1-Phenyl-6,7-disubstituted-2-(3-disubstituted-aminopropyl)-1,2,3,4-tetrahydroisoquinolines as Possible Antitubercular Agents

P. Kumar, K. N. Dhawan, K. Kishor, K. P. Bhargava(1)

Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow-226003, India

and

R. K. Satsangi

Department of Chemistry, Lucknow University, Lucknow-226007, India

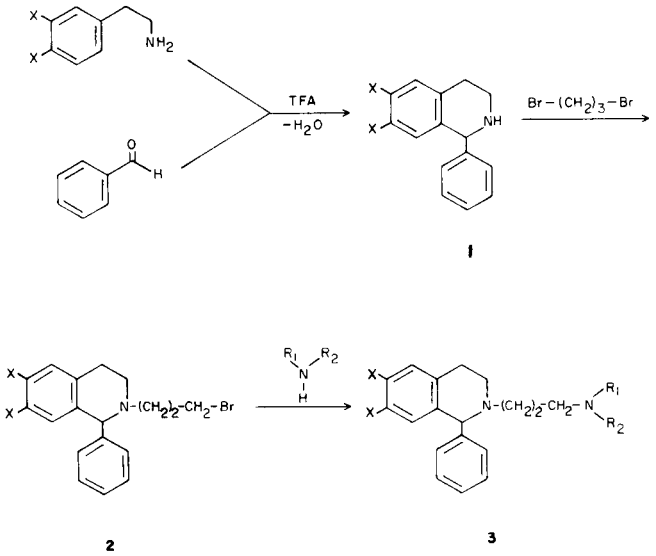
Received August 18, 1980

The condensation of 3,4-disubstituted phenylethylamine and benzaldehyde furnished 1-phenyl-6,7-disubstituted-1,2,3,4-tetrahydroisoquinolines **1** which on reaction with 1,3-dibromopropane gave 1-phenyl-6,7-disubstituted-2-(3-bromopropyl)-1,2,3,4-tetrahydroisoquinolines **2**. The reaction of **2** with different secondary amines resulted in the synthesis of **3**. The compounds **3** were screened for their *in vitro* antitubercular activity against *Mycobacterium smegmatis*, and some of them have been found to be total inhibitors of *M. Smegmatis*.

J. Heterocyclic Chem., **19**, 677 (1982).

Tetrandrin, an alkaloid, has been found to be a strong tuberculostatic agent (2) 6,7-Disubstituted-2-methyl-1,2,3,4-tetrahydroisoquinoline has been found to be an antitubercular agent (3). Many compounds containing substituted aminopropyl group have also been found to be potential tuberculostats (4-6). Therefore, it was thought worthwhile to alkylate 1-phenyl-6,7-disubstituted-1,2,3,4-tetrahydroisoquinoline **1** at it's position-2 by substituted amino-*n*-propyl group to prepare the compounds **3** *via* compounds **2** (Scheme I).

Scheme I



1-Phenyl-1,2,3,4-tetrahydroisoquinoline **1a** and 1-phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline **1b** were synthesised by dehydrative cyclization between benzaldehyde and phenyl ethyl amine and 3,4-dimethoxyphenyl ethylamine, respectively.

Trifluoroacetic acid was used as a cyclizing agent. The compounds were identified by their correct elemental analysis and by their ir spectra. The important peaks in the ir are 3450 (sec. N-H stretch), 2900 (alkyl C-H stretch), 1580 (sec. N-H bending) and 1460 (alkyl C-H bending).

Compounds **1** were treated with 1,3-dibromopropane in an equimolar ratio, so as to allow only one bromo group to react with the secondary amino group of **1**. Thus, the respective 1-phenyl-2-(3-bromopropyl)-1,2,3,4-tetrahydroisoquinolines **2** were synthesised and were characterised by their elemental analysis and ir spectra. The absence of the peaks at 1680 and 3450 cm^{-1} in the ir confirmed the absence of the N-H group proton of **1**.

The reaction of **2** with different secondary amines led to the formation of 1-phenyl-6,7-disubstituted-2-(3-disubstitutedaminopropyl)-1,2,3,4-tetrahydroisoquinolines **3**. The aforesaid **3** were identified by their correct elemental analysis, and ir and nmr spectra. The compounds **3** gave negative test for bromine.

The preliminary and final compounds **2** and **3**, respectively, have been screened for their *in vitro* antitubercular activity (7) against *Mycobacterium smegmatis*. The results of the screening are given in Table 1.

Three standard antitubercular drugs *p*-aminosalicylic acid (PAS), isonicotinic acid hydrazide (INH) and streptomycin were also screened out against *M. smegmatis* simultaneously, so as to make a comparison between the potency of the compounds synthesised and the standard drugs. The bacteria proved to be resistant against PAS and INH, while streptomycin inhibited their growth at a concentration of 16 μg/ml of the medium (minimum inhibitory concentration = 16 μg/ml). Four of the final compounds **3a, 3b, 3c** and **3d** were found to check the growth of *M. smegmatis in vitro* at the concentration of 20 μg/ml of the culture medium. Two other compounds **3e** and **3g** could reduce the vigour of growth of mycobacteria up to the extent of about 50-100 colonies and thus exhibited a tuberculostatic trend. Compounds **2a, 2b** and **3f** were

Table 1

1-Phenyl-6,7-disubstituted-2-(3-disubstitutedaminopropyl-1,2,3,4-tetrahydroisoquinolines (**3**) and their *In Vitro* Antitubercular Screening

Compound No	$-N<^{R_1}_{R_2}$	M.p.	Yield %	Elemental Analysis % Found / Calcd.			pKa	Intensity of Growth of *Mycobacterium smegmatis* at the Concentration of (a)			
	X = H			C	H	N		10μg/ml	20μg/ml	40μg/ml	Blank
3a	2-benzothiazolylamino	118	75	75.3 75.2	6.4 6.5	10.5 10.5	4.0	+ +	−	−	
3b	3,4-dimethoxyanilino	120	70	77.5 77.6	7.5 7.5	7.1 7.0	3.8	+ +	−	−	C_1 + + +
	X = OCH_3										
3c	N,N-dicyclohexylamino	236	60	78.3 78.4	9.4 9.4	5.6 5.7	3.8	+ +	−	−	
3d	2-ethylanilino	232	68	78.2 78.1	8.0 7.9	6.6 6.5	3.9	+ +	−	−	C_2 + + +
3e	pyrrolidino	218	62	75.7 75.8	8.5 8.4	7.4 7.4	5.4	+ +	+	+	
3f	morpholino	175	65	72.8 72.7	8.1 8.1	7.1 7.1	6.5	+ + +	+ + +	+ + +	
3g	4-(3-chlorophenyl)piperazino	126	65	71.4 71.3	7.2 7.1	8.5 8.3	4.4	+ +	+	+	

(a) Abbreviations: − = Complete inhibition of *M. smegmatis;* + = About 50-100 colonies of mycobacteria; + + = About 100-200 colonies of mycobacteria; + + + = Confluent growth of *M. smegmatis.*

found to be inactive against *M. smegmatis.*

Though no definite structure-activity relationship could be established in the compounds **2** and **3**, it is obvious that the exocyclic amino group plays an important role towards the antitubercular activity of the compounds. Compounds **2a** and **2b** are completely inactive (exocyclic amino group is absent), this observation is further strengthened by comparing the antitubercular activity of compounds **3a-d** with those of **3e-g**, where the cyclic amino group at side chain destroys the activity of compounds. It is also evident that the activity is also related to the p*K*a of the compounds. The active compounds have a p*K*a between 3.8-4.0 (**3a-d**).

EXPERIMENTAL

The melting points were taken in open capillaries using an A. R. sulphuric acid bath. The ir spectra were taken on an ir grating Perkin-Elmer spectrophotometer (potassium bromide disks). The nmr spectra were taken in deuteriochloroform at 90 MHz.

1-Phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) and 1-Phenyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**1b**).

Benzaldehyde (0.005 mole) and the appropriate phenylethylamine (0.050 mole) were taken in benzene (100 ml) and refluxed through a Dean-stark trap for 1 hour until no more water was collected. The solution was concentrated under vacuum. Thereafter, trifluoroacetic acid (40 ml) was added to the solution, and the solution was again refluxed for 5 hours. Following neutrallization with solid sodium carbonate, the solution was then extracted with ether (3-4 times). The etheral layer was dried over anhydrous sodium sulphate and acidified with a little hydrochloric acid. A thick precipitate was formed which was recrystallized from ethanol-hydrochloric acid, giving **1a**, yield 68%, m.p. 212°.

Anal. Calcd. for $C_{15}H_{15}N$: C, 86.1; H, 7.2; N, 6.7. Found: C, 86.2; H, 7.1; N, 6.6.

Compound **1b** was obtained in 86% yield, m.p. 256-258°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1; N, 5.20. Found: C, 75.9; H, 7.0; N, 5.1

1-Phenyl-2-(3-bromopropyl)-1,2,3,4-tetrahydroisoquinoline (**2a**) and 1-Phenyl 2-(3-bromopropyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2b**).

The appropriate compound **1** (0.03 mole) and 1,3-dibromopropane (0.03 mole) were refluxed in absolute ethanol (20 ml) for 3 hours in the presence of dry sodium carbonate (0.03 mole). The contents were filtered hot and the excess of alcohol was distilled. The solid thus separated, was washed well with cold water, filtered and recrystallized from methanol/ether giving **2a**, yield 67%, m.p. 127°.

Anal. Calcd. for $C_{18}H_{20}BrN$: C, 65.4; H, 6.1; N, 4.2. Found: C, 65.5; H, 6.1; N, 4.1.

Compound **2b** was obtained in 60% yield, m.p. 82°.

Anal. Calcd. for $C_{20}H_{24}BrNO_2$: C, 59.4; H, 5.9; N, 6.9. Found: C, 59.5; H, 5.9; N, 6.8.

1-Phenyl-6,7-dimethoxy-2-(3-dicyclohexylaminopropyl)-1,2,3,4-tetrahydroisoquinoline (**3c**).

Compound **2b** (0.005 mole) and *N,N*-dicyclohexylamine (0.005 mole) were refluxed in dry benzene (20 ml) in the presence of triethylamine (0.01 mole) for about 2.5 hours. The excess of solvent was distilled and the contents were cooled to give the crystallized crude product, which was washed well with cold water and recrystallized from benzene/petroleum ether, yield 60%, m.p. 236°, p*K*a 3.8; ir 3050, 2900, 2800, 1500, 1450, 1370, 1340, 1320, 880 and 750 cm^{-1}; nmr: 1.20 (m), 1.9 (s) 2.1 (t), 2.4 (t), 2.50 (s), 3.72 (t), 3.72 (s), 7.12 (s), 7.75 (s). The other compounds **3** were also synthesised in a similar manner (Table 1).

Anal. Calcd. for $C_{32}H_{46}N_2O_2$: C, 78.4; H, 9.4; N, 5.7. Found: C, 58.3; H, 9.4; N, 5.6.

Acknowledgement.

We are thankful to Dr. K. Shanker, Dr. Satyavrat, for their continous help and to Dr. S. Ahmad, Senior Research Assistant for the assistance in compilation of data. One of the authors (P.K.) is grateful to I.C.M.R., New Delhi for the award of fellowship to him.

REFERENCES AND NOTES

(1) For correspondence.

(2) S. A. Vichkanova, L. V. Makarova and L. F. Soloveva, *Farmako Toksikol.*, **36**, 74 (1973); *Chem. Abstr.*, **78**, 106079n (1973).

(3) R. Seidelmann, R. Schmiecheu, R. Horowski, W. Kehr, D. Patenschat and G. Paschelke; German Patent 2154,162, *Chem. Abstr.*, **79**, 189304 (1973).

(4) W. D. Vigetrus and S. Manius, German Patent 2,246,279, *Chem. Abstr.*, **81**, 636809 (1974).

(5) H. L. Yale, U. S. Patent Application 281,422; *Chem. Abstr.*, **80**, 83090c (1975).

(6) J. Molnan, I. Belade and I. Folder; *Zentralbl. Bacteriol. Parisitenkd., Infectionskr. Hyg. Abt. 1, Orig.*, **39**, 521 (1977); *Chem. Abstr.*, **88**, 115748j (1978).

(7) J. C. Gould, in "Medical Microbiology" R. Cruickshank, E.L.B.S. and C. Livingstone, Eds., 11th Ed., 1972, p. 903.