Studies on Indenopyridine Derivatives and Related Compounds. II (1). Stereochemistry of 1-Substituted 9-Phenyl-1,3,4,4a,9,9a-hexahydro-4-hydroxy-2*H*-indeno[2,1-*b*]pyridines and Their Acetates

Takushi Kurihara and Hiroshi Hirano

Osaka College of Pharmacy, 2-10-65, Kawai, Matsubara, Osaka, Japan

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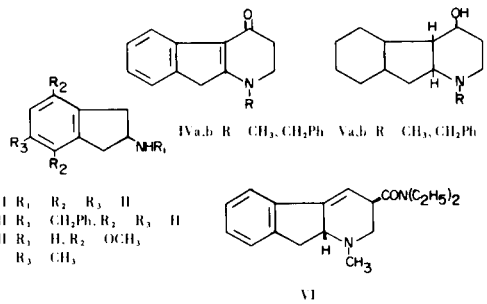
Chemical and catalytical reduction of 1-methyl- or 1-benzyl-9-phenyl-1,3,4,9-tetrahydro-2*H*-indeno[2,1-*b*]pyridin-4-ones (VIIa,b) afforded 1-methyl- or 1-benzyl-9-phenyl-1,3,4,4a,9,9a-hexahydro-4-hydroxy-2*H*-indeno[2,1-*b*]pyridines (IXa,b), which gave the corresponding acetates (Xa,b) by treatment with acetic anhydride and pyridine. Based upon a detailed study of 100 MHz nmr spectra of these compounds, it was concluded that the hydroxy group of IXa,b has an axial configuration taking B/C *cis* stable form which has the large aromatic group equatorial with respect to the piperidine ring, whereas the acetoxy group of Xa,b is equatorial taking an unfavorable B/C *cis* unstable form which has the large aromatic group axial with respect to the piperidine ring.

Early investigators have reported that 2-aminoindans possess interesting biological properties. For example, 2-aminoindan (I) (2) and 2-benzylaminoindan (II) (3), considered as cyclic analogs of amphetamine, exhibit significant bronchodilating and analgesic properties. Sam, *et al.*, (4) reported the synthesis and pharmacological results of various cyclic 2-aminoindans such as morpholino, piperidino *et al.*, derivatives. Barfknecht (5) also reported the synthesis and activities test of 2,5-dimethoxy-4-methylphenylisopropylamine, known as a potent hallucinogen.

SCHEME I



VI

In our previous paper (1), we reported the syntheses and stereochemistry of 1,4-disubstituted hexahydro-9*H*-indeno[2,1-*b*]pyridine as one of the interesting 2-aminoindan analogues. Among them, since 1-methyl-1,2,3,4-tetrahydro-9*H*-indeno[2,1-*b*]pyridin-4-one (IVa) and its dihydro alcohol (Va) had some biological activities, we decided to prepare the C_9-phenyl analog and its dihydro derivatives. Recently Craig, *et al.*, (6) reported the synthesis of *N*,*N*-diethyl-1-methyl-1,2,3,9a-tetrahydro-9*H*-indeno[2,1-*b*]-pyridin-3-carboxamide (VI) as simplified analog of lysergic acid diethylamide. Hereby we wish to report the syntheses and stereochemistries of the title compounds.

Reaction of 1-phenyl-2-indanone, prepared by the method of Blomquist (7), with ethyl 3-methyl- or 3-benzylaminopropanoate (8, 9) in the presence of trifluoroacetic acid (10) in refluxing xylene resulted in the formation of 1-methyl- or 1-benzyl-9-phenyl-1,3,4,9-tetrahydro-2*H*-indeno[2,1-*b*]pyridin-4-ones (VIIa and VIIb) in yields of 72% and 78%, respectively. These structural assignments were mainly obtained from ir, uv and the ferric chloride color test as described in the experimental. The stereochemistry of C_9 having a quasi-axial phenyl ring was readily deduced from the following evidence. By a comparison of nmr spectra of VIIa or VIIb with IVa,b in deuteriochloroform, the *N*-methyl or *N*-benzyl resonances of IVa,b appear at δ 2.93 or δ 4.44, whereas those of VIIa,b at δ 2.78 or δ 4.30 shifted upfield of 0.14-0.15 ppm. If the C_9-phenyl ring situated quasi-axial bring the *N*-methyl or *N*-benzylic protons into the zone of shielding of the C_9-phenyl ring, this accounts for the upfield shift. This isomer, however, would be a more sterically crowded molecule than the other.

Reduction of vinylogous amides (VIIa,b) with sodium borohydride gave 1-methyl-9-phenyl-1,3,4,4a,9,9a-hexahydroxy-2*H*-indeno[2,1-*b*]pyridine (IXa) of m.p. 207-208° and 1-benzyl-9-phenyl-1,3,4,4a,9,9a-hexahydro-4-hydroxy-2*H*-indeno[2,1-*b*]pyridine (IXb) of m.p. 118-119°, accom-

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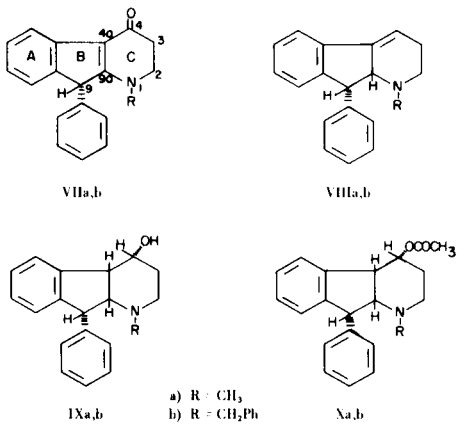
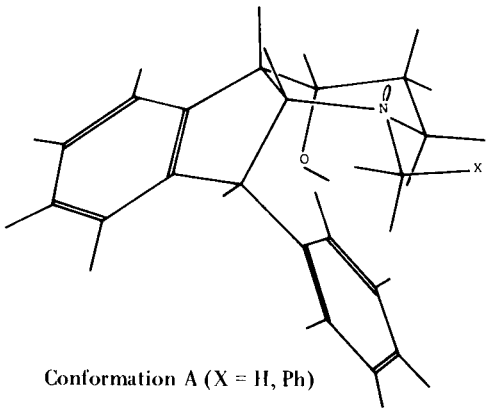
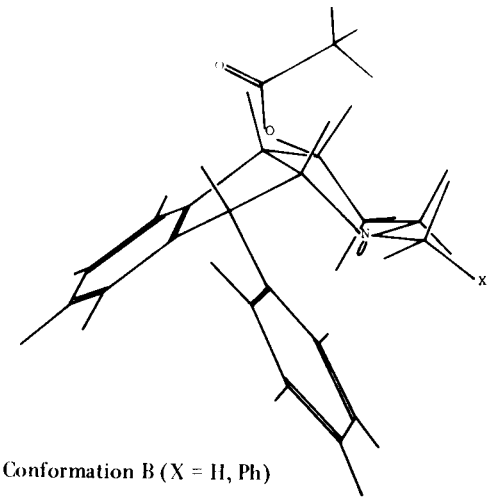




Conformation A (X = H, Ph)



Conformation B (X = H, Ph)

panied by 1-methyl-9-phenyl-1,3,9,9a-tetrahydro-2*H*-indeno[2,1-*b*]pyridine (VIIIa) and 1-benzyl-9-phenyl-1,3,9,9a-tetrahydro-2*H*-indeno[2,1-*b*]pyridine (VIIIb), respectively. The isolation of each of the corresponding isomer failed. Catalytic hydrogenation of VIIa over platinum oxide in methanol resulted in IXa as a single product in 94% yield, indicating that the reduction was stereospecific at all four centers of asymmetry (carbons 4, 4a, 9, and 9a). Since by inspection of the Drieding model, the approach of a proton (or hydride anion) from the opposite side (β-side) to C_9-phenyl ring (α-side) would be preferable, the protons at carbon 4, 4a, 9, and 9a are all disposed β-oriented *cis* to one another. In agreement with our previous report (1), these should have an axial hydroxy group taking B/C *cis* stable form which has the large aromatic group equatorial with respect to the piperidine ring (11) (conformation A).

A further indication of these stereochemical assignments was provided by the 100 MHz nmr spectra by the aid of double irradiation shown in Table I. The nmr data of IXa (in deuteriodimethyl sulfoxide) and IXb (in deuteriochloroform) clearly shows that these have a quasi-axial C_9-phenyl ring (no change in stereochemistry at C_9 occurred during reduction), a C_4-hydroxy group situated axial and a B/C *cis* ring junction. These results with the combination of assumptions described above decided the conformational structure of IXa,b as shown.

Both alcohols were acetylated with acetic anhydride in pyridine to give the acetylated derivatives (Xa,b). It is interesting to note that the nmr spectra showed the C_4-proton at δ 5.20 (m, H/W 17 cps) in Xa and δ 5.34 (m, H/W 17 cps) in Xb, indicating that the acetoxy groups have an axial configuration. This result can be reasonably explained as follows. In either IXa or IXb, there is severe crowding between the C_4-hydroxy group and the phenyl ring at C_9. This crowding would give rise to a conformational change to an unfavorable B/C *cis* unstable form (conformation B), which has the large aromatic group axial with respect to the piperidine ring, by introduction of a bulky acetoxy group at C_4. This crowding is not manifested in conformation B. Furthermore, the fact that the *N*-methyl or *N*-benzylic protons in acetates Xa,b resonated at a higher field than alcohols IXa,b would strongly support the above stereochemical assignment, because, in conformation B, the C_9-phenyl ring gave the stronger shielding effect on *N*-methyl or *N*-benzylic protons than in conformation A.

In this connection, it is worth noting that Craig (8) has concluded the conformational structure of ethyl 4-hydroxy-1-methyl-1,2,3,4,4a,9a-hexahydro-9*H*-indeno[2,1-*b*]pyridin-3-carboxylate to be the B/C *cis* unstable form similar to conformation B.

TABLE I

The Nmr Data given in δ Value at 100 MHz, J Value in the Parenthesis is in cps (in $CDCl_3$)

	IXa	IXb	Xa	Xb
C_4-*H*(OH)	4.26 (q, 4) (a)	4.19 (q, 4)		
C_4-*H*($OCOCH_3$)			5.20 (m, H/W 17)	5.34 (m, H/W 17)
C_4-H($OCOCH_3$)			2.13 (s)	2.02 (s)
C_{4a}-*H*		3.38 (d.d, 3,8)	3.66 (b.t, 5)	3.70 (b.t, 5)
C_9-*H*	5.11 (d, 5) (a)	4.76 (d, 8)	4.28 (d, 5)	4.37 (d, 7)
C_{9a}-*H*		3.69 (t, 8)	3.21 (t, 5)	3.66 (t, 5)
N-CH_3	1.80 (s)		1.20 (s)	
N-CH_2Ph (b)		3.36 (q, 13)		3.09 (q, 14)

(a) Data in deuteriodimethylsulfoxide. (b) The chemical shift of this was calculated as a central value because this showed a typical AB type doublet.

EXPERIMENTAL

All melting points are uncorrected. The ir and uv spectra were taken with JASCO Model IRA-1 and Shimadzu UV-200 spectrophotometers. The nmr spectra were taken with Varian A-60 and Varian HA-100 spectrometers using tetramethylsilane as the internal standard. The mass spectra were taken with a Hitachi Mass Spectrometer RMU-7L.

1-Methyl-9-phenyl-1,3,4,9-tetrahydro-2*H*-indeno[2,1-*b*]pyridin-4-one (VIIa).

A mixture of 1-phenyl-2-indanone (26.9 g.) and ethyl 2-methylaminopropanoate (17 g.) dissolved in dry xylene (200 ml.) in the presence of trifluoroacetic acid (1 ml.) was refluxed under a nitrogen stream with a Dean Stark water separator until no more water was detected (required about 2 hours). To the reaction mixture, cooled to 50°, was added further trifluoroacetic acid (5 ml.) and the mixture was refluxed for 3 hours, whereupon a deep violet color developed. After cooling, the precipitate was collected by filtration, washed with cold xylene (20 ml.) and recrystallized from methanol giving pale pink needles (21.5 g.), m.p. 171-172°. Concentration of the filtrate and addition of a small amount of methanol gave an additional crop. Recrystallization from methanol gave VIIa (4.3 g.), total yield was 72%; ferric chloride color test: dark green; ir ν max (potassium bromide): 1623, 1585 and 1575 cm^{-1} (N-C=C-CO), uv λ max (99% ethanol): 282 nm (log ε 4.24), 366 (3.93); nmr δ (deuteriochloroform): 2.78 (3H, s, NCH_3), 4.51 (1H, s, CH), 7.95 (1H, broad d, J = 8 Hz, 5-H).

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.88; H, 6.22; N, 5.09. Found: C, 82.73; H, 6.22; N, 4.95.

1-Benzyl-9-phenyl-1,3,4,9-tetrahydro-2*H*-indeno[2,1-*b*]pyridin-4-one (VIIb).

A mixture of 1-phenyl-2-indanone (5.5 g.) and ethyl 2-benzylaminopropanoate (6 g.) in dry xylene (50 ml.) was worked up in the same manner described for the synthesis of VIIa giving pale pink needles (7.25 g.) (78%), m.p. 165-166°, recrystallized from ethanol; ferric chloride color test: dark green; ir ν max (potassium bromide): 1620, 1585, and 1572 cm^{-1} (N-C=C-CO); uv λ max (99% ethanol): 282 nm (log ε 4.15), 365 (3.86); nmr δ (deuteriochloroform): 4.30 (2H, s, NCH_2Ph), 4.69 (1H, s, CH), 8.01 (1H, broad d, J = 8 Hz, 5-H).

Anal. Calcd. for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.00; H, 6.45; N, 3.90.

Reduction of VIIa with Sodium Borohydride.

To a hot solution of VIIa (5 g.) in ethanol (50 ml.) was added sodium borohydride (1.5 g.) in small portions and the mixture was refluxed until the disappearance of VIIa on thin-layer chromatography (tlc) required 3-4 hours. After neutralization with dilute acetic acid, most of the solvent was evaporated *in vacuo* below 40°. The residue was poured into water and extracted with chloroform. The organic phase was dried (magnesium sulfate) and evaporated *in vacuo* leaving a dark violet residue (4.4 g.). Crystals which were insoluble in benzene were collected by filtration and recrystallized from benzene to give IXa as white crystals (2.45 g.) m.p. 207-208°; ir ν max (potassium bromide): 3180 cm^{-1} (OH).

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01. Found: C, 81.52; H, 7.58; N, 4.83.

The filtrate was condensed and the residue was chromatographed on an alumina column with benzene as the eluent. On evaporation of the first violet eluate, a residue was repurified on an alumina preparative tlc to give a crystalline VIIIa, which could not be recrystallized; uv λ max (99% ethanol): 253 nm (log ε 4.25), 288 (3.72), 298 (3.70); nmr δ (deuteriochloroform): 2.20 (3H, s, NCH_3), 4.38 (1H, d, J = 8 Hz, CHPh), 6.13 (1H, broad s, CH=C); ms: m/e 261 (M^+).

Hydrogenation of VIIa with Platinum Oxide Catalyst.

A solution of VIIa (0.5 g.) in methanol (50 ml.) was hydrogenated over a platinum oxide (0.2 g.) using a Skita apparatus for 10 hours. The catalyst was removed by filtration and the solvent was evaporated *in vacuo*. The crystalline residue was recrystallized from benzene to give IXa (0.47 g.) (94%), m.p. 207-208°, which was identical with the sample prepared above by comparison of their ir spectra.

Reduction of VIIb with Sodium Borohydride.

To a hot solution of VIIb (3.9 g.) in ethanol (50 ml.) was added sodium borohydride (1.3 g.) in small portions. The reaction mixture was treated as described for the reduction of VIIa giving a dark violet residue (3.1 g.). Chromatographic separation over an alumina column with benzene as the eluent followed by evaporation gave VIIIb (0.45 g.) as crude crystals from the first fraction. Recrystallization from *n*-hexane gave an analytical sample as pale violet needles, m.p. 149-151°; uv λ max (99% ethanol): 253 nm (log ε

4.14), 287 (3.67), 297 (3.67); nmr δ (deuteriochloroform): 2.88 and 4.03 (each 1*H*, d, d, J = 14 Hz, NCH_2Ph), 4.50 (1H, d, J = 8 Hz, CHPh), 6.13 (1H, broad s, CH=C); ms: m/e 337 (M^+), 246 (M^+-CH_2Ph).

Anal. Calcd. for $C_{25}H_{23}N$: C, 88.98; H, 6.87; N, 4.15. Found: C, 89.12; H, 7.05; N, 4.30.

From the second pale yellow eluate was obtained IXb (1.8 g.) recrystallized from *n*-hexane to give colorless needles, m.p. 118-119°; ir ν max (potassium bromide): 3190 cm^{-1} (OH).

Anal. Calcd. for $C_{25}H_{25}NO$: C, 84.47; H, 7.09; N, 3.94. Found: C, 84.60; H, 7.27; N, 3.67.

1-Methyl-9-phenyl-1,3,4,4a,9,9a-hexahydro-4-acetoxy-2*H*-indeno-[2,1-*b*]pyridine (Xa).

A solution of IXa (0.5 g.), pyridine (1 ml.) and acetic anhydride (40 ml.) was heated with stirring at 70° for 4 hours (because IXa is very difficultly soluble in acetic anhydride). The mixture was poured into ice water, made alkaline with sodium bicarbonate and extracted with chloroform. The organic phase was dried (magnesium sulfate) and evaporated *in vacuo*. The residue was recrystallized from petroleum ether to give colorless needles (0.35 g.), m.p. 109-110°; ir ν max (potassium bromide): 1720 cm^{-1} (CO).

Anal. Calcd. for $C_{21}H_{23}NO_2$: C, 78.47; H, 7.21; N, 4.36. Found: C, 78.49; H, 7.33; N, 4.07.

1-Benzyl-9-phenyl-1,3,4,4a,9,9a-hexahydro-4-acetoxy-2*H*-indeno-[2,1-*b*]pyridine (Xb).

A solution of IXb (0.5 g.), pyridine (1 ml.) and acetic anhydride (10 ml.) was allowed to stand over night at room temperature. The mixture was poured into ice water, made alkaline with sodium bicarbonate and extracted with chloroform. The organic phase was dried (magnesium sulfate) and evaporated *in vacuo*. The residual oil was purified by passing through an alumina column using benzene as the eluent to give a pure oil (0.42 g.); ir ν max (chloroform): 1718 cm^{-1} (CO). The perchlorate of Xb was recrystallized from 95% ethanol to give colorless needles, m.p. 243-245°.

Anal. Calcd. for $C_{27}H_{28}ClNO_6$: C, 65.12; H, 5.65; N, 2.81. Found: C, 65.00; H, 5.42; N, 2.81.

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