apparently accompanied by loss of H_2S. Mass spectrographic examination of the crystals showed the expected M^+. This product was used in the next step where separation of a pure product proved less complicated.

7-Deoxy-7(*R*)-thiolincomycin (10).—Methyl 7-deoxy-7(*R*)-thiolincosaminide (**9**) (5.2 g) was treated with 4.14 g of *trans*-4-*n*-propyl-L-proline[3a] to give 6.26 g of crude product. Chromatography ($CHCl_3$–MeOH, 4:1) gave 5.96 g of **10**, $[\alpha]D$ +125° (H_2O), as an amorphous solid. The hydrochloride salt also was not crystalline. *Anal.* ($C_{18}H_{34}N_2O_5S_2$) C, H, N.

Methyl 7-Deoxy-6-deamino-6,7-aziridinothiolincosaminide (13).—Amino sugar **4** (1 g) was treated with K_2CO_3 in boiling DMF. Crystallization of the residue from MeOH after distillation of the DMF afforded 370 mg of **13**, mp 192–198°, and 160 mg, mp 182–189°. Two recrystallizations (MeOH–$AcCH_3$) gave crystals, mp 203–220° dec, $[\alpha]D$ +320° (DMSO). Only one spot was noted on tlc and the melting point was unchanged for further recrystallizations. *Anal.* ($C_9H_{17}NO_4S$) C, H, N.

Methyl 7-Deoxy-7(*S*)-thiolincosaminide (14).—A suspension of 1.5 g of aziridine **13** in 30 ml of *i*-PrOH saturated with H_2S at 0° was heated in a glass bomb on a steam bath for 5 hr. Filtration of the cooled reaction mixture yielded 1.6 g of **14**, mp 190–197°, which when recrystallized (EtOH) melted at 195–198°. *Anal.* ($C_9H_{19}NO_4S_2$) C, H, N, S.

The pentaacetate (**14a**), mp 266–268°, was prepared by acylation of **14** with Ac_2O–C_5H_5N in the usual manner. *Anal.* ($C_{19}H_{29}NO_9S_2$) C, H, N, S.

7-Deoxy-7(*S*)-thiolincomycin Hydrochloride (15).—In the manner previously described,[3b] 6.8 g of **14** was condensed with 5.2 g of *trans*-4-*n*-propyl-L-proline to yield 10.2 g of crude product. Chromatography ($CHCl_3$–MeOH, 4:1), followed by conversion to the hydrochloride, afforded 4.35 g of amorphous solid, $[\alpha]D$ −161° (H_2O). *Anal.* ($C_{18}H_{35}ClN_2O_5S_2$) C, H, N. Rechromatography of the free base gave an analytical sample. *Anal.* ($C_{18}H_{34}N_2O_5S_2$) C, H, N, S.

Methyl 6-Deamino-7-deoxythiolincosaminide (12). Method A.—Aziridine **13** (235 mg) was treated with HONO[7] followed by catalytic hydrogenation over 10% Pd–C in MeOH to give 60 mg of **12** ($AcCH_3$), mp 189–190°. *Anal.* ($C_9H_{18}O_4S$) C, H, S.

Method B.—Disulfide **11** (4.4 g) was heated at reflux for 18 hr with hydrazine hydrate. Chromatography ($CHCl_3$–MeOH, 4:1) followed by crystallization (H_2O) yielded 100 mg of **12**, mp 178–182°. Ir, mass spectra, and nmr data indicated identity with **12** prepared by method A.

Thioamidolincomycin Tetraacetate Hydrochloride (17·HCl).—Lincomycin tetraacetate (19.5 g), prepared by acylation of lincomycin with Ac_2O–C_5H_5N, was treated with 7 g of P_4S_{10} in aqueous dioxane as previously described. Conversion of the crude product to the hydrochloride yielded 24.6 g of **17**·HCl which gave 9.0 g of **17**·HCl, mp 207–214°, from $AcCH_3$–H_2O. Recrystallization gave **17**·HCl, mp 221–225° (hygroscopic). *Anal.* ($C_{26}H_{43}ClN_2O_9S_2$) C, H, N, S, Cl.

Thioamidolincomycin (18).—Five grams of **17**·HCl was treated with 0.5 *N* 50% aqueous methanolic NaOH at 26° for 1 hr. The crude product (3.5 g) was obtained by extraction with $MeCl_2$. Crystallization (aqueous MeOH) afforded 300 mg of **18**, mp 221–226°, and a second crop of 530 mg of **18**, mp 195–205°. The analytical sample was further purified by chromatography (EtOAc–AcMe–H_2O, 8:5:1). *Anal.* ($C_{18}H_{34}N_2O_5S_2$) C, H, N, S.

Thioamidoclindamycin Triacetate (19).—In the manner described above, clindamycin was converted to the triacetate and treated with P_4S_{10}. After twice chromatographing (C_6H_{12}–AcMe, 2:1) 120 mg of **19**, mp 178–181°, was obtained from 4 g of triacetate. *Anal.* ($C_{24}H_{39}ClN_2O_7S_2$) C, H, N, S.

7-Deoxy-7(*S*)-chlorothiamidolincomycin (20).—Triacetate **19** (12.9 mg) was treated with dilute alkali in aqueous AcMe for 25 min. Only one spot was noted on tlc moving about where expected. The solution was acidified and lyophilized. Purification was not attempted.

Solvolysis of 19.—A solution of 10 mg of **19** in 50% aqueous DMF was heated at reflux for 17 hr. A more polar product which reacted very rapidly with Lemieux reagent (characteristic of thiols) was noted on tlc. The pH was adjusted to 10.5 and after 1 hr evaporated *in vacuo*. The major spot on tlc (C_6H_{12}–AcMe, 2:1) ($CHCl_3$–MeOH, 10:1) moved with and was not separated from **10** on 8-in. tlc plates. For visualization Lemieux reagent, I_2, and bioautograph *vs. S. lutea* were employed.

Acknowledgment.—The authors are indebted to Dr. D. J. Mason for *in vitro* antibacterial testing, to C. Lewis for *in vivo* assays, and to R. J. Reid for technical assistance.

The Relationship between Structure, Stereochemistry, and Diuretic Activity in the 2-Amino-α-phenylcyclohexanemethanol Series, a New Class of Diuretic Agents. II[1]

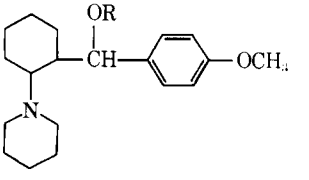
L. L. SKALETZKY, B. E. GRAHAM, AND J. SZMUSZKOVICZ

Research Laboratories of The Upjohn Company, Kalamazoo, Michigan 49001

Received May 29, 1969

A series of 1,3-amino alcohols and 1,3-amino ethers were made for diuretic testing. The four diastereoisomers of both the alcohols and methyl ethers (I, R = H and CH_3, respectively) were synthesized and the relationship of stereochemistry to diuretic activity is discussed. 1-[2-(*p*,α-Dimethoxybenzyl)cyclohexyl]-piperidine (**2**) was resolved and the *d* enantiomorph (**3**) was chosen for further pharmacologic evaluation.

In this paper, a new class of diuretic agents[2] illustrated by structure I is reported. Compounds of structure type I have three asymmetric centers and, in the case of both the alcohols and methyl ethers (I, R = H and CH_3, respectively), the four possible diastereoisomers or racemates have been synthesized. Stereochemistry is a prime factor in the correlation of structure with biological activity and in the study of receptor surfaces.[3] We therefore undertook a detailed study of the relationship between stereochemistry and diuretic activity in this class of compounds.



I

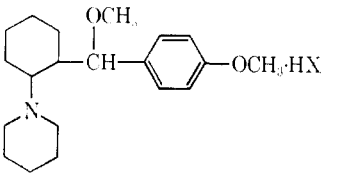
(1) Paper I: J. Szmuszkovicz and L. L. Skaletzky, *J. Org. Chem.*, **32**, 3300 (1967).

(2) For a review of diuretic agents: (a) H.-J. Hess in "Annual Reports in Medicinal Chemistry, 1967," C. K. Cain, Ed., Academic Press Inc., New York, N. Y., 1968, p 62, and previous Annual Reports; (b) G. de Stevens, "Diuretics," Academic Press, Inc., New York, N. Y., 1963.

(3) (a) E. J. Ariëns, *Mol. Pharmacol.*, **1**, 232 (1964); (b) P. S. Portoghese, A. A. Mikhail, and H. J. Kupferberg, *J. Med. Chem.*, **11**, 219 (1968), and references noted therein.

TABLE I

1-[2-(*p*,α-DIMETHOXYBENZYL)CYCLOHEXYL]PIPERIDINES



III

Compd	No.	Stereochemistry[a] Cyclohexane	Stereochemistry[a] Side chain	HX	Diuretic activity,[b] % increase in urine excretion over controls, mg/kg *po* Screening studies 5	Screening studies 20	Development studies[f] 0.5	1.0	2.5	5.0	10	20	40	LD_{50}, mg/kg[d] Mice, ip	Rats, *po*
1	IIIA	*cis*	*threo*	HCl·CH_3OH	19	32								75	
2	*dl*-IIIB	*cis*	*erythro*	HCl[c]	58	122	4	10	21	67	94	120	141	42[c]	
3	*d*-IIIB	*cis*	*erythro*	HCl	37	105	27	14	31	52	76	137	141	40	92
4	*l*-IIIB	*cis*	*erythro*	HCl	36	98	5	15	26	36	80	83	97	56	
5	IIIC	*trans*	*erythro*	Base	47	106								75	
6	IIID	*trans*	*threo*	Base[e]	16	20								1000[e]	

[a] See ref 4. [b] *Per os* in rats; for comparison a standard reference compound ethoxzolamide has the following screening values at 5 and 20 mg/kg, 102 and 132%, respectively. [c] The free base gave screening values of 73 and 142% at 5 and 20 mg/kg, respectively. The LD_{50} (mice) was 562 mg/kg ip. [d] Spearman–Karber method for 95% confidence limits. Upjohn Sprague–Dawley rats and Upjohn Rockland mice were used. [e] The base was an oil. [f] These per cent volumes were obtained during electrolyte studies (see Table VII for *d*-IIIB).

The diastereoisomeric alcohols and methyl ethers of structure I (R = H and CH_3, respectively) in the *cis-erythro* and *trans-erythro*[4] series were active diuretic agents in rats while the *cis-* and *trans-threo*[4] isomers were less active at comparable doses (see Tables I and II). The *cis-erythro* methyl ether (**2**) was resolved and the *d* enantiomorph (**3**) was chosen for further pharmacologic evaluation.

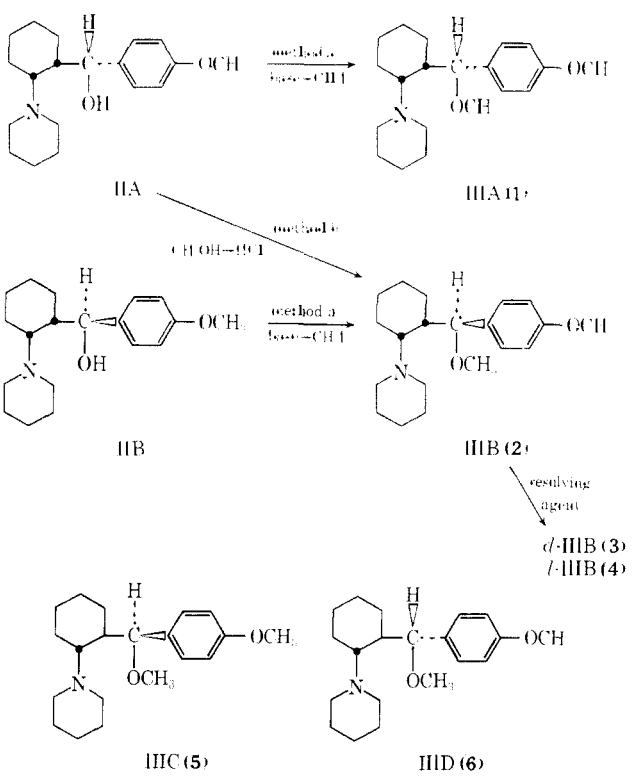
The conformations of the four diastereoisomeric alcohols (II) have been unequivocally established.[1,5] Each of these isomeric alcohols exist in solution as a unique conformation due to two important factors: (a) hydrogen bonding between the hydroxyl and piperidine nitrogen, and (b) relative "effective" size of the benzylic side chain and piperidine group on the cyclohexane (chair) ring.[1] In the *cis* alcohols, the conformational studies have established that *cis-threo* alcohol (IIA) has the piperidine group axial and the benzylic side chain equatorial on the cyclohexane ring while the *cis-erythro* isomer (IIB) has the piperidine group equatorial and the side chain axial. The difference in diuretic activity of the two *cis* alcohols has been rationalized on the basis of these conformational differences (see Discussion).

Chemistry.—The synthesis and elucidation of stereochemistry of the four racemic amino alcohols II and methyl ethers III have been described.[1] The synthesis of the two *cis* methyl ethers IIIA[6] and IIIB is outlined in Chart I and the two *trans* methyl ethers IIIC and IIID were made in a similar manner. The two *cis* racemates (or *trans* racemates) have the same relative stereochemistry at the cyclohexane ring junctions but differ in the configuration at the side-chain benzylic carbon.

Methyl ether IIIB was resolved; the four racemic methyl ethers IIIA, IIIB, IIIC, and IIID and optical isomers of IIIB are listed in Table I.

A series of analogs of III is listed in Table II. The ethers were made by methods a and b of Chart I.

CHART I



The majority of *cis* amino alcohols required in the preparation of the ethers (Tables I and II) were made by the general procedures c–f of Chart II and are listed in Tables II (**8–11**) and III. Several of the *cis* amino alcohols were made by two or more methods,

(4) The terms *erythro* and *threo* refer to the configuration at the benzylic side-chain carbon. For the definitions of *erythro* and *threo*, see ref 1. *cis* and *trans* refer to the stereochemistry of groups on the cyclohexane ring.

(5) Recent nmr conformation studies on *cis-threo* alcohol (IIA) deuterated in the cyclohexane ring has given the following results. The free base of IIA exists in solution as a single conformation with the piperidine group axial and benzylic side chain equatorial on the cyclohexane (chair) ring. In contrast, the hydrochloride of IIA in water has the piperidine equatorial and the benzylic side chain axial. This striking difference in conformation between the free base and the hydrochloride is primarily due to the importance of hydrogen bonding in the former. These conformation studies will be published elsewhere.

(6) Roman numerals are used to represent the general structure and letters A, B, C, and D to represent the specific racemate. Arabic numerals refer to compounds listed in the tables.

thereby interrelating the stereochemistry of compounds prepared by these procedures. In the cases where the stereochemistry was not established, compounds made by the same methods were assumed to have similar stereochemistry.

The *cis*-A series of amino alcohols was made by general methods c–e of Chart II and representative examples follow.

Method c.—Condensation of dione IV with piperidine gave the vinylogous amide V which was reduced catalytically with 2 moles of hydrogen to amino alcohol IIA. Catalytic reduction of V with 1 mole of hydrogen gave the intermediate *cis* ketone VI.

Method d.—Several *cis*-A alcohols were made as illustrated in the case of **69**. The benzyloxy ether (**65**) was made by method c. Methylation of phenol **67** gave methyl ether IIA thereby establishing the stereochemistry of **67** and related derivatives.

Method e.—The preparation of 2-piperidino-α-(3,4,5-trimethoxyphenyl)cyclohexanemethanol (**42**, Table III) is illustrated. Compound **42** was also prepared by method c and the two materials were identical. The amino alcohol (**42**) has diuretic activity and a series of related analogs was made (Table III).

Method f.—The best method of preparation of the *cis*-B amino alcohols was the isomerization of the *cis*-A amino alcohols (obtained by methods c–e) with trifluoroacetic acid.

Method g.—The synthesis of *cis*-2-piperidino-α-(*o*-hydroxyphenyl)cyclohexanemethanol (**62**) is given in Chart III. The stereochemistry of **62** was established by methylation to **63** (prepared by method c). Salicylaldehyde was treated with 1-cyclohexen-**1**-ylpiperidine in Skellysolve B and the resulting adduct VII was hydrogenolyzed with PtO_2 in AcOH to **62**. Amino alcohol (**62**) was treated with anhydrous HCl in CH_3OH (method b) to give methyl ether **34** whose stereochemistry was established as shown.

Esters of the amino alcohols were prepared by treating the alcohol with an acid anhydride and are listed in Table II (**12–17**).

A number of bis(α,α-phenyl)-2-piperidinocyclohexanemethanols were synthesized as illustrated in Chart IV and are listed in Table IV and these compounds have good diuretic activity at the doses shown.

Relationship of Stereochemistry to Diuretic Activity.—The amino alcohols (II) and ethers (III) have three asymmetric centers in which the ring junction can be either *cis* or *trans* and the side-chain configuration either *erythro* or *threo*. However, on the basis of the established stereochemistry and structure–activity relationships for these compounds, the cyclohexylpiperidine moiety is suggested to be the principal structural feature required for diuretic activity.

In general, for the amino alcohols and ethers, the *erythro* racemates in both the *cis* and *trans* series possess the diuretic activity (*i.e.*, *cis*-B and *trans*-C are more active than *cis*-A and *trans*-D racemates). Examination of Table I indicates that two of the 1-[2-(*p*,α-dimethoxybenzyl)cyclohexyl]piperidines, racemates IIIB and IIIC, are potent diuretic agents in rats while the other two racemates, IIIA and IIID, are less active at comparable doses. The diastereoisomeric amino alcohols II (**8–11**, Table II) also show a similar spectrum of diuretic activity.

The activities of various other compounds (**83–98**) are given in Table V.

A number of factors may be responsible for this spectrum of diuretic activity of the four racemates of II and III including possible differences in metabolism and absorption of these compounds. However, a consistent picture based on consideration of the established stereochemistry of these racemates may be proposed to explain the diuretic results.

Elucidation of the stereochemistry of methyl ether (III) and amino alcohol (II) racemates has been reported[1,5] and a summary of this stereochemical information for the amino alcohols (II) is given in Table VI.

In the amino alcohols and the ethers, the active *erythro-cis* and *-trans* racemates have the piperidine group equatorial on the cyclohexane ring (see Table VI). In contrast, the piperidine ring in the *cis-threo* alcohol (IIA) is axial. The conformation of the piperidine substituent in the inactive *threo* ether (IIIA) has not been established. Since the ethers cannot form a hydrogen bond, the conformation of IIIA with the piperidine group equatorial may be in predominance.[5]

In summary, two important stereochemical factors appear to influence diuretic activity in this class of compounds: (a) configuration at the side-chain carbon —*erythro* isomers are most active diuretic agents at the doses shown; and (b) conformation of the piperidine substituent on cyclohexane ring—racemates with an equatorial piperidine are most active.

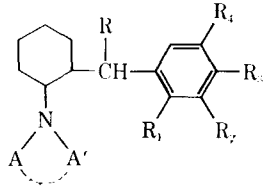
To test the importance of an equatorial piperidine for diuretic activity, 1-cyclohexylpiperidine hydrochloride (Table V, **96**), *cis*-2-piperidinocyclohexanemethanol hydrochloride (**97**), and *trans*-2-piperidinocyclohexanemethanol hydrochloride (**98**) were tested for diuretic activity. These three compounds would be expected to have the large piperidine group essentially equatorial, although *cis*-2-piperidinocyclohexanemethanol hydrochloride (**97**) may exist as an equilibrium mixture of conformations with axial and equatorial piperidines. *trans*-2-Piperidinocyclohexanemethanol hydrochloride (**98**) and **1**-cyclohexylpiperidine hydrochloride (**96**) were found to have significant diuretic activity while *cis*-2-piperidinocyclohexanemethanol hydrochloride (**97**) was less active at comparable doses. The suggestion that the equatorial piperidine portion of the molecule of III may be responsible for part of the diuretic activity is consistent with the structure–activity relationships for analogs of III (see Tables I and II). For example, *dl*-IIIB and optical isomers *d*-IIIB and *l*-IIIB (Table I, **2–4**) have approximately the same diuretic activity, but the *d* isomer is much less anticholinergic than the *l* or *dl* isomers. Also, variation in the size of the benzylic ether in the active *erythro* (B racemate) series appears to have only a small effect on diuretic activity (*cf.* **2**, **28**, and **29**).

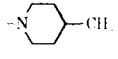
In conclusion, one basic structural requirement for diuretic activity of amino alcohols and amino ethers related to II and III may be the 1-cyclohexylpiperidine moiety (*i.e.*, it has both affinity and intrinsic activity[3a]). This point will require further substantiation.

Structure–Activity Relationships.—In analogs of the amino ethers (*i.e.*, analogs of IIIB), the relative configuration of the side-chain benzylic carbon is very important as discussed before, the *erythro* (B and C) isomers being the most active. For maximal diuretic

TABLE II

1-AMINO-2-BENZYLCYCLOHEXANES



No.	Stereochemistry		R	R_1	R_2	R_3	R_4	Method	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses	Diuretic act.[a] % increase in urine excretion over controls —Dose, mg./kg. po— 5	20
7[b]		$N(CH_2)_5$	H	H	H	OCH_3	H							12	48
8[b]	A	$N(CH_2)_5$	OH	H	H	OCH_3	H	e	71					2	24
9[b]	B	$N(CH_2)_5 \cdot HCl$	OH	H	H	OCH_3	H	f	71.5					16	46
10[b]	C	$N(CH_2)_5$	OH	H	H	OCH_3	H							−1	28
11[b]	D	$N(CH_2)_5$	OH	H	H	OCH_3	H							−20	14
12	A	$N(CH_2)_5 \cdot HCl$	$OCOCH_3$	H	H	OCH_3	H		86	207–208	I–E	$C_{21}H_{32}ClNO_3$	C, H, Cl, N	−4	10
13	B	$N(CH_2)_5 \cdot HCl$	$OCOCH_3$	H	H	OCH_3	H		90	201	Et–E	$C_{21}H_{32}ClNO_3$	C, H, Cl, N	13	73
14	A	$N(CH_2)_5 \cdot HCl$	$OCOCH_2CH_3$	H	H	OCH_3	H		85.5	195–195.5	I	$C_{22}H_{34}ClNO_3$	C, H, Cl, N	−3	−4
15	B	$N(CH_2)_5 \cdot HCl$	$OCOCH_2CH_3$	H	H	OCH_3	H		91	192–193	Et–E	$C_{22}H_{34}ClNO_3$	C, H, Cl, N	10	70
16	B	$N(CH_2)_5 \cdot HCl$	$OCOCH_2CH_2COOH$	H	H	OCH_3	H		30	185–186	Et–E	$C_{23}H_{34}ClNO_5$	C, H, Cl, N	−2	25
17	B	$N(CH_2)_5$	$OCOC_6H_5$	H	H	OCH_3	H		74.5	131–132	S	$C_{26}H_{33}NO_3$	C, H, N	−29	8
18	B	$N[(CH_2)_2]_2O$	OCH_3	H	H	OCH_3	H	b	92.5	99–100	Et	$C_{19}H_{29}NO_3$	C, H, N	14	79
19	B	$N(CH_2)_4 \cdot HClO_4$	OCH_3	H	H	OCH_3	H	b	56	155–156	I	$C_{19}H_{30}ClNO_6$	C, H, Cl, N	30	114
20	B	$N(CH_2)_6$	OCH_3	H	H	OCH_3	H	a		*d*		$C_{21}H_{33}NO_2$	C, H, N	21	33
21	A	$N(CH_2)_6 \cdot HCl \cdot CH_3OH$	OCH_3	H	H	OCH_3	H	a	16	187–191	M–E	$C_{22}H_{38}ClNO_3$	C, H, Cl, N	5	24
22	B	$N[(CH_2)_2]_2NCH_3$	OCH_3	H	H	OCH_3	H	b	71.5	103–104.5	Et–W	$C_{20}H_{32}N_2O_2$	C, H, N	−5	42
23	B		OCH_3	H	H	OCH_3	H	b	94	112–113	Et	$C_{24}H_{33}NO_2$	C, H, N	69	100
24	B		OCH_3	H	H	OCH_3	H	b	93	109–111	Et	$C_{23}H_{33}NO_2$	C, H, N	99	142
25	B		OCH_3	H	H	OCH_3	H		49.5	58–59	I–W	$C_{17}H_{27}NO_2$	C, H, N	33	56
26	B	$NHCH_3 \cdot C_2H_2O_4$[c]	OCH_3	H	H	OCH_3	H	b	52	223–224	M–E	$C_{18}H_{27}NO_6$	C, H, N	−2	−6
27	B	$NH_2 \cdot C_4H_4O_4$[f]	OCH_3	H	H	OCH_3	H	b	32	142–145	Me–E	$C_{19}H_{27}NO_6$	C, H, N	−2	54
28	B	$N(CH_2)_5 \cdot HCl$	OCH_2CH_3	H	H	OCH_3	H	b	38	209–210	I–E	$C_{21}H_{34}ClNO_2$	C, H, Cl, N	32	134
29	B	$N(CH_2)_5 \cdot HCl(H_2O)_{0.5}$	$OCH_2CH_2CH_3$	H	H	OCH_3	H	b	62[d,g]	190–194	I–E	$C_{22}H_{36}ClNO_2 \cdot (H_2O)_{0.5}$	H, Cl, N; C	56	99
30	B	$N(CH_2)_5$	OCH_2CH_2OH	H	H	OCH_3	H	b	72	111–112.5	S	$C_{21}H_{33}NO_3$	C, H, N	6	88

No.	Stereochemistry	A–A′	R	R_1	R_2	R_3	R_4	Method	Yield, %	Mp, °C	Recrystn solvent	Formula	Analyses	Diuretic act.[c] % increase in urine excretion over controls —Dose, mg/kg po— 5	20
31	B	$N(CH_2)_5 \cdot HCl$	OCH_3	H	H	OCH_2CH_3	H	b	83[g]	206-207	Ac–E	$C_{21}H_{34}ClNO_2$	C, H, Cl, N	−4	104
32	B	$N(CH_2)_5$	OCH_3	H	H	OCH_2CH_2OH	H	b	54	88–89	Et–W	$C_{21}H_{33}NO_3$	C, H, N	40	59
33	B	$N(CH_2)_5$	OCH_3	H	H	$OCH_2C_6H_5$	H	b	87	100–101	M	$C_{26}H_{35}NO_2$	C, H, N	2	35
34	B	$N(CH_2)_5$	OCH_3	OH	H	H	H		76	113–114.5	S	$C_{19}H_{29}NO_2$	C, H, N	61	140
35	B	$N(CH_2)_5 \cdot HCl$	OCH_3	OCH_3	H	H	H	b	30	220–221	Me–E	$C_{20}H_{32}ClNO_2$	C, H, Cl, N	80	132
36	B	$N(CH_2)_5 \cdot CH_3SO_3H \cdot H_2O_{0.5}$	OCH_3	OCH_3	H	CH_3	H	b	46	93–95	Me-E	$C_{22}H_{37}NO_5S \cdot (H_2O)_{0.5}$	C, H, N	45	168
37	B	$N(CH_2)_5$	OCH_3	H	CH_3	OCH_3	CH_3	b	75	68–69	Et	$C_{22}H_{35}NO_2$	C, H, N	75	144
38	B	$N(CH_2)_5$	OCH_3	H	OCH_3	OCH_3	OCH_3	b	27[h]	89–90	M	$C_{22}H_{35}NO_4$	C, H, N	8	60
39	A	$N(CH_2)_5 \cdot HCl$	OCH_3	H	OCH_3	OCH_3	OCH_3	a	34	224–225	M–E	$C_{22}H_{36}ClNO_4$	C, H, Cl, N	19	78
40	B	$O{\leftarrow}N(CH_2)_5 \cdot H_2O$	OCH_3	H	H	OCH_3	H		55	108–110	Ea	$C_{20}H_{33}NO_4$	C, H, N	6	54

[a] M, methanol; I, 2-propanol; E, ether; Et, ethanol; W, water; Me, methyl ethyl ketone; S, Skellysolve B; Ac, acetonitrile; Ea, ethyl acetate; P, pentane; Pe, petroleum ether (bp 30–60°). [b] For preparation, see ref 1. [c] See Table I, footnote *b*. [d] The free base was an oil. [e] Oxalic acid. [f] Maleic acid. [g] The yield based on recovered starting material (**42**) was 89.5%. [h] C: calcd, 67.58; found, 66.65.

activity the benzylic carbon should have an ether substituent, *i.e.*, replacement of the benzylic methyl ether by H, OH, or –OCOR resulted in decreased activity (*cf.* **2**, **7**, **9**, **13**, Tables I and II). The amine may be pyrrolidine, piperidine, or 3-azabicyclo[3.2.2]nonane; a secondary amine (**26**, Table II) and the primary amine (**27**) were less active. The aromatic ring may be substituted by *o*- or *p*-methoxy or an *o*-hydroxy group (*cf.* **2**, **34**, **35**, Tables I and II); methyl substitution on the aromatic ring appears to increase activity (*cf.* **2**, **36**, **37**). Introduction of two methyl groups *para* to the piperidine substituent in the cyclohexane ring increases activity (**83**, Table V). The N-oxide of IIIB was less active (**40**, Table II).

A large number of 1,3-amino alcohols were made and the majority (Table III; Table II, **8**–**11**) were less active than the corresponding methyl ethers at the doses shown. Maximal diuretic activity in the amino alcohols was found in compounds (**41**, **42**, **53**, **54**, Table III).

In the bis aromatic series, amino alcohols (**78**, **80**, **81**, Table IV) were the most active.

Experimental Section

Biological Methods. Diuretic Assay (Rats).—Modifications of the method of Lipschitz, *et al.*,[7] were employed for diuretic assays. Upjohn Sprague–Dawley male rats (200 ±10 g on test day) were hydrated orally with physiological saline (25 cc/kg) and starved for 18 hr. Water was allowed *ad lib.* Water was removed 1.5 hr before test time. At test time individually weighed rats were again hydrated (25 cc/kg) with saline and the test compound was incorporated in this load. Groups of seven rats (in individual metabolism cages) were routinely used at each dose level of each test compound. Seven untreated control rats (saline only) were used for each assay. Diuretic responses for the 5-hr test period were calculated in terms of per cent increase in urine excretion in excess of the controls. Statistical analysis of excretion data on 1280 control rats shows the mean excretion (per cent of load) to be 83.51 ± 19.23 SD. Sodium, potassium, chloride, and pH determinations were done on interesting compounds and dose–response relationships were determined. All diuretic studies were carried out in a temperature (24.5°) and humidity (48%) controlled laboratory.

Diuretic Assay (Dogs).—Compounds active in rats were often further evaluated orally in six trained purebred female beagle dogs. Assay procedure for dogs was identical with that for rats except their bladders were drained (by catheter) 1 hr after the saline load, just prior to drug administration. This urine collection was discarded and not used in calculations of diuretic response.

Each dog served as her own control. Urine volumes, electrolytes (Na, K, Cl), and pH values on drug days were compared to those on control days. Top 95% confidence limits have been established for each dog for urine volume and electrolytes. These top limits in each parameter were used as a control basis for significant diuretic activity and electrolyte excretion when testing drugs in these dogs.

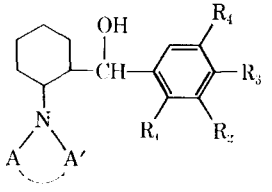
Pharmacology.—Representative compounds of the amino ethers, amino alcohols, and bis aromatic amino alcohols were further evaluated as diuretic agents. On the basis of diuretic activity and electrolyte excretion patterns in the rat and dog, toxicity in mice and rats, and anticholinergic activity (isolated gut) *d*-IIIB (Table I, **3**) was chosen for clinical evaluation. This compound was found to have an atropine index of $^1/_{800}$ to $^1/_{1000}$ on the rabbit ileum while the *l* and *dl* isomers for comparison had anticholinergic activity $^1/_{200}$th of atropine. The rat study shown in Table VII shows *d*-IIIB to be an orally effective diuretic–saluretic agent with minimal effects on potassium excretion. The dog study (Table VIII) shows *d*-IIIB to be an orally effective diuretic–saluretic agent in all dogs with a significant kaliuretic effect in three of the six dogs.

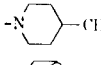
General Pharmacology.—A general pharmacologic profile was

(7) W. L. Lipschitz, Z. Hadidian, and A. Kerpesar, *J. Pharmacol. Exp. Therap.*, **79**, 97 (1943).

TABLE III

2-AMINO-α-PHENYLCYCLOHEXANEMETHANOLS



No.	Stereochemistry		R1	R2	R3	R4	Method	Yield, %	Mp, °C	Recrystn[a] solvent	Formula	Analyses	Diuretic act.[c] % increase in urine excretion over controls — Dose, mg/kg *po*— 5	20
41[b]	A	$N(CH_2)_6 \cdot HCl$	H	OCH_3	OCH_3	OCH_3	c	34					19	98
42	A	$N(CH_2)_5 \cdot HCl$	H	OCH_3	OCH_3	OCH_3	e[d]	40	265–266	M	$C_{21}H_{34}ClNO_4$	C, H, Cl, N	6	87
43	A	$N(CH_2)_4 \cdot HCl$	H	OCH_3	OCH_3	OCH_3	c	56[e]	216–217	I	$C_{20}H_{32}ClNO_4$	C, H, Cl, N	16	68
44	A	$N[(CH_2)_2]_2O \cdot HCl$	H	OCH_3	OCH_3	OCH_3	c	42	205–206	M–E	$C_{20}H_{32}ClNO_5$	C, H, Cl, N	−5	2
45	A	$N[(CH_2)_2]_2NCH_3 \cdot 2HCl \cdot (CH_3OH)_{0.5}$	H	OCH_3	OCH_3	OCH_3	c	31	232–233	M	$C_{21}H_{36}Cl_2N_2O_4 \cdot (CH_3OH)_{0.5}$	C, H, Cl, N	8	−4
46	A	$N(CH_3)_2 \cdot HCl$	H	OCH_3	OCH_3	OCH_3	e	28	221–222	M–E	$C_{18}H_{30}ClNO_4$	C, H, Cl, N	−17	20
47	A	$N(CH_2)_6 \cdot HCl$	H	OCH_3	OCH_3	H	e	50	225–226	Et	$C_{21}H_{34}ClNO_3$	C, H, Cl, N	13	62
48	A	$N(CH_2)_6 \cdot HCl$	H			H	e	50	233–234	Et	$C_{20}H_{36}ClNO_3$	C, H, Cl, N	17	22
49	A	$N(CH_2)_6 \cdot HCl$	H	H	OCH_3	H	e	50.5	230–231	Et	$C_{20}H_{32}ClNO_2$	C, H, Cl, N	−9	20
50	B	$N(CH_2)_6$	H	H	OCH_3	H	f	34	94–95.5	E	$C_{20}H_{31}NO_2$	C, H, N	6	50
51	A	$N(CH_2)_6 \cdot HCl$	H	H	CF_3	H	e	34	263–264	M	$C_{20}H_{29}ClF_3NO$	C, H, Cl, N	−6	−10
52	A	$N(CH_2)_6 \cdot HCl$	H	H	H	H	c	9	276–277	M	$C_{19}H_{30}ClNO$	C, H, Cl, N	9	9
53	A	$N(CH_2)_6 \cdot HCl$	H	CH_3	OCH_3	CH_3	c	38	250–251	Et	$C_{22}H_{36}ClNO_2$	C, H, Cl, N	27	91
54	A	$N(CH_2)_5 \cdot HCl$	H	CH_3	OCH_3	CH_3	c	52	259–260	Et	$C_{21}H_{34}ClNO_2$	C, H, Cl, N	25	74
55	A	$CH_3\overset{+}{N}(CH_2)_6\ I^-$	H	OCH_3	OCH_3	OCH_3		67.5	191–193	M–E	$C_{23}H_{38}INO_4$	C, H, N	−2	2
56	A	$O{\leftarrow}N(CH_2)_5 \cdot H_2O$	H	OCH_3	OCH_3	OCH_3		65	157–158	Ea	$C_{21}H_{35}NO_6$	C, H, N	7	32
57	A	$N[(CH_2)_2]_2O$	H	H	OCH_3	H	c	81.5	111–112	Et	$C_{18}H_{27}NO_3$	C, H, N	2	1
58	A	$N(CH_2)_4$	H	H	OCH_3	H	c	9	146–147	Et	$C_{18}H_{27}NO_2$	C, H, N	22	−2
59	A	$N[(CH_2)_2]_2NCH_3$	H	H	OCH_3	H	c′	37	132–133	Et	$C_{19}H_{30}N_2O_2$	C, H, N	−5	0
60	A		H	H	OCH_3	H	c	61	93–94	S	$C_{20}H_{31}NO_2$	C, H, N	−10	23
61	A		H	H	OCH_3	H	c′	16	114.5–115.5	S	$C_{22}H_{33}NO_2$	C, H, N	15	32
62	A	$N(CH_2)_5$	OH	H	H	H	g	80	122–122.5	S	$C_{18}H_{27}NO_2$	C, H, N	31	38
63	A	$N(CH_2)_5$	OCH_3	H	H	H	c	16	99–100	E–P	$C_{19}H_{29}NO_2$	C, H, N	11	28
64	A	$N(CH_2)_5 \cdot HCl$	OCH_3	H	CH_3	H	e	16.5	256–256.5	Et–E	$C_{20}H_{32}ClNO_2$	C, H, Cl, N	−2	8

No.	Stereochemistry	A–A′	R_1	R_2	R_3	R_4	Method	Yield, %	Mp, °C	Recrystn[a] solvent	Formula	Analyses	Diuretic act.[c] % increase in urine excretion over controls (—Dose, mg/kg po— 5	20
65	A	$N(CH_2)_5$	H	H	$OCH_2C_6H_5$	H	e	53	148.5–149.5	Et	$C_{25}H_{33}NO_2$	C, H, N	5	−3
66	B	$N(CH_2)_5 \cdot HCl$	H	H	$OCH_2C_6H_5$	H	f	39[e]	238–240 dec	Et–E	$C_{25}H_{34}ClNO_2$	C, H, Cl, N	7	12
67	A	$N(CH_2)_5 \cdot HCl$	H	H	OH	H	d	91.5[e]	204–204.5	Et–E	$C_{18}H_{28}ClNO_2$	C, H, Cl, N	7	24
68	B	$N(CH_2)_5$	H	H	OH	H	d	86	180–182	Et	$C_{18}H_{27}NO_2$	C, H, N	7	29
69	A	$N(CH_2)_5 \cdot HCl$	H	H	OCH_2CH_3	H	d	63	221–222	Et–E	$C_{20}H_{32}ClNO_2$	C, H, Cl, N	0	25
70	A	$N(CH_2)_5$	H	H	$OCH_2CH{=}CH_2$	H	d	89	71–72	E–P	$C_{21}H_{31}NO_2$	C, H, N	18	17
71	A	$N(CH_2)_5 \cdot HCl$	H	H	CH_3	H	c	66	251–253	M–E	$C_{19}H_{30}ClNO$	C, H, Cl, N	1	3
72	A	$N(CH_2)_5 \cdot HCl$	CH_3	H	CH_3	H	c	4	239–240	M–E	$C_{20}H_{32}ClNO$	C, H, Cl, N	12	13
73[b]	A	$NHCH_3$	H	H	OCH_3	H							7	15
74[b]	B	$NHCH_3$	H	H	OCH_3	H							0	−12
75[b]	A	$NH_2 \cdot HCl$	H	H	OCH_3	H							−15	3
76[b]	B	NH_2	H	H	OCH_3	H							−21	−23

[a] See Table II, footnote *a*. [b] For preparation see ref 1. [c] See Table I, footnote *b*. [d] Compound **42** was prepared by method *c* in 48% yield. [e] Yield of free base. [f] In hydrogenation step used EtOH–AcOH.

obtained on *d*-IIIB as follows. Intravenously in anesthetized dogs small doses were ineffective on the mean arterial blood pressure while larger doses (4–8 mg/kg) produced prolonged depressor responses. No anticholinergic, anticholinesterase, adrenergic, adrenolytic, histaminic, or antihistaminic actions were observed. Epinephrine responses were potentiated.

The suggestion of hypotensive activity was not borne out in aortic intubated[8] unanesthetized normotensive rats.

In anesthetized cats (pentobarbital or chloralose) and a decerebrate cat (ether anesthesia) *d*-IIIB did not function as a neuromuscular blocking agent.

In the rat hind paw edema (carageenin induced) assay *d*-IIIB exhibited antiinflammatory activity equal to phenylbutazone but only at high doses bordering toxic levels and therefore cannot be considered specifically antiinflammatory.

No phototoxicity was observed in rats following oral doses of 38.7 mg/kg.

In the mouse *d*-IIIB did not antagonize electroshock convulsions or aid in their induction nor did it afford protection against thiosemicarbazide or strychnine lethality. Ambient temperatures tested had no effect on the lethality of *d*-IIIB, suggesting it is not a sympathomimetic agent.

Intraperitoneally in mice the LD_{50} was found to be 40 mg/kg (35.9–44.7).[9] Orally in rats the LD_{50} was 91.6 mg/kg (76.6–109.5).[9]

Chemical Methods.[10] **2-[(*p*-Benzyloxy)benzoyl]cyclohexanone** was prepared from 1-cyclohexen-1-ylpyrrolidine and *p*-benzyloxybenzoyl chloride as previously described in the case of IV.[1] The crude diketone did not require purification *via* the copper complex. It was triturated with Et_2O to obtain material suitable for further use: 73% yield, mp 112–117°. A sample was recrystallized for analyses from C_6H_6: mp 111–111.5°. *Anal.* ($C_{20}H_{20}O_3$) C, H.

***cis*-2-Piperidino-α-(*p*-benzyloxyphenyl)cyclohexanemethanol (65)** was prepared in a manner analogous to that described for the preparation of **8** (method c).[1] The product precipitated from solution during the hydrogenation step and was separated from the catalyst by addition of sufficient EtOH, heating to boiling, and filtering. On cooling, the product separated from solution: yield 53%, mp 146.5–147.5. The analytical sample melted at 148.5–149.5 (EtOH).

***cis*-2-Piperidino-α-(*p*-hydroxyphenyl)cyclohexanemethanol Hydrochloride (67).**—A suspension of 10 g (0.0264 mole) of **65** in 300 ml of CH_3OH was hydrogenated in the presence of 1.0 g of 10% Pd–C for 24 hr at an initial hydrogen pressure of 3.5 kg/cm². The mixture was filtered, the filtrate was evaporated to dryness, and residue was crystallized from EtOH–H_2O (1:1): 7.0 g (91.5%), mp 177–177.5. Recrystallization from EtOH raised the melting point to 179–180°. *Anal.* ($C_{18}H_{27}NO_2$) C, H, N. The hydrochloride was prepared and crystallized from EtOH–Et_2O: mp 204–204.5°.

***cis*-2-Piperidino-α-(*p*-ethoxyphenyl)cyclohexanemethanol Hydrochloride (69).**—A mixture of 2.85 g (0.01 mole) of **67** and 0.45 g of 53.3% NaH mineral oil dispersion in 50 ml of dry DMSO was stirred for 1 hr. A solution of 2.0 g (0.01 mole) of ethyl *p*-toluenesulfonate in 15 ml of Et_2O was added over 30 min, and the mixture was stirred for 5 hr and poured into ice–water. The product was extracted into Et_2O which was washed with H_2O, dried (Na_2SO_4), and evaporated to an oil. A hydrochloride was prepared with ethereal HCl and crystallized from EtOH–Et_2O: 2.2 g (63%), mp 218–219°. The analytical sample melted at 221–222° (EtOH–Et_2O).

1,2,3,4,4a,9a-Hexahydro-4a-piperidinoxanthen-9-ol (89) was prepared by a modification of the procedure of Paquette.[11] A solution of 61 g (0.5 mole) of salicylaldehyde and 83 g (0.5 mole) of distilled 1-cyclohexen-1-ylpiperidine in 500 ml of Skellysolve B was allowed to stand 24 hr at room temperature and then cooled at 0° for 1–4 days. The solid which separated was filtered and washed with Skellysolve B to give 102 g of crude product, mp 84–90°. The yellowish solid was crystallized from Skellysolve

(8) Modifications of the method of J. R. Weeks and J. A. Jones, *Proc. Soc. Exp. Biol. Med.*, **104**, 646 (1960).

(9) Spearman–Karber method (D. J. Finney, "Statistical Method in Biological Assay," Hafner Publishing Co., New York, N. Y., 1952, p 524).

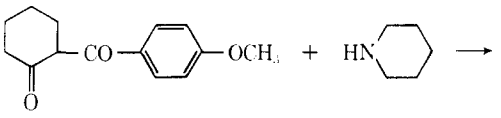
(10) Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are uncorrected. The ir, uv, and nmr spectra were compatible with the assigned structures. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

(11) L. A. Paquette and H. Stucki, *J. Org. Chem.*, **31**, 1232 (1966).

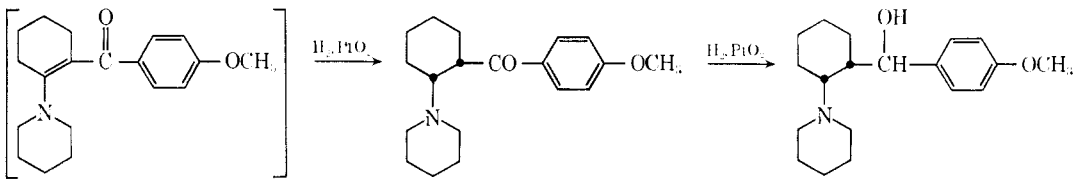
CHART II

cis-A Alcohols

Method c



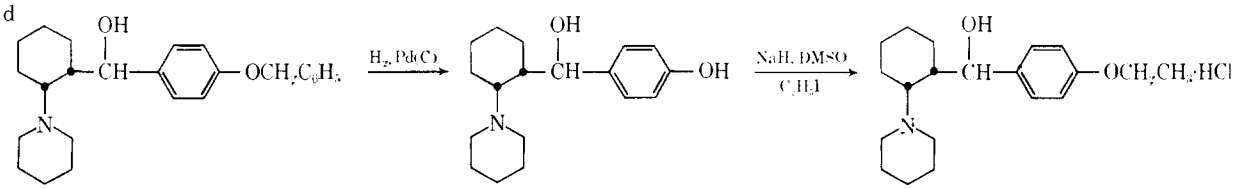
IV



V VI (**90**), *cis* ketone IIA (**8**)

$2H_2$, PtO_2

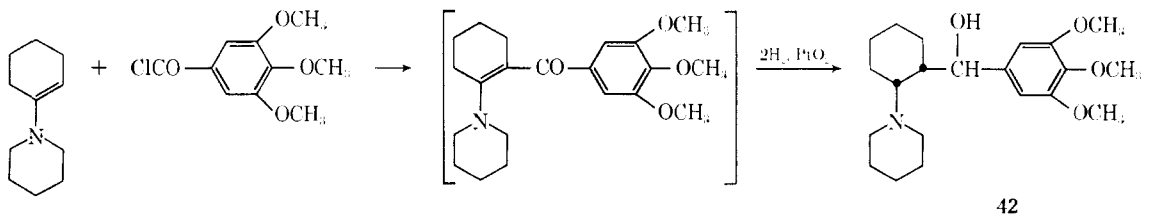
Method d



65 **67** **69**

IIA (**8**)

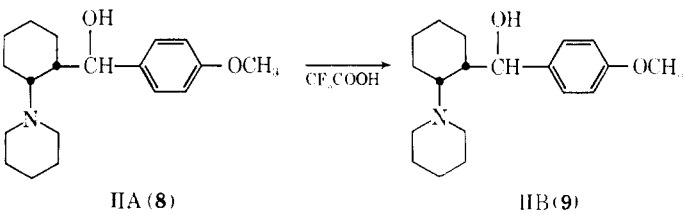
Method e



42

cis-B Alcohols

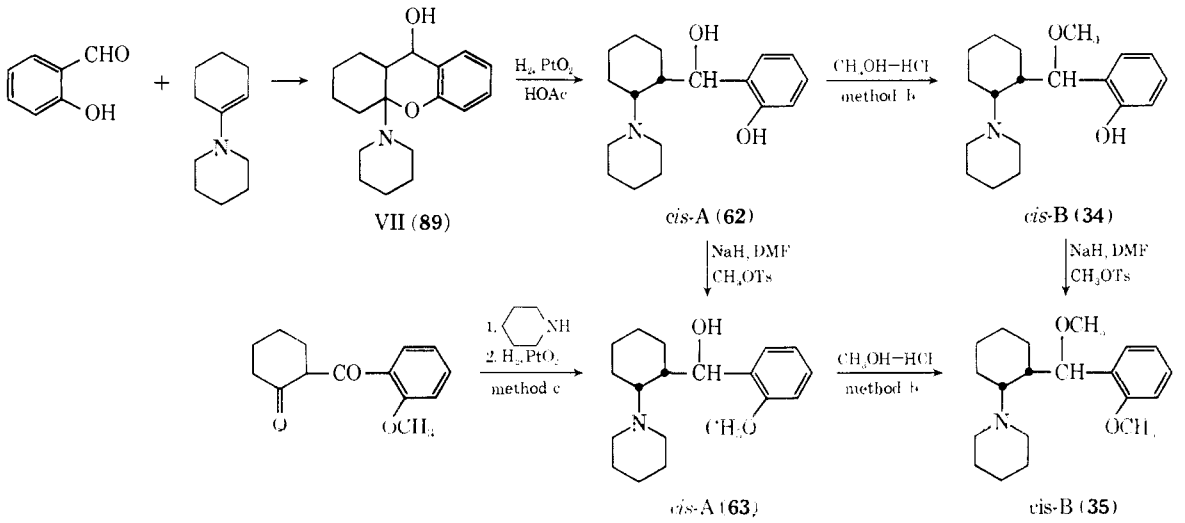
Method f



IIA (**8**) IIB (**9**)

CHART III

Method g

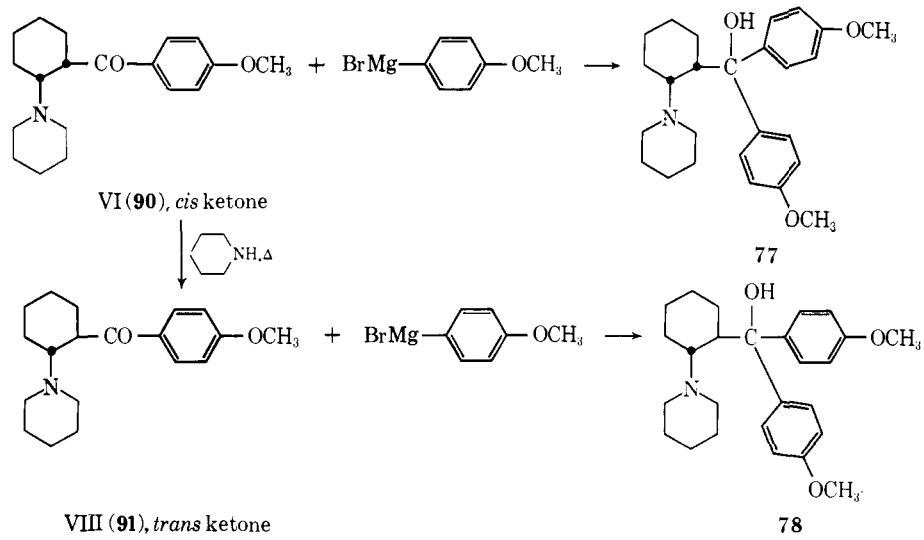


VII (**89**) *cis*-A (**62**) *cis*-B (**34**)

cis-A (**63**) cis-B (**35**)

CHART IV

Method h



Method i

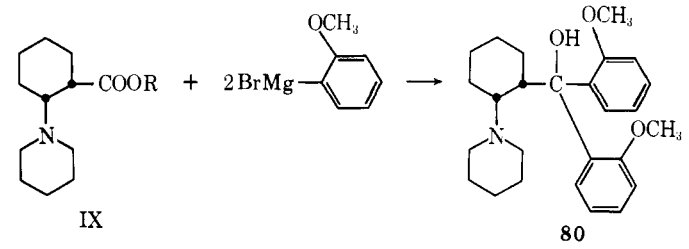
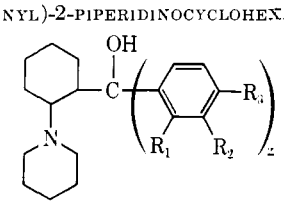


TABLE IV

BIS(α,α-PHENYL)-2-PIPERIDINOCYCLOHEXANEMETHANOLS



No.	Ring junction	R_1	R_2	R_3	Method	Yield,[b] %	Mp, °C	Recrystn[a] solvent	Formula	Analyses	Diuretic act.[c] % increase in urine excretion over controls Dose, mg/kg *po* 5	20
77	*cis*	H	H	OCH_3	h	65[d]	135–136	E–Pe	$C_{26}H_{35}NO_3$	C, H, N	25	71
78	*trans*	H	H	OCH_3	h	51	111–113	S	$C_{26}H_{35}NO_3$	C, H, N	46	96
79	*cis*	H	OCH_3	H	i	5.5	145–146	S	$C_{26}H_{35}NO_3$	C, H, N	4	29
80	*cis*	OCH_3	H	H	i	60	197–198	Me	$C_{26}H_{35}NO_3$	C, H, N	70	133
81	*cis*	OCH_2CH_3	H	H	i	63	185–187	Me	$C_{28}H_{39}NO_3$	C, H, N	48	124
82	*cis*	H	H	OCH_2CH_3	i	5.5	164–165	S	$C_{28}H_{39}NO_3$	C, H, N	2	1

[a] See Table II, footnote *a*. [b] The yields are calculated on the basis that compound IX is the ethyl ester. Compound IX is a mixture of methyl and ethyl esters; see Experimental Section. [c] See Table I, footnote *b*. [d] Yield of **77** by method i was 21%.

B to give 66 g (46%) of **89** as an off-white solid melting at 84–86°. Recrystallization from Skellysolve B gave the analytical sample melting at 86–87°.

***cis*-2-Piperidino-α-(*o*-hydroxyphenyl)cyclohexanemethanol (62).**—A solution of 25.8 g (0.090 mole) of **89** in 200 ml of AcOH was hydrogenated in the presence of 1.0 g of PtO_2 for 4 hr at an initial hydrogen pressure of 3.5 kg/cm². The mixture was filtered, the filtrate was evaporated *in vacuo*, and the solid residue was triturated with Et_2O to give 30.6 g of the AcOH salt of **62**, mp 199–201° (softens −190°). The AcOH salt was converted to the free base with $NaHCO_3$. The product was extracted into CH_2Cl_2 which was washed with NaCl solution, dried (Na_2SO_4), and evaporated to a pink solid. This solid was crystallized from Skellysolve B: 20.6 g (80%), mp 119–121°. Recrystallization from Skellysolve B raised the melting point of **62** to 122–122.5°.

***cis*-2-Piperidino-α-(*o*-methoxyphenyl)cyclohexanemethanol (63).**—A mixture of 5.8 g (0.02 mole) of **62** and 0.90 g of 53.3% NaH mineral oil dispersion in 50 ml of dry DMF was stirred for 15 min at room temperature and then cooled to 0–5°. A solution of 3.8 g (0.02 mole) of methyl *p*-toluenesulfonate in 5 ml of DMF was added over 5 min. The mixture was stirred for 45 min at 0–10°, then for 5 hr at room temperature, and allowed to stand 16 hr. The mixture was evaporated *in vacuo* and the residue dissolved in Et_2O–H_2O. The Et_2O layer was washed with H_2O and NaCl solution, dried ($MgSO_4$), and evaporated to a gum which was crystallized from pentane in two crops: 4.05 g, mp 98–100°; 0.75 g, mp 98.5–100.5; the combined yield was 80%. Mixture melting point with authentic **63** prepared by method c showed no depression and the ir spectra were identical.

***cis*-1-[2-(*o*-Hydroxy-α-methoxybenzyl)cyclohexyl]piperidine (34).**—A solution of 29 g (0.10 mole) of **62** in 1 l. of CH_3OH containing 50 g of anhydrous HCl was heated at reflux for 16 hr. The solution was evaporated *in vacuo*. The residue was dissolved in cold water, basified with 10% Na_2CO_3, and extracted

Table V

Miscellaneous Compounds

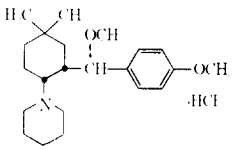
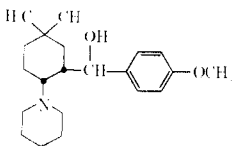
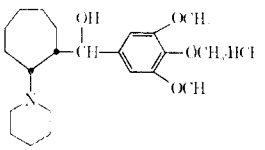
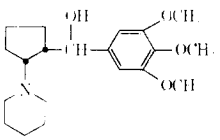
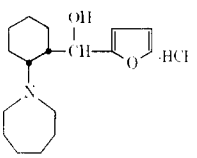
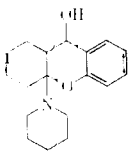
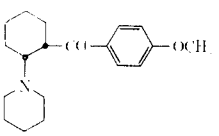
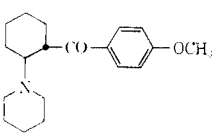
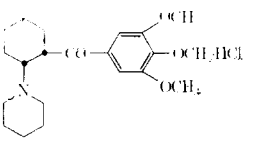
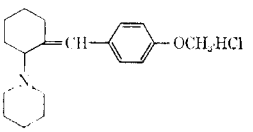
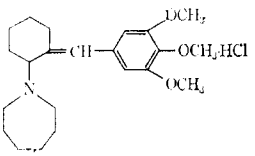
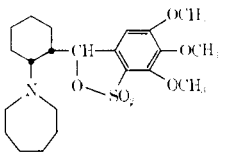
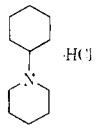
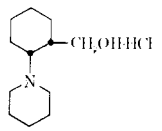
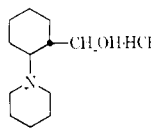
No.	Structure	Stereochemistry	Method	Yield, %	Mp, °C	Recrystn[a] solvent	Formula	Analyses	Diuretic act'y % increase in urine excretion over controls Dose, mg/kg po 5	20
83		B	b	58[d]	205–206	1-E	$C_{22}H_{36}ClNO_2$	C, H, Cl, N	125	160
84		A	c	30	133–135	Et	$C_{21}H_{33}NO_2$	C, H, N	~2	56
85		A	c	18	243–244	M	$C_{22}H_{36}ClNO_4$	C, H, Cl, N	~8	6
86		Isomer I			91–92	E–Pe	$C_{20}H_{31}NO_4$	C, H, N	14	50
87		Isomer II			119–120	E–Pe	$C_{20}H_{31}NO_4$	C, H, N	3	19
88		A			191–192	M–E	$C_{17}H_{23}ClNO_2$	C, H, Cl, N	4	5
89				46	86–87	S	$C_{15}H_{23}NO_2$	C, H, N	13	9
90[b]		*cis*							−5	27
91[b]		*trans*							13	34
92[b]		*cis*							17	56
93[b]									−6	9
94[b]									−10	−4

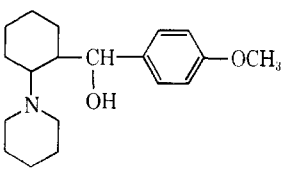
TABLE V (*Continued*)

No.	Structure	Stereochemistry	Method	Yield, %	Mp, °C	Recrystn[a] solvent	Formula	Analyses	Diuretic act.[c] % increase in urine excretion over controls Dose, mg/kg *po* 5	20
95[b]									−11	5
96[d]									9	77
97[e]		*cis*			243–245	Et	$C_{12}H_{24}ClNO$	C, H, Cl, N	−10	23
98[e]		*trans*			198–199	Et–E	$C_{12}H_{24}ClNO$	C, H, Cl, N	10	74

[a] See Table II, footnote *a*. [b] For preparation see ref 1. [c] See Table I, footnote *b*. [d] Free base available commercially. [e] Unpublished work. [f] Yield of free base.

TABLE VI

STEREOCHEMISTRY OF 2-PIPERIDINO-α-(*p*-METHOXYPHENYL)CYCLOHEXANEMETHANOLS



II

Racemate (II)	Diuretic act.[a]	Configuration side chain	Cyclohexane ring junction	Conformation (chair) Piperidine	Conformation (chair) Side chain
IIA (8)	Low	*threo*	*cis*	Axial	Equatorial
IIB (9)	High	*erythro*	*cis*	Equatorial	Axial
IIC (10)	Low	*erythro*	*trans*	Equatorial	Equatorial
IID (11)	Inactive	*threo*	*trans*	Equatorial	Equatorial

[a] The test dose is 20 mg/kg *po* in rats; see Table II.

TABLE VII

DIURETIC AND URINE ELECTROLYTE AND pH DETERMINATIONS WITH *d*-IIIB ORALLY IN RATS[a]

Test compd and dose, mg/kg *po*	Total urine excreted/ group of 7 rats, cc	% change from controls	Total Na excreted, mequiv	Total K excreted, mequiv	Total Cl excreted, mequiv	Urine pH
Control	25.5		3.29	1.02	3.76	6.2
d-IIIB						
0.5	32.5	27	3.72	1.21	4.25	6.3
1.0	29.0	14	3.57	1.08	3.92	6.3
2.5	33.3	31	4.02	0.94	4.42	6.3
5.0	39.1	52	4.73	1.10	5.34	6.4
10.0	44.5	76	6.00	1.29	6.17	6.7
20.0	59.9	137	7.68	1.61	7.78	6.7
40.0	61.1	141	7.70	1.46	7.44	7.0
80.0	6/7 died					

[a] Conclusions: *d*-IIIB produced significant diuretic and saluretic activity at doses of 2.5–40 mg/kg but was lethal at 80 mg/kg; total Na and Cl excretions increased at effective doses and doubled the controls at 20 mg/kg; total K excretions increased moderately at the two top doses (20 and 40 mg/kg); urine pH increased to neutral at the high dose.

with CH_2Cl_2. The CH_2Cl_2 extract was washed with H_2O and NaCl solution, dried ($MgSO_4$), and evaporated to a solid which was crystallized from EtOH to give 26.1 g (86%) of **34**, mp 113–115°. The analytical sample was recrystallized from EtOH and then Skellysolve B, mp 113–114.5°.

***cis*-1-[2-(*o*,α-Dimethoxybenzyl)cyclohexyl]piperidine Hydrochloride (35).**—Compound **34** was methylated as described in the preparation of **63** except that the DMF reaction mixture was poured into water and extracted with Et_2O. The Et_2O layer was washed with H_2O, dried ($MgSO_4$), and evaporated to an oil. This oil was chromatographed on neutral alumina (Woelm), activity I, eluting with 10% Et_2O–Skellysolve B. The eluted free base was converted to a hydrochloride which was crystallized from EtCOMe–Et_2O: yield 65%, mp 222–223° dec. It was identical with an authentic sample of **35** (prepared by method b) by mixture melting point and identical infrared spectra.

***cis*-α,α-Bis(*p*-methoxyphenyl)-2-piperidinocyclohexanemethanol (77).**—A solution of 9.03 g (0.03 mole) of **90** in 100 ml of anhydrous Et_2O was added over 25-min period to a solution of *p*-methoxyphenylmagnesium bromide prepared from 11.2 g (0.06 mole) of *p*-bromoanisole and 1.45 g (0.06 g-atom) of Mg turnings in 125 ml of Et_2O. The mixture was stirred for 3 hr, then decomposed by addition of 50 ml of H_2O. The solution was decanted from an amorphous solid which was

Table VIII

Diuretic and Urine Electrolyte and pH Determinations with *d*-IIIB Orally in Dogs[b]

Dog no.	Test compd and dose, mg/kg *po*	Urine vol: Top limit for 95% CI, cc/kg[a]	Urine vol: Total excreted, cc/kg	Sodium: Top limit for 95% CI, mequiv[a]	Sodium: Total excreted, mequiv	Potassium: Top limit for 95% CI, mequiv[a]	Potassium: Total excreted, mequiv	Chloride: Top limit for 95% CI, mequiv[a]	Chloride: Total excreted, mequiv	Urine pH
2G11	Control	17		24		5		27		6.5
	d-IIIB, 10		36		54		7		68	6.3
3843	Control	20		21		3		21		7.5
	d-IIIB, 10		46		44		2		44	7.8
4116	Control	20		28		5		30		7.2
	d-IIIB, 10		40		51		3		53	7.6
4118	Control	18		27		5		27		6.8
	d-IIIB, 10		36		46		4		46	7.6
4127	Control	15		27		4		25		7.0
	d-IIIB, 10		45		66		5		71	7.1
2L13	Control	13		22		4		25		6.1
	d-IIIB, 10		49		77		6		85	7.1

[a] 95% CI from 29 tests (24 for dog 2L13). All volume and electrolyte figures were adjusted to nearest whole numbers. [b] Conclusions: *d*-IIIB orally by capsule at 10 mg/kg produced significant diuretic and saluretic activity in all six dogs; significant kaliuretic activity was observed in three of six dogs; in general, urine pH values changed only slightly.

then washed with Et_2O. The combined Et_2O layer was washed with H_2O and NaCl solution, dried (Na_2SO_4), and evaporated to give 15 g of crude product. Crystallization from Et_2O–petroleum ether (bp 30–60°) afforded two crops: 5 g, mp 135–136°; 3.0 g, mp 134–135°. The combined yield was 65%.

2-Piperidinocyclohexanecarboxylic Acid Methyl and Ethyl Esters (IX).—The ethyl 2-cyclohexanonecarboxylate obtained from Aldrich Chemical Co. contained 35–40% of the corresponding methyl ester. A solution of 300 g of the esters of 2-cyclohexanonecarboxylic acid, 450 g of piperidine, and 5.0 g of *p*-toluenesulfonic acid monohydrate in 4 l. of C_6H_6 was heated at reflux for 3.5 days using a Dean–Stark trap (collected 27 ml of H_2O). The mixture was concentrated *in vacuo*. The residue was dissolved in 400 ml of absolute EtOH. The solution was divided into three portions and each portion was hydrogenated in the presence of 1.5 g of PtO_2 at an initial pressure of 3.5 kg/cm². In 6 hr, about 80–90% of the required amount of hydrogen was absorbed. The runs were combined and filtered. The filtrate was evaporated *in vacuo* and the oil residue was dissolved in 2 l. of 10% HCl and 1 l. of Et_2O. The acid layer was separated and basified (20% NaOH) and the oil product was extracted into Et_2O. The Et_2O layer was washed with H_2O, dried (Na_2SO_4), and concentrated to an oil. This oil was distilled (twice) to give 136.7 g of IX, bp 140–162° (12 mm). The nmr spectrum is consistent with a mixture of ethyl and methyl esters of IX in ratio of 2:1. This material was suitable for use in the subsequent Grignard reaction.

***cis*-α,α-Bis(*o*-methoxyphenyl)-2-piperidinocyclohexanemethanol (80).**—A solution of 12 g of IX in 100 ml of Et_2O was added over 30 min to a stirred refluxing mixture of *o*-methoxyphenylmagnesium bromide prepared from 37.5 g (0.20 mole) of *o*-bromoanisole and 4.9 g (0.2 g-atom) of Mg turnings in 250 ml of Et_2O. The mixture was refluxed for 2.5 hr and decomposed in the cold by the addition of cold H_2O followed by dilution with a solution of 200 g of NH_4Cl in 1.5 l. of H_2O. The mixture was extracted with CH_2Cl_2 which was washed with water, dried (Na_2SO_4), and evaporated to a solid. It was recrystallized from EtCOMe to give 12.5 g (60%) of **80**, mp 195–196°. The analytical sample melted at 197–198° (EtCOMe). This material was identical with a sample of **80** (prepared by method h) by mixture melting point and comparison of infrared spectra.

Resolution of *cis*-1-[2-(*p*,α-Dimethoxybenzyl)cyclohexyl]piperidine (2).—A hot solution of 16 g (0.0505 mole) of **2** and 19.5 g (0.0505 mole) of O,O-di-*p*-tolyl-L-tartaric acid in 25 ml of absolute EtOH and 25 ml of EtOAc was diluted with 200 ml of warm EtOAc and filtered. After standing overnight the *l*-base L-acid which separated was collected, washed with 50 ml of EtOAc, and dried *in vacuo*: 11.5 g, mp 151–152°. A sample was crystallized from EtOH–EtOAc: mp 159–160°, $[\alpha]^{24}D$ −103° (CH_3OH). *Anal.* ($C_{40}H_{49}NO_{10}$) C, H, N. Ten grams of the salt was converted to the *l*-base with 5% Na_2CO_3–CH_2Cl_2. The crude *l*-base was recrystallized twice from EtOH: 3.2 g, mp 106.5–107.5°, $[\alpha]^{24}D$ −61° ($CHCl_3$). The hydrochloride (**4**) was crystallized from *i*-PrOH–Et_2O: mp 227–228° dec, $[\alpha]^{24}D$ −58° (CH_3OH). *Anal.* ($C_{20}H_{31}NO_2 \cdot HCl$) C, H, Cl, N. The *d*-base was prepared using O,O-di-*p*-tolyl-D-tartaric acid or by crystallization from EtOH of the crude free bases liberated from the mother liquors of the *l*-base L-acid. The *d*-base melted at 106–107° (EtOH), $[\alpha]^{24}D$ +65° ($CHCl_3$). The hydrochloride (**3**) was crystallized from *i*-PrOH–Et_2O: mp 230–231° dec, $[\alpha]^{24}D$ +60° (CH_3OH). *Anal.* ($C_{20}H_{31}NO_2 \cdot HCl$) C, H, Cl, N.

Acknowledgment.—The authors are indebted to R. A. Zandt and W. E. Brown for the diuretic and urine electrolyte studies and L. G. Laurian for laboratory assistance. We also wish to thank W. A. Freyburger, E. Smits, H. F. Kurtz, E. M. Glenn, R. J. Collins, W. Veldkamp, R. G. Carlson, and J. G. Ceru for the numerous other pharmacologic and toxicologic determinations.