane (60 ml), and 45% KOH solution (16 ml) was heated in a N_2-filled stainless steel bomb at 150–160° for 16 h. When cool, the reaction mixture was extracted with ether (2 × 100 ml) and the extract was washed with saturated NaCl solution (2 × 100 ml) and then with water (100 ml). The ethereal solution was extracted with 2.75 *N* HCl (40 ml) and then with water (2 × 40 ml). Basification of the combined aqueous extract with 2.5 *N* NaOH (70 ml) and extraction with ether (2 × 100 ml), afforded a yellow solid, 6.33 g, m.p. 95–96.5°. Recrystallization of the crude product from diisopropyl ether (63 ml) gave 4.56 g (62%) of **21**, m.p. 97.5–99°; ν_{max} (KBr) 3295, 3080, 1520, 1290, 1275; δ (DMSO-d_6) ~7.90–7.74 and 7.17–7.0 (2H and 1H, 2m, aryl H), 4.23 and 3.56 (2H and 2H, 2s, OCH_2), 2.79 (2H, s, CH_2N), 0.9 (6H, d, CH_3, J = 6½ Hz). The signal for the methine proton was largely obscured by the CH_2—N and DMSO signals, and the OH and NH gave a broad signal centered on 3.5 p.p.m. Analyzed (C, H, N) for $C_{13}H_{18}N_2O_5$.

*7-Amino-3-isopropylaminomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin (**49**)*

Hydrogenation of **21** (1.5 g, 5.32 mmol) in ethanol (25 ml) at 40 p.s.i. and room temperature in the presence of 5% palladium-on-charcoal (400 mg) gave 990 mg (74%) of **49**, m.p. 96.5–97.5° (benzene); ν_{max} (KBr) 3440, 3358, 1513, 1225, 1067; δ ($CDCl_3$) 6.78–6.63 and 6.35–6.12 (1H and 2H, 2m, aryl H), 4.03 and 3.77 (2H and 2H, 2s, OCH_2), 3.32 (4H, bs, OH, NH and NH_2), 2.91 (2H, s, CH_2N), 2.76 (1H, septet, methine, J = 6 Hz), 1.05 (6H, d, CH_3, J = 6 Hz). Analyzed (C, H, N) for $C_{13}H_{20}N_2O_3$.

*3,7-Dihydroxy-3-isopropylaminomethyl-3,4-dihydro-2H-1,5-benzodioxepin (**14**)*

A mixture of **13** (200 mg, 0.716 mmol), $Ba(OH)_2 \cdot 8H_2O$ (1.08 g, 3.42 mmol), and water (3.2 ml) in an evacuated glass pressure tube was heated at 160–165° for 16 h. The reaction mixture was poured into boiling water (60 ml) with stirring and CO_2 was passed through, until all Ba^{2+} ions had been precipitated. The suspension was filtered

through Celite and evaporated to a pale brown scale (187 mg). This solid was chromatographed by the dry column technique on Baker 3405 silica gel using 3% methanol in ether as the solvent, affording 70.5 mg (39%) of **14** as the second component to be eluted. After drying in air at 60° the solid has m.p. 108–110° but drying at 80° (0.1 Torr) raises the m.p. to 133–134.5° (pure **14** had m.p. 133.5–135° (benzene)); ν_{max} (KBr), for solid of m.p. 108–110°, 3465, 3360, 3300, 3285, 1510, 1209, 1158; ν_{max} (KBr), for solid of m.p. 133.5–135°, 3450–3260 (v br), 1509, 1470, 1155; δ (CD_3CN) ~6.79–6.61 and 6.36–6.19 (1H and 2H, 2m, aryl H), 4.0 (5H, superimposed singlets, OH, NH, OCH_2), 3.54 (2H, s, OCH_2), 2.84 (2H, s, CH_2N), 2.72 (1H, septet, methine, J = 6 Hz), 1.02 (6H, d, CH_3, J = 6 Hz). Analyzed (C_9H, N) for $C_{13}H_{19}NO_4$.

3,6-Dihydroxy-3-isopropylaminomethyl-3,4-dihydro-2H-1,5-benzodioxepin Hydrobromide (51)

A solution of **50** free base (600 mg, 2.24 mmol) in 48% HBr (10 ml) was heated under reflux for 10 h, then evaporated to dryness at 50–55° (10 Torr). A solution of the residue in alcohol was treated with charcoal, filtered, and evaporated to dryness. Recrystallization of the solid from methanol – ethyl acetate yielded 596 mg (80%) of **51**, m.p. 193–195° (pure **51** has m.p. 196–197° (MeOH–EtOAc)); ν_{max} (KBr) 3430, 3350 (both broad), 1485, 1224, 1059. Analyzed (C, H, Br, N) for $C_{13}H_{19}NO_4 \cdot HBr$.

3-Hydroxy-3-(1-nitroethyl)-3,4-dihydro-2H-1,5-benzodioxepin (80)

Nitroethane (6.32 ml, 88 mmol) was added to a mechanically stirred slurry of potassium *t*-butoxide (8.98 g, 80 mmol) in dry ether (165 ml). To the thick suspension, cooled below 10°, was added a solution of **3** (13.12 g, 80 mmol) in ether (40 ml) slowly over ½ h. After 3 h at room temperature, the reaction mixture was acidified with acetic acid (4.80 g, 80 mmol) in dry ether (40 ml); more ether (500 ml) was added and the mixture filtered. Evaporation of the filtrate gave 16.1 g (83%) of crude **80** used in the next stage.

3-(1-Aminoethyl)-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin Hydrochloride (38)

Method D, Table 5

Crude **80** (16.1 g, 67.3 mmol) in ethanol (100 ml) was hydrogenated in a Parr low pressure hydrogenerator in the presence of 5% palladium-on-charcoal. Hydrogen uptake was about 85% of theory. After filtration and evaporation, the crude product was taken up in ether (125 ml) and extracted with 5 *N* HCl (3 × 15 ml). Basification (20% NaOH solution) of the acid extract and extraction with ether gave an oil which was converted to a hydrochloride salt with HCl in ethanol; 6.0 g (36%) of crude **38** m.p. 192–203° was obtained. Upon recrystallization from ethanol the m.p. was raised to 204–206°; ν_{max} (KBr) 3300, 1492, 1251, 1040, 751; δ (DMSO-d_6) 6.84 (4H, s, aryl H), 4.52 and 4.33 (2H, 2d, OCH_2, J = 12½ Hz), 4.10 and 4.06 (2H, 2d, OCH_2, J = 12½ Hz), 3.60 (1H, quartet, methine, J = 7 Hz), 1.37 (3H, d, CH_3, J = 7 Hz). Analyzed (C, H, Cl, N) for $C_{11}H_{15}NO_3 \cdot HCl$.

3-Hydroxy-3-(1-nitropropyl)-3,4-dihydro-2H-1,5-benzodioxepin (81)

Compound **81** was prepared from **3** and 1-nitropropane by the method described for **80** and was used without purification.

3-(1-Aminopropyl)-3-Hydroxy-3,4-dihydro-2H-1,5-benzodioxepin Hydrochloride (39)

Hydrogenation of **81** at atmospheric pressure in the presence of Raney nickel yielded 31% of **39**, m.p. 197–198°; ν_{max} (KBr) 3305(b), 1502, 1267, 1050, 770. Analyzed (C, H, Cl, N) for $C_{12}H_{17}NO_3 \cdot HCl$.

3-Dimethylaminomethyl-3-hydroxy-3,4-dihydro-2H-1,5-benzodioxepin Hydrochloride (75)

A mixture of **5** free base (3.20 g, 16.4 mmol), 88% formic acid (43 g), and 37% formalin (3.0 ml) was heated under reflux for 17 h. Basification of the reaction mixture with 20% NaOH (10 ml) and extraction with ether (2 × 50 ml) afforded an oil (3.4 g) which was converted to a hydrochloride salt, 2.84 g, m.p. 119–230°. The crude product was recrystallized twice from isopropanol to give 1.64 g (38%) of **75**, m.p. 118–120°, clearing at *ca.* 210°; ν_{max} (KBr) 3225(br), 1501, 1260, 761. Analyzed (C, H, Cl, N) for $C_{12}H_{17}NO_3 \cdot HCl$.

3'-Isopropyl-7-nitro-2'-phenyl-3,4-dihydro-2H-1,5-benzodioxepin-3-spiro-5'-oxazolidine (22)

A mixture of **21** (1.41 g, 5 mmol), benzaldehyde (530 mg, 5 mmol), acetic acid (1 drop), and isopropanol (10 ml) was distilled slowly and isopropanol was added to keep the volume constant. After 3 h, the mixture was set aside at 5° overnight. The product was collected and recrystallized from isopropanol, giving 620 mg of solid, m.p. 151–152°. Further distillation of the mother liquors and work-up as before gave another 490 mg of product, m.p. 150–151° (for a total of 60%) and 430 mg (30%) of **21** was recovered (pure **22** has m.p. 152.5–153.5°); ν_{max} (KBr) 1522, 1347, 1282; δ ($CDCl_3$) 7.95–7.5 (2H, m, aryl H), 7.42 (5H, s, phenyl), 7.03–6.85 (1H, dd, aryl H), 4.88 (1H, s, OCHN), 4.51 (2H, s, OCH_2), 4.07 (1H, dd, 1H of OCH_2, J = 11 Hz, J' = 2 Hz), 3.63 (1H, d, 1H of OCH_2), 3.23 (1H, dd, 1H of CH_2N, J = 10½ Hz, J' = 2 Hz), ~2.75 (1H, septet, methine, J = 7 Hz), 2.68 (1H, d, 1H of CH_2N, J = 10½ Hz), 0.98 (3H, d, CH_3, J = 7 Hz), 0.84 (3H, d, CH_3, J = 7 Hz). The two doublets for CH_3 overlap to form a triplet.[5] Analyzed (C, H, N) for $C_{20}H_{22}N_2O_5$.

7-Amino-3'-isopropyl-2'-phenyl-3,4-dihydro-2H-1,5-benzodioxepin-3-spiro-5'-oxazolidine (23)

A solution of **22** (92.5 mg, 0.25 mmol) in ethyl acetate (5 ml) was hydrogenated at atmospheric pressure in the presence of 5% palladium-on-charcoal (20 mg) until the theoretical amount of hydrogen had been absorbed. Work-up afforded 104 mg of oil. The product was too labile for purification but t.l.c. (silica gel – $CHCl_3$) showed the presence of a trace of **22** as the only impurity in the product.

3-Hydroxy-3-isopropylaminomethyl-7-methanesulfonamido-3,4-dihydro-2H-1,5-benzodioxepin Oxalate (25)

Crude **23** (352 mg, obtained from **22** (376 mg, 1.015 mmol)) was dissolved in dry ether and 1,4-diazabicyclo-

[5]The long-range coupling of one of the dioxepin protons with one of the oxazolidine protons (due to a W arrangement) gives an insight into the conformation of the spiro-fused ring system. This spectrum was recorded at the 220 MHz NMR Centre, Sheridan Park, Ontario.

[2.2.2]octane (118 mg, 1.065 mmol) was added. Methanesulfonyl chloride (105 mg, 1.065 mmol) in dry ether (5 ml) was added dropwise with stirring, and after 1 h the solid was filtered off and discarded. Evaporation of the filtrate afforded crude **24**, 387 mg (91%). Thin-layer chromatography on Eastman silica gel showed the presence of one major and two minor constituents but preparative t.l.c. on a 2-mm silica gel plate did not give a good separation, possibly because of hydrolysis of the product. The crude material from the plate (227 mg, 0.54 mmol) in methanol (3 ml) was treated with oxalic acid dihydrate (70 mg, 0.55 mmol) and the solution was chilled thereby yielding 108 mg (47%) of **25**, m.p. 207–209° dec. (pure **25** has m.p. 214–215° dec.); ν_{max} (KBr) 1500, 1315, 1146; m/e = 330 (M^+).

Anal. Calcd. for $C_{14}H_{22}N_2O_5S\cdot(COOH)_2$: C, 45.70. Found: C, 45.08.

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