Benzomorphan Related Compounds. III. (1).
Structural Determination of Δ^3- and Δ^4-Tetrahydropyridines by Nuclear Magnetic Resonance

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Observation of the nmr spectra of several Δ^3- and Δ^4-tetrahydropyridines hydrochlorides provides a useful method for the structural determination of this type of compound. The Δ^3-isomers exist as one predominant epimer only whereas the Δ^4-isomers exist as a mixture of the two possible epimers. The respective assignments are discussed in view of the criteria previously applied in the study of this type of compound.

Introduction.

2-Benzyl-Δ^3- and Δ^4-tetrahydropyridines are useful synthetic intermediates since their cyclization leads to 6,7-benzomorphans, which are pharmacologically interesting for their analgesic properties (2). Similarly, some 2-thenyltetrahydropyridines of this type have been recently described (1,3), as precursors of thienomorphans, which also have potential analgesic activity.

Preparation of 2-benzyl (or 2-thenyl)-1,3,4-trialkyltetra-hydropyridines may be carried out by different procedures. Either the reduction of the corresponding 1,2-dihydro-compounds (easily accesible by Freund's reaction) (4) or the Stevens rearrangement of the appropriate quaternary ammonium salts (5) or the sodium borohydride reduction of 1,3,4-trialkylpyridinium salts (6) afford unambiguously
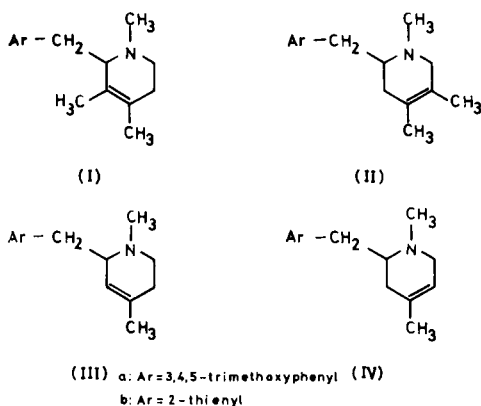

(I)   (II)

(III)   (IV)

a: Ar=3,4,5-trimethoxyphenyl
b: Ar=2-thienyl

Δ^3-tetrahydropyridines (I), whereas reduction of 2-benzyl (or 2-thenyl)-1,4,5-trialkylpyridinium salts leads unambiguously to Δ^4-tetrahydropyridines (II), (1).

On the contrary, preparation of 2-benzyl (or 2-thenyl)-1,4-dialkyltetrahydropyridines effected by reduction of either 1,2-dihydropyridines or of the corresponding pyridinium salts, leads to a mixture of the two isomers, Δ^3- and Δ^4- (III and IV), which only differ in the position of the double bond and both of which give, on cyclization, the same 2,5-dialkyl-6,7-benzo (or thieno) morphan (1,7).

Although the Δ^3-isomer is generally predominant in the reduction of 1,2-dihydropyridines (7,8) and the Δ^4- is the major product of the sodium borohydride reduction of pyridinium salts (9), it is of interest to have methods that allow an unequivocal assignment of their structures. May et al., (7,10) have proposed a method based on the comparison of the chemical shifts of the olefinic and allylic methylene protons in the nmr spectra of both isomers. In the Δ^3-tetrahydropyridines (III), the first of these signals appears at higher field values (0.2 ppm) than in the Δ^4-isomers (IV), due to the anisotropy of the aromatic ring. Similarly, the 3-CH_2 protons of the Δ^4-tetrahydropyridines appear at higher fields than do the 5-CH_2 protons of the Δ^3-isomers.

Results.

Nmr spectral data of 1,3,4-trimethyl-2-(3,4,5-tri-methoxybenzyl)-1,2,5,6-tetrahydropyridine (Ia) (11) and its hydrochloride salt are given in Table 1. The N-methyl singlet in the free base is split into a doublet in its hydro-

chloride due to the NH/N-CH₃ coupling. This kind of coupling has been detected in several ammonium salts (12) and it may be expected to disappear upon increasing the interchange rate of the nitrogen proton with the solvent. This rate is a function of the solvent polarity and the pH of the solution, *i.e.* interchange will be favoured when both pH and solvent polarity are increased. Thus, in the Ia hydrochloride spectrum in deuterium oxide, the N-methyl appears again as a singlet, due to the interchange of the acidic proton for deuterium. The same occurs in water (pH, 5.35), thus indicating a fast exchange in the nmr time range.

Table I

Chemical Shifts of Ia, IIa and IVa, (δ values).

	H-Ar	O-CH₃	N-CH₃	=C-CH₃
Ia Base (a)	6.51 s	3.81 s	2.37 s	1.61 s
Ia Hydrochloride (a)	6.26 s	3.84 s 3.79 s	2.81 d	1.73 s 1.61 s
Ia Hydrochloride (b)	6.65s	3.85 s 3.77s	2.85s	1.76-1.68
IIa Base (a)	6.38 s	3.83 s	2.43 s	1.58 s
IIa Hydrochloride (a)	6.48 s 6.43 s	3.82 s 3.78 s	2.84 t	1.67 s
IIa Hydrochloride (b)	6.74 s	3.93 s 3.83 s	3.05 s 2 97 s	1.73 s
IVa Base (a)	6.36 s	3.78 s	2.42 s	1.64 s
IVa Hydrochloride (a)	6.51 s 6.48 s	3.86 s 3.82 s	2.88 t	1.76 s
IVa Hydrochloride (b)	6.76 s	3.96 s 3.86 s	3.10 s 3.02 s	1.81 s

(a) Deuteriochloroform as solvent. (b) Deuterium oxide as solvent.

As seen in Table I, the spectrum of 1,4,5-trimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine (IIa) is very similar to that of its isomer Ia whereas the spectrum of its hydrochloride (deuteriochloroform) differs in its general aspect since it shows N-methyl and aromatic proton signals as apparent triplet and doublet, respectively (Scheme 2). This increase in complexity is explained by the existence of IIa hydrochloride as two epimers, *cis* and *trans*, since the nitrogen atom becomes a new chiral center. Each epimer will exist in several conformations; any mutual transformation, however, implies release of the acidic proton, inversion of nitrogen configuration and further capture of a proton (Scheme 3). Therefore, the signal observed for the N-methyl is the result of the superposition of the doublets of both epimers.

This kind of isomerism has been previously detected in other ammonium salts (13). An increase in either the polarity of the solvent or the pH of the solution should
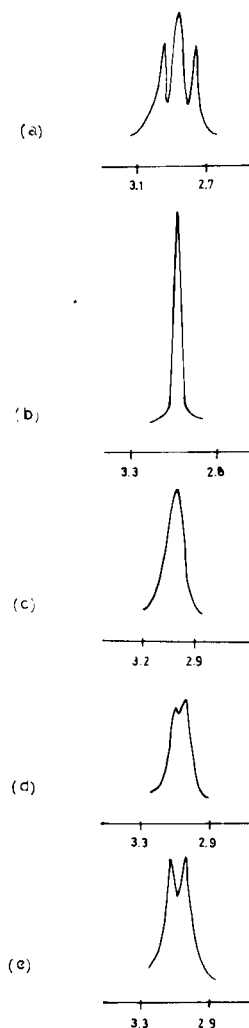

60 MHz nmr signal of the N-methyl protons of IIa as a function of solvent polarity and pH. (a) deuteriochloroform; (b) water, pH 6.95; (c) water, pH 3.70; (d) water, pH 2.75; (e) water, pH 1.00.

lead to a faster interchange and consequently to coalescence of the signal. Indeed as may be seen in Scheme 2, the spectrum of IIa hydrochloride in water at pH 6.95 shows N-methyl protons as a sharp singlet, thus indicating that mutual interconversion of both epimers is fast enough to make them undistinguishable by nmr. As the pH decreases, the interconversion rate diminishes until, at pH 1, the signals of both epimers are clearly differentiated. The protonic interchange rate, however, is too high for the NH/N-CH₃ coupling to be noticed. In the same way a doublet is observed in deuterium oxide, which is consistent with the presence of both epimers, since in this case the NH/N-CH₃ coupling cannot take place. On the other hand,
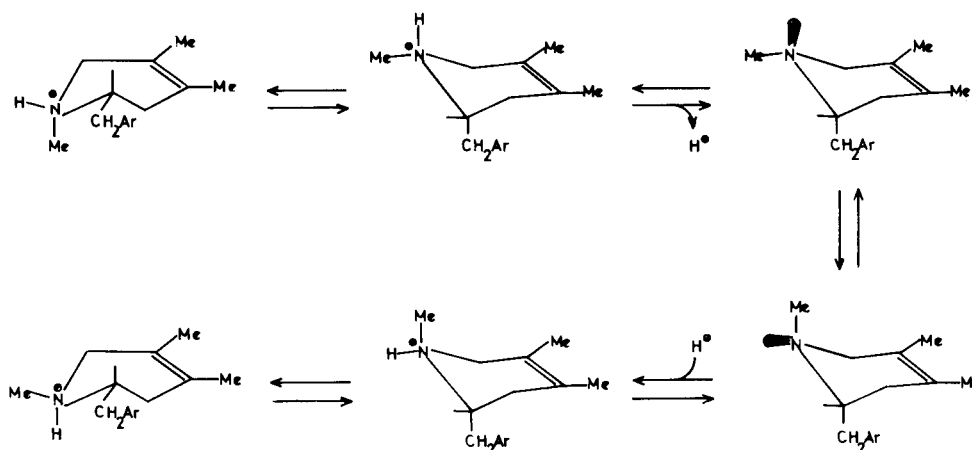
the spectrum of IIa hydrochloride recorded in deuterio-chloroform shows one differentiated aromatic proton signal for each epimer, but not when recorded in water at acidic pH.

According to Garbisch's work (14) on 6-substituted 1-phenylcyclohexenes and Sakashita's (15) on 3-chloro and 3-bromocyclohexenes, there is a preference for substituents in allylic position to adopt a pseudo-axial position. By analogy (16), this could be assumed to be the determining factor for the existence of only one epimer of Ia. In Scheme 4, the N-methyl group is represented in an equatorial position in both cis and trans epimers; according to the mentioned criteria, the cis epimer is expected to be the most stable one. In the case of IIa, however, it may be assumed that there is not such a difference in stability between the cis and trans epimers (Scheme 3) (both have substituents in the homoallylic position) their presence being therefore detectable by nmr.
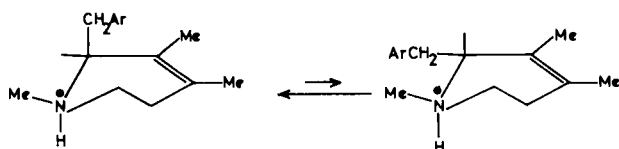
This difference in the epimeric ratio of Ia and IIa is found again in compounds 1,3,4-trimethyl-2-(2-thenyl)-1,2,5,6-tetrahydropyridine (Ib) and 1,4,5-trimethyl-2-(2-thenyl)-1,2,3,6-tetrahydropyridine (IIb) (1,3a): N-methyl protons appear as singlets in the nmr spectra of the free bases, (Table II) whereas they appear as a triplet in the IIb.HCl spectrum (two epimers interconverting and interchanging their acidic protons slowly) and as a singlet in the Ib.HCl spectrum (one epimer interchanging its acidic proton rapidly).

Table II

Chemical Shifts in Deuteriochloroform, (δ values).

	N-CH$_3$	=C-CH$_3$
Ib Base	2.39 s	1.59 s
Ib Hydrochloride	2.84 s	1.76 s
IIb Base	2.40 s	1.58 s
IIb Hydrochloride	2.85 t	1.67 s
IIIb Base	2.42 s	1.66 s
IIIb Hydrochloride	2.91 s	1.78 s
IVb Base	2.41 s	1.64 s
IVb Hydrochloride	2.86 t	1.75 s

Discussion.

The observed differences in the nmr spectra of I and II hydrochlorides allow for a general validity criterion which permits the structural elucidation of tetrahydropyridines of the type shown in Scheme 1.

It has already been mentioned that nmr spectra of the hydrochlorides of I-type compounds in deuteriochloroform show exclusively the signals corresponding to one of the epimers, whereas in II-type compounds the signals of both possible epimers appear. The assignment of Ia and IIa structures effected in this way coincides with the assignment according to May, et al. The allylic methylene of Ia appears as a broad signal between δ 1.80 and 2.20 ppm whereas the 3-methylene of IIa appears upfield, between δ 1.73 and 2.01 ppm. These differences are non-existent, however, in Ib and IIb compounds since, in both of them, the allylic methylene signals are found to be in the same position, δ 1.8-2.1 ppm.

In contrast with the previous cases, the structures of compounds 1,4-dimethyl-2-(2-thenyl)-1,2,5,6-tetrahydropyridine (IIIb) and 1,4-dimethyl-2-(2-thenyl)-1,2,3,6-tetrahydropyridine (IVb) are not definitively known in view of their synthetic processes of obtention (1). Assignment of

their structures can neither be made considering the signal of allylic C_5- and C_3-methylenes since both of them have the same chemical shift, although it can be partially achieved by considering the shift of the olefinic proton. In one of the isomers it appears at δ 5.27 ppm whereas in the other one, it appears at δ 5.37, thus allowing assignment of IIb and IVb structures, respectively. A more accurate assignment can be achieved by consideration of the hydrochloride spectra of both isomers in deuteriochloroform. In the same way as in I- and II-type compounds, only one epimer is observed in IIIb (N-methyl signal: broad singlet), whereas both epimers can be detected in IVb (N-methyl signal: apparent triplet), thus enabling an unambiguous assignment.

Finally, application of the same criteria to the determination of the double bond position in the major compound resulting from sodium borohydride reduction of 1,4-dimethyl-2-(3,4,5-trimethoxybenzyl)pyridinium bromide, leads to assignment of IVa structure to it, i.e., 1,4-dimethyl-2-(3,4,5-trimethoxybenzyl)-1,2,3,6-tetrahydropyridine (Δ^4-isomer). Indeed, in the free base spectrum N-methyl and aromatic protons appear as singlets whereas in the hydrochloride spectrum in deuteriochloroform they appear as triplet and doublet, respectively, and thus clearly indicate the presence of two epimers, as it corresponds to all compounds with a Δ^4-double bond discussed in this paper. Furthermore, the comparison of IVa and 1,4-dimethyl-2-(p-methoxybenzyl)-1,2,3,6-tetrahydropyridine spectra (7) shows the coincidence of both C_3-allylic methylene (δ 1.74-2.03 ppm) and olefinic proton (δ 5.36 ppm) signals, in contrast with the diamagnetical shift that could be expected for a Δ^3-tetrahydropyridine structure. On the other hand the application of May's criteria is more difficult in this case since only one of both isomers is available.

Conclusion.

It can be deduced from the observation of the nmr spectra of the hydrochlorides of several tetrasubstituted tetrahydropyridines that the Δ^3-isomers exist as an only predominant epimer, whereas the Δ^4-isomers exist as two interconvertible epimers in fast protonic interchange conditions. The observation of those spectra is therefore a useful method for the structural determination of this kind of compounds. The same criteria have also been applied to several trisubstituted tetrahydropyridines (III and IV) whose structures were not a priori unambiguously known.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a R-12 Perkin-Elmer Spectrometer (60 MHz, TMS at δ 0.0 ppm as internal standard) with deuteriochloroform as solvent unless otherwise indicated. Chemical shifts are reported as δ values in parts per million (ppm). Samples at acidic and basic pH were prepared by addition of trifluoroacetic acid or pyridine, respectively, until desired pH.

Syntheses of compounds Ia, Ib, IIb, IIIb and IVb has been previously reported (1,11).

Tetrahydropyridines IVa and IIa have been synthesized following the procedure previously indicated for the compound Ia (11) from 3,4,5-trimethoxybenzaldehyde and the lithium derivative of the appropriate 2-bromopyridine. The resulting carbinols, 3,4,5-trimethoxyphenyl (4-methyl-2-pyridyl) carbinol (Va) and 3,4,5-trimethoxyphenyl (4,5-dimethyl-2-pyridyl) carbinol (Vb), were transformed into their chlorides with thionyl chloride and then reduced, without further purification, with zinc dust and hydrochloric acid to the corresponding 2-benzylpyridines, VIa and VIb, respectively. Quaternization of these compounds led to the ammonium salts, VIIa and VIIb which, on reduction with sodium borohydryde, were converted into the expected tetrahydropyridines IVa and IIa, respectively (see Tables III and IV).

Acknowledgments.

Table III

Analyses

Compound	M.p. °C	Formula	Carbon %		Hydrogen %		Nitrogen %		Halide %	
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
IIa. HCl	204-206	$C_{18}H_{28}ClNO_3$	63.24	63.53	8.26	8.57	4.09	3.97	10.37	10.53
IVa. HCl	196-197	$C_{17}H_{26}ClNO_3$	62.28	62.42	7.99	8.15	4.27	4.30	10.81	10.62
Va	96-97	$C_{16}H_{19}NO_4$	66.41	66.36	6.62	6.68	4.84	4.67	----	----
Vb	125-127	$C_{17}H_{21}NO_4$	67.30	67.09	6.98	7.24	4.62	4.67	----	----
VIa. HCl	184-186	$C_{16}H_{20}ClNO_3$	62.03	62.27	6.50	6.65	4.52	4.37	11.44	11.31
VIb. HCl	186-189	$C_{17}H_{22}ClNO_3$	63.05	63.08	6.84	6.97	4.33	4.45	10.94	10.90
VIIa	159-160	$C_{17}H_{22}BrNO_3.H_2O$	52.85	52.92	6.26	6.51	3.60	3.24	20.68	20.61
VIIb	165-167	$C_{18}H_{24}INO_3$	50.35	50.40	5.63	5.64	3.26	3.57	29.56	29.60

Table IV

Chemical Shifts in Deuteriochloroform (δ values).

Compound	H6	H5	H3	Ar-H	-CH-	-CH2-	-NCH3	-OCH3	C-CH3
Va	8.40 d	7.10	6.95	6.60 s	5.60 s	----	----	3.80 s	2.29 s
Vb	8.25 s	----	6.91 s	6.60 s	5.58 s	----	----	3.80 s	2.20 s
VIa. HCl	8.55 d	7.68	7.45	6.80 s	----	4.47 s	----	3.87 s (6H) / 3.80 s (3H)	2.60 s
VIb. HCl	8.36 s	----	7.38 s	6.75 s	----	4.38 s	----	3.84 s (6H) / 3.78 s (3H)	2.45 s / 2.35 s
VIIa	9.47 d	7.68 d	7.43 s	6.70 s	----	4.62 s	4.62 s	3.83 s	2.55 s
VIIb	9.20 s	----	7.43 s	6.71 s	----	4.60 s	4.49 s	3.80 s	2.41 s

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