14 000); ^{1}H NMR (Me_2SO-d_6) δ 11.30 (s, N_3H), 5.90 (m, $C_1'H$, C_5H), 4.19 (m, $C_5'H$, $C_4'H$, $C_3'H$, $C_2'H$, CH_2, C_6H), 1.26 ppm (t, CH_3). Anal. ($C_{11}H_{15}N_3O_9$) C, H, N.

Antimicrobial. The compounds synthesized for this study were assayed for antimicrobial activity using strains of *Escherichia coli* (*Ec*), *Pseudomonas aeruginosa* (*Ps*), *Staphylococcus aureus* (*Sa*), *Candida albicans* (*Ca*), and *Trichophyton mentagrophytes* (*Tm*) isolated in the clinic. In vitro sensitivity of these organisms to this series of 5,6-dihydro-5-nitrouracils was quantitatively determined by broth dilution assay. Serial dilutions were prepared in chemically defined medium in a range from 0.4 to 0.005 μmol/ml. The minimal inhibitory concentration (MIC) was recorded as the highest dilution of compound which prevented visible growth of the pathogen. Bacterial and yeast MIC's were read following 24 h of incubation at 35°. Dermatophyte inhibition was read after 48 h of incubation at 30°.

Although 5-diazouracil (1) [MIC (μmol/ml) *Sa* 0.01, *Ps* 0.04, *Ec* 0.02] and 5-diazo-6-hydroxy-1,6-dihydrouracil (2) [MIC (μmol/ml) *Sa* 0.02, *Ps* 0.02, *Ec* 0.01] inhibited the in vitro growth of bacteria, none of the nitro-substituted compounds, **5**–**12**, were inhibitory at broth concentrations of 0.4 μmol/ml or less. Antifungal activity was not detected for any compounds of this series.

References and Notes

(1) T. H. Weisman and L. E. Loveless, *Proc. Soc. Exp. Biol. Med.*, **86**, 268 (1954).
(2) E. Previc and S. Richardson, *J. Bacteriol.*, **97**, 416 (1969).
(3) D. E. Hunt and R. F. Pittillo, *Appl. Microbiol.*, **16**, 1792 (1968).
(4) T. C. Thurber and L. B. Townsend, *J. Heterocycl. Chem.*, **9**, 629 (1972).
(5) I. Wempen, I. L. Doerr, L. Kaplan, and J. J. Fox, *J. Am. Chem. Soc.*, **82**, 1624 (1960).
(6) N. Miller and P. A. Ceratti, *J. Am. Chem. Soc.*, **89**, 2767 (1967).
(7) C. H. Evans, A. S. Jones, and R. T. Walker, *Tetrahedron*, **29**, 1611 (1973).
(8) K. V. Rao and D. Jackman, *J. Heterocycl. Chem.*, **10**, 213 (1973).
(9) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds", Prentice-Hall, Englewood Cliffs, N.J., 1965, p 99.
(10) V. M. Nesterov and T. S. Safonova, *Khim. Geterotsikl. Soedin.*, **8**, 1088 (1970).

Optical Isomers of 2-(2-Ethoxyphenoxymethyl)tetrahydro-1,4-oxazine (Viloxazine) and Related Compounds

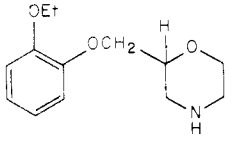
Ralph Howe,* Thomas Leigh, Balbir S. Rao, and Alexander H. Todd

Imperial Chemical Industries, Pharmaceuticals Division, Alderley Park, Macclesfield, Cheshire, England.

Received November 26, 1975

The optical isomers of 2-(2-ethoxyphenoxymethyl)tetrahydro-1,4-oxazine (viloxazine) and 2-(3-methoxyphenoxymethyl)tetrahydro-1,4-oxazine have been prepared and absolute configurations have been assigned. In their action on the central nervous system the *S* isomers are at least ten times more potent than the *R* isomers. The intermediate 4-benzyl-2-(*p*-toluenesulfonyloxymethyl)tetrahydro-1,4-oxazine has been resolved. Its isomers provide a convenient starting point for the preparation of optical isomers of viloxazine analogues of known configuration.

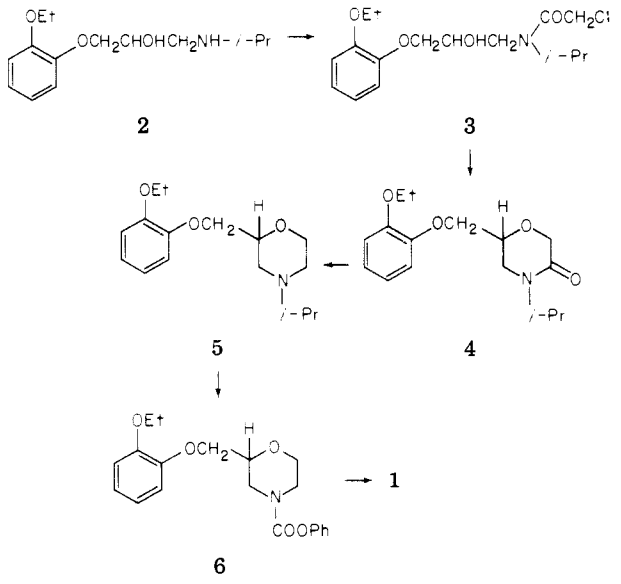
The synthesis of the psychotropic agent (±)-2-(2-ethoxyphenoxymethyl)tetrahydro-1,4-oxazine (**1**, viloxazine)[1] and its effects on laboratory animals have been described by Mallion et al.[2-4] Controlled studies have shown that viloxazine is an effective antidepressant in man.[5-7] It was of interest to resolve the racemate to provide the optical isomers for biological study and also to assign absolute configurations to the isomers. For clarity, the isomers will be referred to from the outset as *R* and *S* isomers rather than (+) and (−) isomers, before the proof of assignment is given. The reason is that for a given isomer the sign of rotation depends upon the solvent.



1

Resolution of (±)-**1** with (−)-*O*,*O*-di-*p*-toluoyltartaric acid[8] gave the salt (*R*)-**1** hydrogen (−)-acid.[9] The mother liquors remaining after the removal of that salt yielded (*S*)-**1** hydrogen (−)-acid. The free base (*R*)-**1** and (*R*)-**1** hydrochloride had low positive rotations when measured in MeOH. In H_2O (*R*)-**1** hydrochloride had a low negative rotation. Because of these low rotations and the small difference in rotation between the two diastereoisomeric salts it was not practicable to monitor the resolution by measuring optical rotation. However, it proved convenient to monitor progress in the research stage by following the change in melting point of the salt with the resolving acid

Scheme I



2 **3** **4** **5** **6**

or of the hydrochloride. Resolution of (±)-**1** with the more expensive (+)-*O*,*O*-di-*p*-toluoyltartaric acid was a more direct route to (*S*)-**1** derivatives.[9] The physical properties of the isomers are given in Table I.

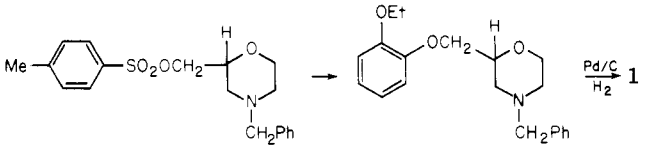
The assignment of absolute configuration to (*R*)-**1** was made following its synthesis from (*R*)-(+)-3-(2-ethoxyphenoxy)-1-isopropylamino-2-propanol [(*R*)-(+)-**2**] by the route shown in Scheme I. The sequence rule is not

Table I. Physical Properties of the Optical Isomers

Compd	Final crystn solvent	Mp, °C	$[\alpha]^{21}D$, deg	Concn in MeOH, %	Formula	Analyses
(*R*)-1 hydrogen (−)-*O*,*O*-di-*p*-toluoyltartrate hemihydrate	MeOH	188–189	−84.0	0.99	$C_{33}H_{37}NO_{11}\cdot 0.5H_2O$	C, H, N, H_2O
(*R*)-1		Oil	+3.1	1.0		
(*R*)-1 hydrochloride	MeOH + EtOAc	166–167	+4.3 −9.2	1.01, 1.03 (H_2O)	$C_{13}H_{20}ClNO_3$	C, H, Cl, N
(*S*)-1 hydrogen (−)-*O*,*O*-di-*p*-toluoyltartrate	MeOH	166–167	−87.8	0.98	$C_{33}H_{37}NO_{11}$	C, H, N
(*S*)-1		Oil	−3.1	1.0		
(*S*)-1 hydrochloride	MeOH + EtOAc	166–167	−4.5	0.99	$C_{13}H_{20}ClNO_3$	C, H, Cl, N
(*S*)-1 hydrogen (+)-*O*,*O*-di-*p*-toluoyltartrate hemihydrate	MeOH	188–189	+84.2	1.10	$C_{33}H_{37}NO_{11}\cdot 0.5H_2O$	C, H, N
(*R*)-5 hydrochloride hemihydrate	MeOH + EtOAc	134–135	−7.8	1.13	$C_{16}H_{26}ClNO_3\cdot 0.5H_2O$	C, H, N
(*S*)-7 hydrogen (+)-*p*-toluenesulfonylglutamate	MeOH	184	+35.3	1.02	$C_{31}H_{38}N_2O_{10}S_2$	C, H, N
(*S*)-7	P[a] + Et_2O	68–70	+20.9	2.0	$C_{19}H_{23}NO_4S$	C, H, N
(*S*)-7 hydrochloride	Acetone	150	+19.4	5.0	$C_{19}H_{24}ClNO_4S$	C, H, N
(*R*)-7	P[a] + Et_2O	68–70	−20.7	2.0	$C_{19}H_{23}NO_4S$	C, H, N
(*R*)-7 hydrochloride	Acetone	150	−19.4	5.0	$C_{19}H_{24}ClNO_4S$	C, H, N
(*R*)-7 hydrogen (+)-*O*,*O*-dibenzoyltartrate	EtOH	160	−82.6	0.7	$C_{37}H_{37}NO_{12}S$	H, N, S; C[b]
(*R*)-9 hydrogen (−)-*O*,*O*-di-*p*-toluoyltartrate	MeOH	169	−94.5	0.94	$C_{32}H_{35}NO_{11}$	C, H, N
(*R*)-9 hydrochloride	MeOH + EtOAc	158	+2.4	1.0	$C_{12}H_{18}ClNO_3$	C, H, Cl, N
(*S*)-9 hydrogen (+)-*O*,*O*-di-*p*-toluoyltartrate	MeOH	169	+93.5	0.94	$C_{32}H_{35}NO_{11}$	H, N; C[c]
(*S*)-9		Oil	−0.9	1.0		
(*S*)-9 hydrochloride	MeOH + EtOAc	158	−2.4 +9.8	1.02, 1.0 (H_2O)	$C_{12}H_{18}ClNO_3$	C, H, Cl, N

[a] P, petroleum ether (bp 40–60°). [b] C: calcd, 61.8; found, 61.3. [c] C: calcd, 63.1; found, 62.6.

Scheme II



7 8

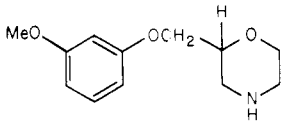
contravened. The absolute configuration of (*R*)-(+)-**2** was proved by Dukes and Smith.[10]

Racemic analogues of viloxazine have been prepared by the route shown in Scheme II. We have resolved the intermediate 4-benzyl-2-(*p*-toluenesulfonyloxymethyl)-morpholine (**7**).[9] Reaction of each isomer with a phenol provides a convenient route to optical isomers of viloxazine analogues of known absolute configuration and avoids the need for a resolution step for each analogue. The *S* isomer of **7** was obtained in 84% yield by resolution of (±)-**7** with (+)-*p*-toluenesulfonylglutamic acid (TGA). The mother liquors from that resolution yielded base rich in (*R*)-**7**, which was converted to its hydrochloride and recrystallized to give optically pure material in 50% yield. A more profitable method was to convert the base rich in (*R*)-**7** to the (+)-*O*,*O*-dibenzoyltartrate salt. Crystallization gave the optically pure salt in 93% yield. The assignment of the *S* configuration to the isomer which has the least-soluble TGA salt was made by converting that isomer to (*S*)-**1**.

The isomers of the viloxazine analogue **9**[3] have also been prepared (Table I). (±)-**9** was resolved using the (+) and (−) isomers of *O*,*O*-di-*p*-toluoyltartaric acid and following the general procedure described for **1**.[9] (*S*)-**9** was also obtained by treating (*S*)-**7** with 3-methoxyphenol using the procedure given for converting (*S*)-**7** to (*S*)-**1**. The absolute

Table II

Compd	Reserpine antag, ED_{10}, mg/kg po	Redn in locomotor act., min effective dose, mg/kg po
(±)-**1**	0.3–1	3–10
(*S*)-**1**	0.1	1
(*R*)-**1**	1–3	30
(±)-**9**	NA 100	3–10
(*S*)-**9**	NA 100	1–3
(*R*)-**9**	NA 100	30–100



9

configurations of the isomers of **9** are based on this reaction.

Biological Results. The racemates and isomers were tested as described previously.[3] Results are displayed in Table II. In both the reserpine-induced hypothermia test, which is indicative of antidepressant activity, and in the locomotor activity test, which is indicative of sedative action, the *S* isomers were at least ten times more potent than the *R* isomers.

Experimental Section

(*R*)-2-(2-Ethoxyphenoxymethyl)tetrahydro-1,4-oxazine [(*R*)-**1**]. A solution of 48 g (0.2 mol) of (±)-**1** in 325 ml of MeOH was added to a stirred solution of 78.2 g (0.2 mol) of (−)-*O*,*O*-di-*p*-toluoyltartaric acid in 325 ml of MeOH at room temperature. After a few hours the solid which had separated was isolated by filtration and the filtrate was retained for further examination. The solid (65 g), mp 176–177°, $[\alpha]^{21}D$ −83.3° (*c* 0.99, MeOH), was

crystallized from MeOH until the melting point and the optical rotation became constant. (*R*)-1 hydrogen (−)-*O,O*-di-*p*-toluoyltartrate hemihydrate was obtained (38 g, 60%).

The free base was obtained by shaking a mixture of 36.9 g of (*R*)-1 hydrogen (−)-*O,O*-di-*p*-toluoyltartrate hemihydrate and 1140 ml of 2 N NaOH (saturated with NaCl) with Et_2O (three 500-ml portions). The Et_2O extract furnished (*R*)-1 as an oil (12.6 g, 90%). Treatment of an Et_2O solution of (*R*)-1 with ethereal HCl gave (*R*)-1 HCl (13.3 g, 90%).

(*S*)-2-(2-Ethoxyphenoxymethyl)tetrahydro-1,4-oxazine [(*S*)-1]. The filtrate retained in the above experiment was evaporated in vacuo to 200 ml. After a few hours the solid which had separated was isolated by filtration: mp 166–167°; $[\alpha]^{21}D$ −88.3° (*c* 1.05, MeOH) (45 g). The solid was crystallized from MeOH until the melting point and the optical rotation became constant. (*S*)-1 hydrogen (−)-*O,O*-di-*p*-toluoyltartrate was obtained (25 g, 40%). (*S*)-1 and (*S*)-1 HCl were obtained as described in the above experiment.

(*S*)-1 hydrogen (+)-*O,O*-di-*p*-toluoyltartrate hemihydrate was obtained from (±)-1 by using (+)-*O,O*-di-*p*-toluoyltartaric acid as resolving acid.

(*R*)-2-(2-Ethoxyphenoxymethyl)-4-isopropyltetrahydro-1,4-oxazine [(*R*)-5]. A solution of 0.44 g (0.039 mol) of chloroacetyl chloride in 5 ml of Et_2O was added during 5 min to a stirred solution of 1.0 g (0.0395 mol) of (*R*)-(+)-**2** and 0.44 g (0.044 mol) of Et_3N in 40 ml of Et_2O. The mixture was stirred for 24 h and then filtered. The filtrate was evaporated to give crude (*R*)-3. A solution of 1.33 g of crude (*R*)-**3** in 5 ml of MeOH was added during 5 min to a solution of 0.93 g of Na in 20 ml of MeOH. The mixture was heated under reflux for 6 h and then evaporated to dryness. The residue was shaken with 20 ml of Et_2O and 5 ml of 10% hydrochloric acid. The Et_2O layer was washed with H_2O, dried, and evaporated to give (*R*)-**4** as an oil. A mixture of 0.4 g of (*R*)-4 and 1.5 g of $LiAlH_4$ in 20 ml of Et_2O was heated under reflux for 6 h and then cooled. EtOAc (10 ml) was added and the mixture was heated under reflux for 10 min to decompose $LiAlH_4$. The organic phase was washed with H_2O (two 10-ml portions) and dried. Ethereal HCl was added and (*R*)-**5** HCl (0.3 g, 24%) separated as a solid.

(*R*)-2-(2-Ethoxyphenoxymethyl)tetrahydro-1,4-oxazine [(*R*)-1] from (*R*)-2-(2-Ethoxyphenoxymethyl)-4-isopropyltetrahydro-1,4-oxazine [(*R*)-5]. A mixture of 0.215 g (0.00077 mol) of (*R*)-**5** (free base) and 0.136 g (0.00087 mol) of phenyl chloroformate in 10 ml of C_6H_6 was heated under reflux for 18 h. The C_6H_6 solution was washed with 15 ml of 1 N HCl and then 15 ml of H_2O. The dried C_6H_6 extract was evaporated to give crude (*R*)-**6**. This was heated under reflux for 18 h with a solution of 0.2 g of KOH in 20 ml of EtOH and then the EtOH was evaporated. The residue was shaken with 10 ml of H_2O and 10 ml of Et_2O. The Et_2O extract was dried, ethereal HCl was added, and (*R*)-1 HCl (0.104 g, 50%) separated as a solid: mp and mmp 165–167°, from MeOH + EtOAc. The mmp with (*S*)-1 HCl was 180–182°. Racemic 1 HCl has mp 185–186°.[2]

(*S*)-4-Benzyl-2-(*p*-toluenesulfonyloxymethyl)tetrahydro-1,4-oxazine [(*S*)-7]. A solution of 18.1 g (0.053 mol) of (±)-**7** in 100 ml of MeOH was added to a solution of 16.0 g (0.053 mol) of (+)-*p*-toluenesulfonylglutamic acid in 50 ml of MeOH and the mixture was allowed to crystallize during 12 h. The mixture was filtered and the filtrate was retained for further examination. The solid (18.3 g) was crystallized from 150 ml of MeOH. (*S*)-7 hydrogen (+)-*p*-toluenesulfonylglutamate (14.0 g) was obtained. This was stirred with a mixture of 30 ml of 2 N NaOH and 100 ml of Et_2O. The Et_2O extract was dried and the Et_2O evaporated to give (*S*)-7 (7.6 g, 84%) and then (*S*)-7 HCl.

(*R*)-4-Benzyl-2-(*p*-toluenesulfonyloxymethyl)tetrahydro-1,4-oxazine [(*R*)-7]. (**a**) The filtrate retained above was concentrated and a further 1.5 g of (*S*)-7 salt was removed. The residual (*R*)-7 was isolated from the mother liquors as the free base as described above. It was converted to the hydrochloride and recrystallized from acetone to give optically pure (*R*)-7 HCl (5.0 g, 50%), from which (*R*)-7 free base was obtained.

(**b**) In another experiment 10.0 g (0.0293 mol) of crude (*R*)-7 isolated from the mother liquors was dissolved in 30 ml of EtOH and mixed with a solution of 10.5 g (0.0293 mol) of (+)-*O,O*-dibenzoyltartaric acid in 20 ml of EtOH. After 12 h the mixture was filtered and the residual solid (18.3 g) was crystallized from 100 ml of EtOH to give (*R*)-7 hydrogen (+)-*O,O*-dibenzoyltartrate (17.0 g). This was converted via the free base (8.4 g, 93%) to (*R*)-7 HCl.

(*S*)-2-(2-Ethoxyphenoxymethyl)tetrahydro-1,4-oxazine [(*S*)-1] from (*S*)-4-Benzyl-2-(*p*-toluenesulfonyloxymethyl)tetrahydro-1,4-oxazine [(*S*)-7]. A mixture of 0.3 g (0.0125 mol) of NaH, 0.7 g (0.005 mol) of 2-ethoxyphenol, 2.0 g (0.0055 mol) of (*S*)-7, and 150 ml of DMF was heated at 100° for 18 h. The mixture was shaken with 300 ml of H_2O and 200 ml of EtOAc. The EtOAc extract was washed with H_2O and dried, and then the EtOAc was evaporated to give (*S*)-**8** (0.9 g, 53%) as an oil. It was converted to (*S*)-**8** HCl. A mixture of 0.9 g of (*S*)-**8** HCl, 0.5 g of 5% Pd/C, and 150 ml of EtOH was shaken in H_2 at room temperature and atmospheric pressure until absorption of H_2 ceased. The mixture was filtered and the solvent evaporated to give (*S*)-1 HCl (0.5 g, 73%), mp and mmp 166–167° (from EtOH).

Acknowledgment. We thank Dr. D. T. Greenwood and his colleagues for providing the biological results.

References and Notes

(1) Vivalan, trademark, the property of I.C.I.
(2) K. B. Mallion, A. H. Todd, R. W. Turner, J. G. Bainbridge, D. T. Greenwood, J. Madinaveitia, A. R. Somerville, and B. A. Whittle, *Nature (London)*, **238**, 157 (1972).
(3) D. T. Greenwood, K. B. Mallion, A. H. Todd, and R. W. Turner, *J. Med. Chem.*, **18**, 573 (1975).
(4) K. B. Mallion, R. W. Turner, and A. H. Todd, U. K. Patent 1 138 405 (1969).
(5) P. F. C. Bayliss, A. R. Dewsbury, J. F. Donald, J. W. Harcup, M. Mayer, R. Million, A. L. Molla, J. E. Murphy, B. Plant, and E. Shaoul, *J. Int. Med. Res.*, **2**, 260 (1974).
(6) I. K. Tsegos and M. Y. Ekdawi, *Curr. Med. Res. Opin.*, **2**, 455 (1974).
(7) P. Pichot, J. Guelfi, and J. F. Dreyfus, *J. Int. Med. Res.*, **3** (Suppl. 3), 80 (1975).
(8) A. Stoll and A. Hofmann, *Helv. Chim. Acta*, **26**, 922 (1943).
(9) R. Howe, T. Leigh, B. S. Rao, and A. H. Todd, German Patent 24 46 046 (1975); U.K. Patent 1 427 097 (1976).
(10) M. Dukes and L. H. Smith, *J. Med. Chem.*, 14, 326 (1971).