SOME *N*-SUBSTITUTED DERIVATIVES OF-1,2,3,6-TETRAHYDRO-4-PHENYLPYRIDINES

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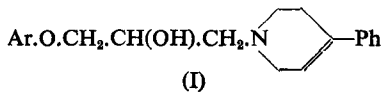
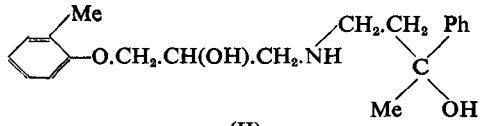
The relationship between structure and hypotensive activity in the title compounds has been investigated.

FOLLOWING the discovery by Beasley, Petrow and Stephenson (1958), that certain 3-aryloxy-1-(1,2,3,6-tetrahydropyrid-1-yl)propan-2-ols possessed appreciable analgesic activity, the preparation of some related derivatives (I) of 1,2,3,6-tetrahydro-4-phenylpyridine (Schmidle and Mansfield, 1956) for pharmacological study was undertaken.



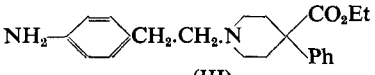
(I)

Four such compounds (I; where Ar = *o*-tolyl, *o*-allylphenyl, *p*-acetamidophenyl and *p*-aminophenyl) and additionally, one related "open chain" analogue (II) derived from 4-amino-2-phenylbutan-2-ol (Mansfield and Schmidle, 1956) were prepared, but none of the compounds possessed analgesic activity.



(II)

Next, following the report of Weijlard and others (1956) and Orahovats, Lehman and Chapin (1957) on the analgesic activity of ethyl 1-(4-aminophenethyl)-4-phenylisonipecotate (III), some formally related 1-aryloxyalkyl-1,2,3,6-tetrahydro-4-phenylpyridines (IV) were prepared. Though these, too, were found to be devoid of analgesic potency, some of the first compounds prepared for routine screening were found to have anti-adrenaline and hypotensive properties when given intravenously to cats.



(III)

a	*b*	*c*	*d*	*e*
R.	O.	$CH_2.CH_2.$	N	Ph

(IV)

In view of this somewhat unexpected result it seemed worthwhile to attempt to delineate the structural requirements for hypotensive potency. To this end a series of compounds was prepared in which the structural features marked (*a*) . . . (*e*) in formula (IV) were varied in turn systematically. Their biological study led to the following conclusions on the relationship between structure and activity:

(*a*) The aryl group R is not absolutely essential for activity, as compounds in which R = H or a lower alkyl group, are still potent. When R is a substituted aryl group however, the position of the substituent in the aromatic nucleus has a definite effect upon potency. Thus, for example, in the tolyl derivatives listed in the Table, *o*- > *m*- > *p*- in hypotensive properties.

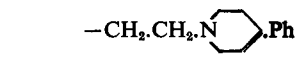
(*b*) The ether linkage in (IV) is not necessary for activity as phenethyl derivatives of 1,2,3,6-tetrahydro-4-phenylpyridine were invariably as active as the corresponding aryloxyalkyl compounds.

(*c*) Limited variation in the length of the methylene chain had but little effect upon potency. Thus, the ethylene compound was only slightly more active than the corresponding tri- or tetra-methylene derivatives.

(*d*) The double bond in the tetrahydropyridine nucleus was not essential for hypotensive activity. The corresponding piperidine derivatives were found to be potent hypotensive agents.

(*e*) The 4-phenyl group represents an essential structural feature. Its removal leads to almost complete loss of activity. Replacement of the 1,2,3,6-tetrahydro-4-phenylpyridine residue (*d*, *e*, IV) by open-chain structures derived from allylethylamine or cinnamylethylamine likewise leads to loss of potency as does substitution of 1,2,3,4-tetrahydroisoquinoline for 1,2,3,6-tetrahydro-4-phenylpyridine.

Hypotensive potency is thus retained by structures differing significantly from (IV), providing such structures involve the unit:



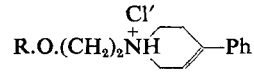
EXPERIMENTAL

1,2,3,6-*Tetrahydro*-1-(2-*hydroxy*-3-o-*tolyloxypropyl*)-4-*phenylpyridine*. A mixture of 1,2-epoxy-3-*o*-tolyloxypropane (5·5 g.) and 1,2,3,6-tetrahydro-4-phenylpyridine (5·8 g.) in benzene (5 ml.) was heated under reflux for 2 hr. and was then diluted with light petroleum (b.p. 40–60°). The *product* (8 g.) which separated on cooling had m.p. 84–86° after crystallisation from benzene-light petroleum (b.p. 60–80°). Found: C, 77·6; H, 7·8; N, 4·6. $C_{21}H_{25}NO_2$ requires C, 78·0; H, 7·8; N, 4·3 per cent. The *hydrochloride* had m.p. 149–151° after crystallisation from ethyl acetate. Found: Cl, 10·2; N, 4·3. $C_{21}H_{26}ClNO_2$ requires Cl, 9·9; N, 3·9 per cent.

1-(3-o-*Allylphenoxy*-2-*hydroxypropyl*)-1,2,3,6-*tetrahydro*-4-*phenylpyridine* prepared by reaction of 3-*o*-allylphenoxy-1,2-epoxypropane with 1,2,3,6-tetrahydro-4-phenylpyridine in benzene solution was obtained

in 67 per cent yield, as a straw coloured oil, b.p. 231° at 0·3 mm. Found: N, 3·7. $C_{23}H_{27}NO_2$ requires N, 4·0 per cent. The *hydrochloride* had m.p. 142° after crystallisation from ethyl acetate-methanol. Found: C, 71·7; H, 7·2; Cl, 9·2; N, 3·8. $C_{23}H_{28}ClNO_2$ requires C, 71·4; H, 7·3; Cl, 9·2; N, 3·6 per cent.

TABLE I



R	m.p. °C	Formula	Found				Required			
			C	H	Cl	N	C	H	Cl	N
H	177–179	$C_{15}H_{18}ClNO$	65·7	7·6	15·0	5·6	65·1	7·6	14·8	5·8
Me	186–188	$C_{14}H_{20}ClNO$	66·1	8·0	—	5·5	66·2	7·9	—	5·5
Et	154–156	$C_{15}H_{22}ClNO$	67·4	8·4	12·9	5·2	67·3	8·3	13·2	5·2
Ph	195–198	$C_{19}H_{22}ClNO$	72·2	7·0	10·9	4·7	72·3	7·0	11·2	4·4
o-Tolyl ..	199–200	$C_{20}H_{24}ClNO$	73·2	6·9	10·8	4·1	72·8	7·2	10·7	4·2
m-Tolyl ..	172–174	$C_{20}H_{24}ClNO$	72·3	7·2	—	4·3	72·8	7·2	—	4·2
p-Tolyl ..	174	$C_{20}H_{24}ClNO$	—	—	11·2	3·9	—	—	10·7	4·2
o-MeO.C_6H_4 ..	174–176	$C_{20}H_{24}ClNO_2$	69·0	6·8	10·6	4·3	69·5	7·0	10·3	4·1
m-Meo.C_6H_4 ..	168–170	$C_{20}H_{24}ClNO_2$	69·7	7·0	10·1	3·9	69·5	7·0	10·3	4·1
p-MeO.C_6H_4 ..	174–177	$C_{20}H_{24}ClNO_2$	69·4	6·8	10·3	4·0	69·5	7·0	10·3	4·1
o-Cl.C_6H_4 ..	173–175	$C_{19}H_{21}Cl_2NO$	65·3	5·9	19·8	3·7	65·1	6·0	20·2	4·0
p-Cl.C_6H_4 ..	193–195	$C_{19}H_{21}Cl_2NO$	65·3	5·9	20·6	3·8	65·1	6·0	20·2	4·0
p-Br.C_6H_4 ..	180–182	$C_{19}H_{21}BrClNO$	58·1	5·3	29·8*	3·4	57·8	5·4	29·2*	3·5
p-AcNH.C_6H_4 ..	232–235	$C_{21}H_{25}ClN_2O_2$	—	—	—	7·5	—	—	—	7·5
p-C_6H_5.C_6H_4 ..	194–198	$C_{25}H_{26}ClNO$	76·6	6·7	9·4	3·5	76·6	6·7	9·0	3·6

* Total Halogen

1-(3-*Acetamidophenoxy*-2-*hydroxypropyl*)-1,2,3,6-*tetrahydro*-4-*phenylpyridine* had m.p. 164–166° after crystallisation from ethanol. Found: C, 71·9; H, 6·7; N, 7·8. $C_{22}H_{26}N_2O_3$ requires C, 72·1; H, 7·2; N, 7·7 per cent. The *hydrochloride* had m.p. 239–240° after crystallisation from methanol-ethyl acetate. Found: C, 65·7; H, 6·6; Cl, 9·1; N, 7·0. $C_{22}H_{27}ClN_2O_3$ requires C, 65·6; H, 6·8; Cl, 8·8; N, 7·0 per cent.

1-(3-p-*Aminophenoxy*-2-*hydroxypropyl*)-1,2,3,6-*tetrahydro*-4-*phenylpyridine dihydrochloride.* The foregoing *p*-acetamido-compound (11·0 g.) was suspended in 6N hydrochloric acid (50 ml.) and the mixture heated under reflux for 2 hr. The resultant solution was evaporated to dryness at reduced pressure and the residual solid crystallised from methanol-ether to yield the *product* (10·2 g.) m.p. 268–270° (decomp). Found: C, 60·0; H, 6·9; Cl, 18·1; N, 6·9. $C_{20}H_{26}Cl_2N_2O_2$ requires C, 60·5; H, 6·6; Cl, 17·9; N, 7·0 per cent.

(3-*Hydroxy*-3-*phenylbutyl*)(2-*hydroxy*-3-o-*tolyloxypropyl*)*amine.* A mixture of 1,2-epoxy-3-*o*-tolyloxypropane (4·9 g.) and 4-amino-2-phenylbutan-2-ol (5·4 g.) was heated under reflux for 6 hr. when excess of solvent was boiled off. The *product* (5·5 g.) was isolated as an oil, b.p. 220–222° at 0·3 mm. Found: C, 72·9; H, 9·8; N, 4·0. $C_{20}H_{27}NO_3$ requires C, 72·9; H, 9·6; N, 4·3 per cent.

1,2,3,6-*Tetrahydro*-4-*phenyl*-1-(2-o-*tolyloxyethyl*)*pyridine.* A mixture of 2-*o*-tolyloxyethyl bromide (21·5 g.) and 1,2,3,6-tetrahydro-4-phenylpyridine (17·5 g.) in methanol (50 ml.) was treated with a solution of potassium hydroxide (5·6 g.) in methanol (30 ml.) and the mixture heated under reflux for 2 hr., when excess of methanol was boiled off.

The residue was diluted with water and the base isolated with ethyl acetate. It (17·5 g.) had b.p. 197–198° at 0·3 mm. Found: N, 5·0. $C_{20}H_{23}NO$ requires N, 4·8 per cent. The *hydrochloride* had m.p. 199–200° after crystallisation from ethanol-ethyl acetate.

1-(2-*Ethoxyethyl*)-4-*phenylpiperidine*. A solution of 2-bromoethyl ethyl ether (7·6 g.) and 4-phenylpiperidine (8·0 g.) in ethanol (60 ml.) containing anhydrous sodium carbonate (2·7 g.) was heated under reflux for 3 hr. The mixture was cooled, diluted with water and the *base* isolated with chloroform. It (9·3 g.) had b.p. 98–102° at 0·05 mm. (n_D^{21} = 1·5154). Found: C, 77·4; H, 9·61; N, 6·2. $C_{15}H_{23}NO$ requires C, 77·2; H, 9·9; N, 6·0 per cent. The *hydrochloride* was very hygroscopic and was not purified.

1-(2-m-*Methoxyphenoxyethyl*)-4-*phenylpiperidine*. A mixture of 2-*m*-methoxyphenoxyethyl bromide (4·8 g.), 4-phenylpiperidine (4·1 g.) and anhydrous sodium carbonate (1·4 g.) in ethanol (80 ml.) was heated under reflux for 9 hr. The *base* was isolated with chloroform as described in the preceding example and converted directly to the *hydrochloride* in ethanol-ether. It (5·2 g.) had m.p. 179–181° after crystallisation from the same solvent mixture. Found: C, 68·8; H, 7·6; N, 4·3. $C_{20}H_{26}ClNO_2$ requires C, 69·1; H, 7·5; N, 4·0 per cent.

1,2,3,6-*Tetrahydro*-4-*phenyl*-1-(2-o-*tolylethyl*)*pyridine*. A mixture of 2-*o*-tolylethyl bromide (10·0 g.), 1,2,3,6-tetrahydro-4-phenylpyridine (8·0 g.) and sodium carbonate (2·7 g.) in ethanol (80 ml.) was heated under reflux for 8 hr. The *product* (8·2 g.) had b.p. 160–166° at 0·2 mm. (n_D^{22} = 1·5900). Found: C, 86·8; H, 8·2; N, 5·0. $C_{20}H_{23}N$ requires C, 86·6; H, 8·4; N, 5·1 per cent. The *hydrochloride* had m.p. 224–228° after crystallisation from anhydrous ethanol. Found: C, 76·7; H, 7·5; Cl, 11·5; N, 4·5. $C_{20}H_{24}ClN$ requires C, 76·5; H, 7·7; Cl, 11·3; N, 4·5 per cent.

4-*Phenyl*-1-(2-o-*tolylethyl*)*piperidine* was obtained (*a*) by reaction of 2-*o*-tolylethyl bromide with 4-phenylpiperidine in ethanol containing anhydrous sodium carbonate. It had b.p. 150–154° at 0·1 mm. (n_D^{22} = 1·5639). Found: C, 86·2; H, 9·0; N, 5·2. $C_{20}H_{25}N$ requires C, 86·0; H, 9·0; N. 5·0 per cent.

(*b*) A solution of 1,2,3,6-tetrahydro-4-phenyl-1-(2-*o*-tolylethyl)pyridine (8·0 g.) in ethanol (50 ml.) was hydrogenated at room temperature in the presence of a 5 per cent palladium-barium sulphate catalyst (1·0 g.). After filtration and concentration the oil was distilled at reduced pressure to yield the *product* (b.p. 150–154° at 0·1 mm.). The *hydrochloride* separated from ethanol in nodules m.p. 253–256°. Found: C, 76·2; H, 8·0; Cl, 11·0; N, 4·6. $C_{20}H_{26}ClN$ requires C, 76·1; H, 8·3; Cl, 11·2; N, 4·4 per cent.

1,2,3,6-*Tetrahydro*-4-*phenyl*-1-(3-o-*tolyloxypropyl*)*pyridine*, was prepared in 55 per cent yield by reaction of 3-*o*-tolyloxypropyl bromide and 1,2,3,6-tetrahydro-4-phenylpyridine as described earlier. The crude base was converted directly into the *hydrochloride* which had m.p. 183–184° after crystallisation from ethanol. Found: C, 73·0; H, 7·5; N, 4·2. $C_{21}H_{26}ClNO$ requires C, 73·3; H, 7·6; N, 4·1 per cent.

1,2,3,6-*Tetrahydro*-4-*phenyl*-1-(4-o-*tolyloxybutyl*)*pyridine hydrochloride* had m.p. 117–120° (from ethanol-ether). Found: Cl, 10·2; N, 4·2. $C_{22}H_{28}ClNO$ requires Cl, 9·9; N, 3·9 per cent.

1-(3-*Ethoxypropyl*)-1,2,3,6-*tetrahydro*-4-*phenylpyridine* had b.p. 48–53° at 0·1 mm. Found: C, 77·9; H, 9·3; N, 5·7. $C_{16}H_{23}NO$ requires C, 78·3; H, 9·4; N, 5·7 per cent.

1,2,3,6-*Tetrahydro*-1-(3-m-*methoxyphenoxypropyl*)-4-*phenylpyridine hydrochloride* had m.p. 163–165° (from ethanol-ether). Found: C, 70·3; H, 7·2; Cl, 10·2; N, 4·0. $C_{21}H_{26}ClNO_2$ requires C, 70·1; H, 7·3; Cl, 9·9; N, 3·9 per cent.

1-(2-*Ethoxyethyl*)-1,2,3,6-*tetrahydropyridine*, had b.p. 74–75° at 7 mm. Found: C, 69·6; H, 11·0; N, 9·4. $C_9H_{17}NO$ requires C, 69·7; H, 11·0; N, 9·0 per cent.

1,2,3,6-*Tetrahydro*-1-(2-o-*tolyloxyethyl*)*pyridine hydrochloride* had m.p. 145–148° (from ethanol-ether). Found: C, 66·0; H, 7·8; Cl, 14·1; N, 5·6. $C_{14}H_{20}ClNO$ requires C, 66·2; H, 7·9; Cl, 14·0; N, 5·5 per cent.

1,2,3,6-*Tetrahydro*-1-(2-m-*methoxyphenoxyethyl*)*pyridine hydrochloride* had m.p. 136–138° (from ethanol-ether). Found: C, 62·1; H, 7·5; Cl, 13·3; N, 5·4. $C_{14}H_{20}ClNO_2$ requires C, 62·3; H, 7·5; Cl, 13·1; N, 5·2 per cent.

1,2,3,6-*Tetrahydro*-1-(2-*tolylethyl*)*pyridine hydrochloride* had m.p. 224–226° (from ethanol-ether). Found: C, 70·8; H, 8·3; Cl, 15·0; N, 6·0. $C_{14}H_{20}ClN$ requires C, 70·7; H, 8·5; Cl, 14·9; N, 5·9 per cent.

Allylethyl(2-o-*tolyloxyethyl*)*amine* was prepared by reaction of 2-*o*-tolyloxyethylamine with allyl bromide in ethanol in the presence of anhydrous sodium carbonate. It had b.p. 142–143° at 10 mm. Found: C, 76·5; H, 9·6; N, 6·5. $C_{14}H_{21}NO$ requires C, 76·6; H, 9·6; N, 6·4 per cent.

Cinnamylethyl(2-o-*tolyloxyethyl*)*amine*. (*a*) Reaction of cinnamyl chloride with 2-*o*-tolyloxyethylamine yielded the *product* as an oil, b.p. 150–152° at 0·05 mm., ($n_D^{19} = 1{\cdot}5671$).

(*b*) Reaction of cinnamylethylamine (b.p. 121–124° at 10 mm. Found: C, 81·6; H, 9·7; N, 9·1. $C_{11}H_{15}N$ requires C, 81·9; H, 9·4; N, 8·7 per cent), with 2-o-tolyloxyethyl bromide in ethanol in the presence of anhydrous sodium carbonate yielded the same *product* described in (*a*). Found: C, 81·7; H, 8·7; N, 4·7. $C_{20}H_{25}NO$ requires C, 81·3; H, 8·5; N, 4·7 per cent.

Dimethyl(2-o-*tolyloxyethyl*)*amine hydrochloride*, had m.p. 175–177° (from ethanol-ether). Found: C, 61·4; H, 8·4; N, 6·7. $C_{11}H_{18}ClNO$ requires C, 61·2; H, 8·4; N, 6·5 per cent.

Diethyl(2-o-*tolyloxyethyl*)*amine hydrochloride*, had m.p. 139–141° (from ethanol-ether). Found: C, 63·6; H, 9·1; Cl, 14·9; N, 5·9. $C_{13}H_{22}ClNO$ requires C, 64·0; H, 9·1; Cl, 14·5; N, 5·7 per cent.

1,2,3,4-*Tetrahydro*-2-(2-m-*methoxyphenoxyethyl*)*isoquinoline hydrochloride*. A mixture of *m*-methoxyphenoxyethyl bromide (9·2 g.), 1,2,3,4-tetrahydroisoquinoline (5·3 g.) and anhydrous sodium carbonate (2·2 g.) in ethanol (100 ml.) was heated under reflux for 8 hr. when excess of ethanol was boiled off. The residue was diluted with water

and the *base* isolated with chloroform. Distillation of the chloroformic solution furnished the crude base (10·4 g.) which was converted to the *hydrochloride* (8·5 g.) in ethanol-ether. Crystallisation from the same solvent mixture yielded the *product*, m.p. 150–152°. Found: C, 67·3; H, 6·9; Cl, 11·5; N, 4·6. $C_{18}H_{22}ClNO_2$ requires C, 67·6; H, 6·9; Cl, 11·1; N, 4·4 per cent.

Tetrahydro-6-methyl-3-(2-phenoxyethyl)-6-phenyl-1,3-oxazine. (*a*) A mixture of 2-phenoxyethyl bromide (20·1 g.) and tetrahydro-6-methyl-6-phenyl-1,3-oxazine (17·7 g.) in ethanol (130 ml.) containing sodium carbonate (5·4 g.) was heated under reflux for 10 hr. After concentration to remove most of the ethanol, the mixture was diluted with water and the base isolated with chloroform. It (13·7 g.) had b.p. 165–170° at 0·05 mm. Found: C, 77·0; H, 7·8; N, 4·6. $C_{19}H_{23}NO_2$ requires C, 76·7; H, 7·8; N, 4·7 per cent.

(*b*) A mixture of 2-phenoxyethylamine hydrochloride (17·4 g.), 40 per cent formaldehyde solution (20 ml.) and α-methylstyrene (11·8 g.) was warmed with stirring. An exothermic reaction occurred at about 60° and this was controlled by cooling. Finally the mixture was heated at about 80° for 5 hr. and was then cooled and diluted with water. It was basified with 50 per cent sodium hydroxide solution and the *base* isolated with benzene. It (3·7 g.) had b.p. 175–185° at 0·4 mm. The *hydrochloride* had m.p. 220–222° (from ethanol). Found: N, 4·2. $C_{19}H_{24}ClNO_2$ requires N, 4·2 per cent. It (3 g.) was recovered unchanged after heating under reflux with concentrated hydrochloric acid (10 ml.) for 4 hr.

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