Synthesis of Some 1-Piperazinecarboxalic Acid Ethyl Ester Derivatives as Possible Antifilarial and Antihypertensive Agents[1]

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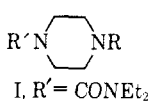
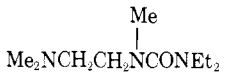
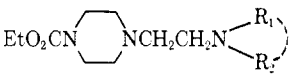
N,N-Diethyl-4-substituted-1-piperazinecarboxamides (I) and 1-piperazinecarboxalic acid Et ester derivatives (II) exhibit pronounced antifilarial activity.[3,4] Further, the ethylenediamine derivative III has also been found to be active against litomosoidal infections.[5] In view of these observations we wished to build up a structural pattern of the type IV wherein 1-piperazinecarboxylic acid Et ester itself will form a part of the ethylenediamine chain.



I, R′ = $CONEt_2$
II, R = CO_2Et



III



IV

Since some piperazine derivatives[6] and also some ethylenediamine derivatives[7] have been reported as potential antihypertensive agents, the antihypertensive effect of compounds IV, in which both terminal N atoms of the ethylenediamine chain form part of heterocyclic moieties (with the exception of **9**) have been studied.

Chemistry.—The substituted ethylenediamine derivatives IV were prepared by the interaction of 4-(β-chloroethyl)-1-piperazinecarboxylic acid Et ester·HCl[8] and appropriate secondary amines in the presence of anhyd K_2CO_3 in abs EtOH. Compounds **1** and **2** have also been prepared by treating piperidinoethyl chloride·HCl[9] and morpholinoethyl chloride·HCl,[9] resp, with 1-piperazinecarboxylic acid Et ester by the same procedure.

Biological Testing. Antifilarial Activity.—Compounds **1–5**, **7**, and **9** that passed the short-term oral toxicity were screened on *L. carinii* infected albino rats generally at a dose level of 200 mg/kg once daily for 5 consecutive days, and the tail blood (4 mm^3) was examined up to day 15. *N,N*-Diethyl-4-methyl-1-piperazinecarboxamide-treated and untreated albino rats were kept as control. Only **1** showed definite microfilaricidal activity even at 100 mg/kg.

Antihypertensive Effects.—All the compounds except **3** as listed in Table I were tested for hypotensive or hypertensive effect on pentobarbital-anesthetized cats of either sex at dose levels of 0.5 mg/kg, 5 mg/kg, and 25 mg/kg iv. The criterion of activity was taken to be a fall in blood pressure by 20 mm for at least 15 min. The hypo- or hypertensive effect is recorded in Table I. Of the 7 compounds tested for antifilarial activity, only one (**1**) was found to possess definite microfilaricidal activity at 100 and 200 mg/kg.

Encouraging antihypertensive activity was observed with a small number of compounds. Maximum activity was observed in **4**, which embodies a 1,2,3,4-tetrahydroisoquinoline moiety at one end of the ethylenediamine chain. In a number of other tetrahydroisoquinoline derivatives, antihypertensive activity has been observed.[10] 3,4-Dihydro-2(*H*)-isoquinoline carboxamidine has been found clinically to be a potent antihypertensive agent.[11] The parent compound, 4-(β-chloroethyl)-1-piperazinecarboxylic acid Et ester·HCl also produced an hypotensive effect.

Experimental Section[12]

Intermediates.—The requisite 4-(β-chloroethyl)-1-piperazinecarboxylic acid Et ester·HCl, piperidinoethyl chloride·HCl, morpholinoethyl chloride·HCl, *N*-phenylpiperazine,[13] *N*-benzylpiperazine,[14] and *N*-(*p*/*m*-chlorophenyl)piperazine[15] were prepd according to the methods available in the lit. 1,2,3,4-Tetrahydroisoquinoline has been prepd by a slight modification[16] of the method of Pyman and coworkers.[17] For the prepn of 1-piperazinecarboxylic acid Et ester, however, a simple method has been developed which has a definite advantage over the lit. proce-

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TABLE I: SUBSTITUTED ETHYLENEDIAMINES IV

No.	N(R1)(R2)	Bp (mm) or mp of base, °C	Mp of hydrochloride, °C	Crystn solvent	Formula[b]	Pressure response, mm: Dose, mg/kg	Fall	Rise
1	*N*-Piperidino	193–195 (4–6)	278–279	A[c]	$C_{14}H_{27}N_3O_2 \cdot 2HCl$	25	Nil	Nil
2	*N*-Morpholino	220–222 (10–12)	285–286	A	$C_{13}H_{25}N_3O_3 \cdot 2HCl$	25	Nil	Nil
3	*N*-Pyrrolidino	173–175 (4–6)	295–296	B	$C_{13}H_{25}N_3O_2 \cdot 2HCl$			
4	*N*-1,2,3,4-Tetrahydroisoquinolino	248–250 (8–10)	265–267	A	$C_{18}H_{27}N_3O_2 \cdot 2HCl$	10	62	Nil
5	4-Benzyl-1-piperazino	253–255 (4–6)	261–262	A	$C_{20}H_{32}N_4O_2 \cdot 2HCl$	25	41	Nil
6	4-*p*-Chlorophenyl-1-piperazino	97	264–265	B	$C_{19}H_{29}ClN_4O_2 \cdot 2HCl$	25	Biphasic	
7	4-Phenylpiperazino	*a*	264–266	A	$C_{19}H_{30}N_4O_2 \cdot 2HCl$	25	Nil	Nil
8	4-*m*-Chlorophenyl-1-piperazino	263–265 (4–6)	266–268	A	$C_{19}H_{29}ClN_4O_2 \cdot 2HCl$	10	55	Nil
9	*i*-Pr_2N	184–187 (4–6)	232–235	C	$C_{15}H_{31}N_3O_2 \cdot 2HCl$	25	Nil	Nil

[a] Decompd during distn. [b] All HCl salts were analyzed for C, H, N, Cl, and the anal. results were within ±0.4% of the theoretical values. [c] A, MeOH; B, EtOH; C, EtOH–Et_2O.

dures.[18] In these, 1,4-piperazinedicarboxylic acid Et ester is invariably formed along with 1-piperazinecarboxylic acid Et ester. Further the methods are tedious and work-up is difficult. In the present procedure, formation of the disubstituted product has been totally avoided. 1-Piperazinecarboxaldehyde[19] is first converted to 4-formyl-1-piperazinecarboxylic acid Et ester[20] which on hydrolysis with NaOH (10%) for 4 hr gave 1-piperazinecarboxylic acid Et ester in 85–90% yield.

Substituted Ethylenediamines IV.—A mixt of 4-(β-chloroethyl)-1-piperazinecarboxylic acid Et ester·HCl (0.05 mole), the appropriate secondary amine (0.05 mole), anhyd K_2CO_3 (0.05 mole), and abs EtOH (50 ml) was refluxed for about 6 hr, and the solvent was removed by distn. The residual material was treated with H_2O and the aq soln after basification with 50% NaOH soln to pH 9 was extd with Et_2O The ext was dried (Na_2SO_4) and concd to afford the desired product as liq which was distd *in vacuo*. In all cases the viscous liquids finally obtd were converted into the corresponding hydrochlorides by passing dry HCl through an Et_2O soln. All compds were characterized as their hydrochlorides. Only **6** (see Table I) gave an anal. pure sample of the base on crystn from petr ether (bp 60–80°). The characteristics of IV have been recorded in Table I.

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Optical Isomers of Mepivacaine and Bupivacaine

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Current interest in the potent local anesthetics mepivacaine and bupivacaine—*N*-methyl and *N*-butyl derivatives of (±)-2′,6′-pipecoloxylidide—(I) prompted us to prepare and study the optical isomers. The parent (±)-I was resolved using dibenzoyl (+)-tartaric acid. Mepivacaine was resolved by crystallization of its quinic acid salts.[1] Although a number of optically active acids were tried as resolving agents for (±)-bupivacaine, no separation of the isomers could be effected until seed crystals were made available by N-butylation of (−)-I and crystallization of its salt with (+)-tartaric acid.

An observation that (+)-mepivacaine·HCl and (−)-bupivacaine·HCl were significantly longer acting than their enantiomers has been reported in an earlier publication from this laboratory.[2] Thus it became of interest to establish their configuration. This was accomplished by preparing from (*R*)-(+)-methyl pipecolate[3] and 2,6-xylidinomagnesium bromide[4] the parent (*R*)-(−)-I identical with (−)-I by resolution of (±)-I. N-Butylation of a sample of this (*R*)-I gave (*R*)-(+)-bupivacaine and N-methylation of (*S*)-I (obtained from resolution of (±)-I) gave (*S*)-(+)-mepivacaine. Thus, the longer-acting (+)-mepivacaine and (−)-bupivacaine isomers are both of the (*S*) configuration.

Experimental Section

Resolution of 2′,6′-Pipecoloxylidide (I).—To a soln of 42.0 g (0.15 mole) of (±)-I in 300 ml of boiling *i*-PrOH was added a soln of 38.0 g (0.10 mole) of dibenzoyl (+)-tartaric acid monohydrate (DBT) in 300 ml of boiling *i*-PrOH. Immediate crystn occurred which was completed by slow stirring while the mixt cooled to 35°. The ppt was collected, washed with *i*-PrOH, and dried at 70° to give 32 g of (+)-base DBT salt, mp 186–189°. This crop was converted to base by suspending in 300 ml each of H_2O and Et_2O and adding 8 ml of 28% NH_4OH. The Et_2O layer was sepd, washed with H_2O, and concd *in vacuo*. The residue was crystd from boiling hexane to give a 12.0-g first crop of the base, mp 130–132°, $[\alpha]^{25}D$ +46.1° (*c* 2.3, 1 *N* HCl). This rotation was unchanged after recrystn from *i*-PrOAc.

The resoln liquor was evapd *in vacuo*, and the residual crude (−)-base DBT salt was converted to base as above and recrystd twice from boiling hexane to give 11.1 g of base, mp 130–132°, $[\alpha]^{25}D$ −46.8° (*c* 2.3, 1 *N* HCl), $[\alpha]^{25}D$ −11.04 (*c* 5, MeOH).

Resolution of (±)-Mepivacaine.—A soln of 46.0 g (0.186 mole) of (±)-mepivacaine (mp 149–151°) with 38.4 g (0.2 mole) of quinic acid (Freas Bros.) and 400 ml of abs EtOH was seeded at 60° and stirred and cooled to 25°. The cryst ppt was collected and recrystd from 300 ml of 95% EtOH to give 34 g of (+)-base quinate, mp 192–195°. This salt was dissolved in 300 ml of H_2O and basified slowly with NH_4OH while rubbing and stirring to induce crystn. The pptd base was collected, washed with H_2O,

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