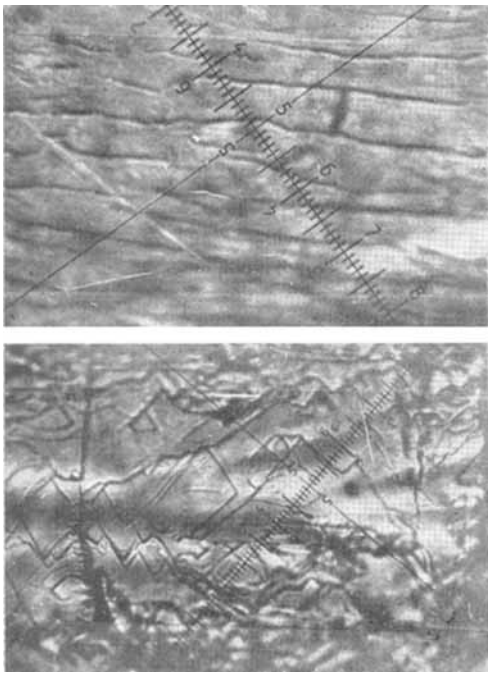

Figure 10—*Effect of FD&C Blue No. 1 on the dissolving face of sulfathiazole single crystal after 15 min. Key:* a, *in 0.1* N *HCl*, b, *in 0.1* N *HCl containing 50 mcg./ml. FD&C Blue No. 1. Magnification: 500×.*

limited to the systems that have been studied, and to the experimental conditions described. The significance of dissolution inhibition in powder systems in presence of a low concentration of the dye is not clear yet. The extension of this study to other powder systems and other water-soluble dyes will contribute to better understanding of the role of water-soluble colorants in drug formulations.

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ACKNOWLEDGMENTS AND ADDRESSES

Received June 5, 1969 from the *Faculty of Pharmacy, University of Montreal, Montreal, Canada 101*

Accepted for publication September 2, 1969.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Montreal meeting, May 1969.

This investigation was supported by the Medical Research Council of Canada.

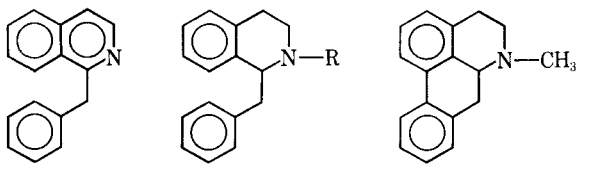
Phenylisoquinolines and Hydroisoquinolines

J. SAM, R. M. SHAFIK*, and K. APARAJITHAN

Abstract □ The synthesis of some derivatives of 5-, 6-, and 7-phenylisoquinoline, 3,4-dihydroisoquinoline, and 1,2,3,4-tetrahydroisoquinoline are described. Results of preliminary pharmacological tests are reported.

Keyphrases □ Phenylisoquinolines—synthesis □ Hydroisoquinolines—synthesis □ Pharmacological screening—phenylisoquinolines, hydroisoquinolines □ IR spectrophotometry—identity

Several alkaloids which incorporate the 1-benzylisoquinoline (I) or tetrahydroisoquinoline (II) moiety in their structures possess interesting biological properties (1, 2). The latter structural feature has been proposed (3) as a precursor in the biosynthesis of the aporphine alkaloids (III). Whereas, extensive investigations (4, 5) have been directed toward the synthesis of 1-benzylisoquinolines, little effort has been expended in studies of arylisoquinolines (VII) and the corresponding hydrogenated derivatives (VIII, X, and XI) (6). Consequently,



I II III

it was of interest to determine whether compounds such as VII and hydrogenated VII possess CNS properties similar to known aporphines (7) (bulbocapnine) and/or cardiovascular properties.

The synthetic approach followed is shown in Scheme I. The nitration of isoquinoline yielded 5-nitroisoquinoline (V) (8). The reduction of the latter compound to 5-aminoisoquinoline (VI) (9, 10) followed by diazotization and coupling with benzene, according to a procedure similar to that described by Cadogan (11) for the preparation of biphenyls, provided 5-phenylisoquinoline. Hydrogenation of VII*a* hydrochloride using plati-

Table I—Phenylisoquinolines and Hydroisoquinolines

No.	R	R′	Method	C_6H_5 Position	Yield, %	M p. °C. (Recrystn. Solvent)[a]	Molecular Formula	Anal., % Calcd.	Found
VII*a*	H	—	A	5	26	185–186(WAc)	$C_{21}H_{14}N_4O_7$[b,c]	C, 58.1 H, 3.3 N, 12.9	C, 57.6 H, 3.7 N, 13.5
VII*b*	H	—	A	5	—	237–239(W)	$C_{16}H_{14}NI$[d,e]	C, 55.4 H, 4.1 N, 4.0	C, 55.5 H, 4.2 N, 4.0
VII*c*	CH_3	—	E	7	60	233–235(WAc)	$C_{22}H_{16}N_4O_7$[c,f,g,h]	C, 58.9 H, 3.6 N, 12.5	C, 58.6 H, 4.0 N, 12.2
VIII*a*	H	H	B	5	98	290–292(W)	$C_{15}H_{16}NCl$[i,j]	C, 73.3 H, 6.6 N, 5.7	C, 73.8 H, 6.6 N, 5.4
VIII*b*	H	H	D	6	76	235–237(W)	$C_{15}H_{16}NCl$[i]	C, 73.3 H, 6.6 N, 5.7	C, 73.4 H, 6.5 N, —
VIII*c*	CH_3	H	D	6	70	231–233(ME)	$C_{16}H_{18}NCl$[i,k]	C, 74.0 H, 7.0 N, 5.4	C, 73.6 H, 7.1 N, 5.3
VIII*d*	H	H	D	7	51	249–251(ME)	$C_{15}H_{16}NCl$[i,l]	C, 73.3 H, 6.6 N, 5.7	C, 73.0 H, 6.9 N, 5.8
VIII*e*	CH_3	H	D	7	70	185(WAc)	$C_{22}H_{20}N_4O_7$[c,m,n]	C, 58.4 H, 4.7 N, 12.4	C, 58.5 H, 4.6 N, 12.8
X*a*	H	—	C	6	45	176–178(E)	$C_{21}H_{16}N_4O_7$[c]	C, 57.8 H, 3.7 N, 12.8	C, 58.8 H, 3.9 N, 13.0
X*b*	CH_3	—	C	6	77	254–256(E)	$C_{22}H_{18}N_4O_7$[c,o]	C, 58.7 H, 4.0 N, 12.4	C, 59.0 H, 4.4 N, 12.3
X*c*	H	—	C	7	40	190–192(E)	$C_{21}H_{16}N_4O_7$[c]	C, 57.8 H, 3.7 N, 12.8	C, 58.0 H, 3.9 N, 12.9
X*d*	CH_3	—	C	7	44	216–218(EW)	$C_{22}H_{18}N_4O_7$[c,p]	C, 58.7 H, 4.0 N, 12.4	C, 59.0 H, 4.0 N, 12.8
XI*a*	H	$CNHNH_2$	F	5	73	222–224(ME)	$C_{16}H_{15}N_3Cl$[i,q]	C, 66.8 H, 6.3 N, 14.6	C, 66.7 H, 6.3 N, 14.0
XI*b*	H	CH_3	G	5	80	228–230(W)	$C_{16}H_{18}NI$[r,s,t]	C, 54.7 H, 5.2 N, 4.0	C, 54.9 H, 5.2 N, 4.1
XI*c*	CH_3	CH_3	H	7	92	237–238(EW)	$C_{17}H_{20}NI$[s,u,v]	C, 55.9 H, 5.5 N, 3.8	C, 56.0 H, 5.4 N, 4.0
XI*d*	CH_3	CH_3	H	7	—	202–204(E)	$C_{18}H_{22}NI$[d,w]	C, 57.0 H, 5.9 N, 3.7	C, 56.8 H, 5.9 N, 3.9
XI*e*	CH_3	$C_{10}H_7ClNO$[x]	I	7	80	140–141(AW)	$C_{26}H_{23}N_2ClO$[i,y]	C, 75.3 H, 5.6 N, 6.8	C, 75.4 H, 5.6 N, 7.0

[a] WAc = water-acetic acid; W = water; ME = methanol-ether; E = ethanol; EW = ethanol-water; P = petroleum ether (30–60°). [b] Free base, b.p. 146–148° (0.6 mm.). [c] Picrate. [d] Methiodide. [e] Calcd. for I: 36.6; Found: 36.8. [f] Free base, b.p. 160° (0.2 mm.). [g] Hydrochloride, m.p. 261–263°(E). [h] Methiodide, m.p. 297–300°(W). [i] Hydrochloride. [j] Calcd. for Cl: 14.4; Found: 14.1. [k] Calcd. for Cl: 13.7; Found 13.9. [l] Calcd. for Cl: 14.4; Found: 14.5. [m] Free base, b.p. 164° (0.65 mm.). [n] Hydrochloride, m.p. 261–263°(E). [o] Hydrochloride, m.p. 263–264° dec.(ME). [p] Free base, m.p. 83–85°(P). [q] Calcd. for Cl: 12.3; Found: 12.6. [r] Free base, m.p. 73–74°(EW). [s] Hydriodide. [t] Calcd. for I: 36.1; Found: 36.0. [u] Free base, b.p. 137° (0.2 mm.). [v] Calcd. for I: 34.8; Found: 34.6. [w] Calcd. for I: 33.5; Found: 33.5. [x] 5-Chloro-8-hydroxy-7-quinolylmethyl. [y] Calcd. for Cl: 8.6; Found: 8.4.

num oxide catalyst yielded 5-phenyl-1,2,3,4-tetrahydroisoquinoline (VIII*a*) whereas VII*b* gave the 2-methyl derivative (XI*b*).

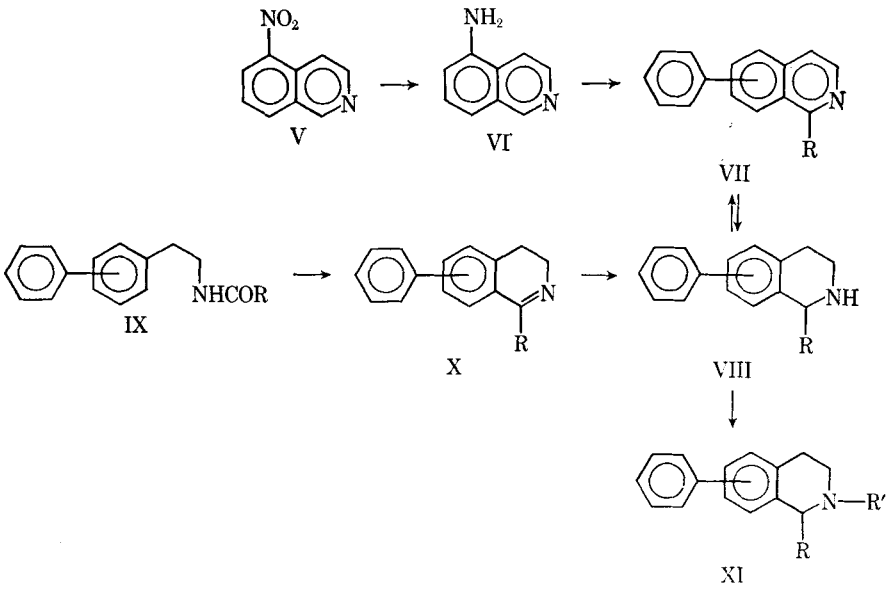
The 6-, and 7-phenyl-2,3-dihydroisoquinolines (X) were prepared *via* the Bischer-Napieralski reaction by heating *N*-acylbiphenylethylamines (IX) with polyphosphoric acid (12). Reduction of X with sodium borohydride provided the 1,2,3,4-tetrahydroisoquinolines (VIII). Dehydrogenation of VIII*e* in *p*-cymene with 10% palladium on carbon (13) provided the corresponding unsaturated isoquinoline (VII*c*).

Heating VIII*a* with cyanamide (14) gave the guanidine derivative (XI*a*). Methylation of VIII*e* yielded the corresponding *N*-methyl derivative (XI*c*). Treating VIII*e* with 5-chloro-8-hydroxyquinoline and formaldehyde provided the Mannich product (XI*e*). The compounds that were prepared are listed in Table I.

PHARMACOLOGICAL RESULTS[1]

Acute effects (Table II) after intraperitoneal injection were observed in male albino mice (20–30 per compound) weighing 25–35 g. Estimated 48-hr. LD_{50} and 95% confidence limits were determined by the method of Horn (15). The method of Irwin (16) was utilized in noting the effects produced.

[1] The authors are grateful to Dr. W. Marvin Davis, Department of Pharmacology, for the pharmacological data.



Scheme I

EXPERIMENTAL[2]

5-Phenylisoquinoline (VIIa)—*Method A*—A solution of 14.4 g. (0.1 mole) of 5-aminoisoquinoline (VI) in 300 ml. of dry benzene was treated with 25 ml. of freshly prepared isoamyl nitrite. The reaction mixture, which turned brown, was heated under reflux on a steam bath for 1 hr. and then allowed to remain at room temperature for 18 hr. The solvent and unreacted isoamyl nitrite were removed by distillation. The dark-colored residue was extracted with hot petroleum ether (30–60°). The pale yellow liquid obtained after the removal of the solvent was distilled under reduced pressure. The picrate (VII*a*) and the methiodide (VII*b*) were prepared in the usual manner and recrystallized.

5-Phenyl-1,2,3,4-tetrahydroisoquinoline (VIIIa)—*Method B*—A solution of 7 g. (0.029 mole) of 5-phenylisoquinoline (VII*a*) in 50 ml. of 1 *N* hydrochloric acid was hydrogenated at 47 p.s.i. with 0.1 g. of PtO_2 catalyst for 12 hr. The mixture was heated to dissolve the solid that had separated and then filtered to remove the catalyst. The hydrogenated product was separated from the cooled filtrate and recrystallized.

N-Acylbiphenylylethylamines (IX)—*N*-[2-(3-Biphenylyl)ethyl]-formamide (IX*a*) and *N*-[2-(4-biphenylyl)ethyl]formamide (IX*c*) were prepared using a procedure similar to that described by Cannon and Webster (12) for the preparation of *N*-acylphenylethylamines. To 0.014 mole of the appropriate 2-biphenylylethylamine was added 22.5 ml. of formic acid and 18 ml. of acetic anhydride. The solution was refluxed for 7 hr. and thereafter diluted with water and extracted with ether. The ether layer was washed subsequently with 10% sodium hydroxide, 10% hydrochloric acid, and water, respectively, and then dried over anhydrous sodium carbonate. The ether was removed under reduced pressure; the crude products (65% of IX*a* and 55% of IX*c*) were used without further purification in Method C.

N-[2-(3-Biphenylyl)ethyl]acetamide (IX*b*), and *N*-[2-(4-biphenylyl)-ethyl]acetamide (IX*d*) were prepared according to the procedure described by Sam *et al.* (17, 18).

6-, and 7-Phenyl-3,4-dihydroisoquinolines (X)—*Method C*—To 61 g. of commercial polyphosphoric acid, heated to 150°, was added with stirring 0.015 mole of the appropriate, dried, *N*-acylbiphenylylethylamine (IX). The mixture was kept at 180–190° for 3 hr. and then set aside for 9 hr. at room temperature. Thereafter, the mixture was diluted with 500 ml. of water and allowed to remain at room temperature for an additional 12 hr. The solution was filtered, rendered alkaline with a solution of 70 g. of sodium hydroxide in 140 ml. of water and then extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. The amine was distilled under reduced pressure and/or converted to a salt in the usual manner and recrystallized.

6-, and 7-Phenyl-1,2,3,4-tetrahydroisoquinolines (VIII)—*Method D*—A solution of the proper phenyl-3,4-dihydroisoquinoline (X) in 80 ml. of ethanol was treated dropwise, while stirring, with a solution of 8 g. of sodium borohydride in 80 ml. of ethanol. The reaction mixture was allowed to remain at room temperature for 18 hr. and then heated under reflux for 1 hr. The ethanol was distilled under reduced pressure and the residue diluted with water and extracted with ether. The ether extract was washed with water and dried over anhydrous sodium sulfate. The ether was evaporated; the residue was distilled under reduced pressure and/or isolated as a salt and recrystallized.

1-Methyl-7-phenylisoquinoline (VIIc)—*Method E*—A mixture of 5.2 g. (0.023 mole) of 1-methyl-7-phenyl-1,2,3,4-tetrahydroisoquinoline (VIII*e*), 5 g. of 10% Pd-C and 350 ml. of dry *p*-cymene was heated under reflux with stirring for 1 hr. The catalyst was removed by filtration and washed with two 50-ml. portions of hot benzene. The combined filtrate was extracted with dilute hydrochloric acid. The acid extract was rendered alkaline with dilute sodium hydroxide, and then extracted with ether. The ether extract was washed with water and dried over anhydrous magnesium sulfate. The residue obtained on evaporation of the ether was distilled. A picrate was prepared in the usual manner and recrystallized.

5-Phenyl-3,4-dihydro-2(1H)-isoquinolinocarboxamidine hydrochloride (IXa)—*Method F*—A mixture of 1.23 g. (0.005 mole) of 5-phenyl-1,2,3,4-tetrahydroisoquinoline (VIII*a*), 0.25 g. (0.006 mole) of cyanamide and 3 ml. of water was heated in an oil bath at 180° for 1.5 hr. The product was isolated from the resulting mixture by recrystallization.

2-Methyl-5-phenyl-1,2,3,4-tetrahydroisoquinoline (XIb)—*Method G*—A suspension of 5.05 g. (0.014 mole) of 5-phenyl-2-methylisoquinolinium iodide (VII*b*) in 50 ml. of water was hydrogenated at 47.5 p.s.i. with 0.1 g. of PtO_2 for 48 hr. The mixture was heated and filtered to remove the catalyst and then cooled. The product was removed by filtration and recrystallized.

1,2-Dimethyl-7-phenyl-1,2,3,4-tetrahydroisoquinoline (XIc)—*Method H*—Methylation of 1.5 g. (0.0067 mole) of 1-methyl-7-phenyl-1,2,3,4-tetrahydroisoquinoline (VIII*e*) by the Eschwiler-Clarke method (17) gave a liquid which was distilled under reduced pressure. A hydriodide and a methiodide (XI*d*) were prepared in the usual manner and recrystallized.

2-[5-Chloro-8-hydroxy-7-quinolylmethyl]-1-methyl-7-phenyl-1,2,3,4-tetrahydroisoquinoline (XIe)—*Method I*—To a solution of 0.49 g. (0.0022 mole) of 1-methyl-7-phenyl-1,2,3,4-tetrahydroisoquinoline (VIII*e*) in 10 ml. of ethanol was added 0.4 g. (0.0022 mole)

[2] All melting points were taken in open glass capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra of all compounds were determined on a Perkin-Elmer model 137 infracord spectrophotometer using KBr pellets. The spectra were consistent with the assigned structures.

Table II—Acute Interperitoneal Toxicity and Symptomatic Observations

No.[a]	LD_{50},mg./kg.	Observations
VIIa[b,c]	242(208–282)	Sedation, ataxia, tremors
VIIb[d]	141(117–170)	Sedation, ataxia, tremors
VIIc[b,c]	521(447–607)	Sedation, ataxia, loss of righting reflex
VIIe[e,c]	187(165–210)	Sedation, tremor, vasodilation
VIIIa[b,c]	96(76–123)	Sedation, convulsion at toxic doses
VIIIb[b,c]	104(86–125)	Slight motor excitation; convulsions at lethal doses
VIIIc[b,c]	141(117–170)	Slight analgesia early followed by long-continuing clonic convulsions
VIIId[b,c]	153(126–184)	Slight analgesia early, clonic convulsions, tremors, and ataxia
VIIIe[b,c]	77(66–89)	Sedation, convulsion at toxic doses
Xb[b,c]	52(45–61)	Long-continuing clonic convulsions
Xd[d]	95(74–123)	Mixed CNS sedation, excitation, slight analgesia
XIa[b,c]	59(44–79)	Depression of motor activity and respiration; ataxia and respiratory failure with lethal doses
XIb[f,c]	383(308–476)	Sedation at sublethal doses; mild clonic convulsions at lethal doses
XIc[f,c]	261(210–325)	Sedation, ataxia; mild clonic convulsions at lethal doses
XIe[d]	328(258–419)	Sedation, ataxia

[a] Refers to compound numbers found in Table I. [b] Hydrochloride. [c] Administered as an aqueous solution. [d] Administered as an aqueous suspension in acacia. [e] Methiodide. [f] Hydrodide.

of 5-chloro-8-hydroxyquinoline and 0.2 ml. of 38% formaldehyde. The mixture was refluxed for 1 hr. and then allowed to remain at room temperature for 18 hr. The product was removed from the cooled solution by filtration and recrystallized.

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ACKNOWLEDGMENTS AND ADDRESSES

Received July 9, 1969 from the *Department of Pharmaceutical Chemistry, The University of Mississippi, University, MS 38677*

Accepted for publication August 28, 1969.

This investigation was supported in part by grant MH 05292 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md. and during a tenure (R.M.S. and K.A.) of a Mississippi Heart Association Fellowship.

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