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Stereochemical Studies of the Isomerization of Novel 2-Alkyl-9-phenyl-2,3,4,4a- and 2,3,4,9-tetrahydro-1*H*-indeno[2,1-*c*]pyridines

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Abstract

The published synthetic route to the antihistaminic tetrahydroindeno[2,1-*c*]pyridines (phenindamines) relies on catalytic reduction of the precursor dihydroindenopyridines. This reduction gives mixtures of 9,9a- and 4a,9a-enes and the clinically active 4a,9a isomer has to be isolated by recrystallization of an appropriate salt. The structure of the product recovered depends on the anion used to isolate the proton salt and appears to be arbitrary.

To rationalize this outcome a series of novel *N*-2 alkylated tetrahydroindeno[2,1-*c*]pyridines and their diene precursors has been synthesized from accessible piperidines. The structures and geometry of the piperidines and the dihydro- and tetrahydroindenopyridines have been determined by ^{1}H and ^{13}C NMR. An unusual feature of the proton spectra of the piperidines is the resonance of the axial protons at lower field than their equatorial counterparts. By controlling the reaction conditions for the reduction of the dihydroindenopyridines to their tetrahydro derivatives the kinetic or thermodynamic product can be selected as required.

A predictable outcome for the reductions investigated was achieved and is generally applicable.

As part of an investigation into the molecular requirements for histamine H_1 antagonism (Nicholson et al 1991; Casy et al 1992a; Salunga et al 1996; Upton & Jaffar 1996), a series of *N*-modified analogues of the clinically-established H_1 antagonist 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1*H*-indeno[2,1-*c*]pyridine tartrate was required. We proposed retaining the tricyclic nucleus which embodied the recognized molecular determinants for antagonism in this pharmacological group. Borea et al (1986) has described a model which relates the distance between the centres of gravity of the two aromatic rings and the angle subtended by the protonated nitrogen (found in all the classical antihistamines) to antagonism at this receptor. We have selected a range of *N*-substituents which vary in their lipophilic and steric properties, as these might be involved in allosteric interactions with the receptor, and their biology is being investigated.

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Plati & Wenner (1949) and Plati et al (1949) described the synthesis of these compounds originally using a Mannich reaction with the appropriate acetophenone, methanal and primary amine hydrochlorides and cyclizing the resulting bis-Mannich salts, in a base-induced Dieckmann reaction, to the corresponding piperidines. Catalytic reduction of the HBr-derived 2,3-dihydro-indenopyridines, from these piperidines, gave tetrahydro compounds. The structure of the majority of the tetrahydroindenopyridinium salts isolated from the reaction mixture at this point, including the hydrobromides, were those in which the non-aromatic double bond was in the 9,9a-position, **1**, (Figure 1) and, fortuitously, the only one in which the ene was positioned at 4a,9a, **2**, was the tartrate. This salt is now in clinical use for the symptomatic relief of allergies, and this isomer of the tetrahydro compounds has been shown to be that responsible for this biological activity (Plati & Wenner 1955). We have described similar, unpredictable behaviour in aryl-substituted analogues (Casy et al 1992b).

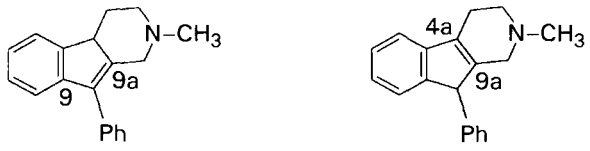

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Figure 1. Structures of the tetrahydroindenopyridines.

In this work we seek to establish reliable reaction conditions for isolating the required analogues which are currently being screened for H_1 antagonism.

Experimental

Melting points were recorded on a Gallenkamp apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded on a Jeol GX270 MHz Fourier-transform NMR spectrometer unless otherwise stated. Proton signals are described as broadened (br) or narrow (n). The ^{13}C NMR was operated at 67·8 MHz and quaternary carbons are described as q. Mass spectra were acquired by the University of Bath Mass Spectrometry Service on a VG Micromass 707E Mass Spectrometer operating in electron-impact (EI) mode at low eV or 70 eV, or in chemical ionization (CI) mode. Elemental analysis was performed by the University of Bath Microanalysis Service. Catalytic hydrogenation was performed by use of a Cook low-pressure hydrogenator of 1-L capacity. Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} plates from Merck and visualized at 254 nm.

The 1-alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidine hydrochlorides **3–8** were synthesized using reported methods (Jaffar & Upton 1996). The mp of our sample of the *N*-benzylpiperidine HCl **4** (203–205°C, from absolute ethanol) differed from that reported (Plati & Wenner 1949, 193–194°C) and full analytical data are recorded; δ_H (base, $CDCl_3$) 1·76 (dt, 1H, J 13·5, 3, H-5eq), 2·07 (br tt, 1H, J 2x 13–14,and ax-ax, ax-eq, H-5ax), 2·7 (m, 3H, H-2ax, H-6ax, H-6eq), 2·93 (br dd, 1H, J 14 and < 4, H-2eq), 3·6 (s, 2H, $C_6H_5CH_2$), 4·3 (br d, 1H, J 8, H-3ax), 5·1 (nd, 1H, J 2·4, OH), 7·3 (m, 13H, ArH), 7·8 (d, 2H, J 7, H-2 and H-6 in 3-benzoyl), δ_C (68·7 MHz, $CDCl_3$) 39·6 C-5, 48·9, 52·6 C-2/6, 50·3 C-3, 62·6 $CH_2C_6H_5$, 72·9 C-4, 124–133·8 Ar CH, 135, 148 Ar Cq, 204 3-CO). (Found: C, 73·7; H, 6·43; N, 3·3. $C_{25}H_{25}NO_2$.HCl requires C, 73·6; H, 6·4; N, 3·4%: m/z 371 (M^+, 1%).

3-Benzoyl-1-butyl-4-hydroxy-4-phenylpiperidine hydrochloride ***6***

This compound was prepared in 90% yield in the same manner; mp 184–186°C (from EtOH). δ_H (salt in $CDCl_3$) 1·0 (t, 3H, J 7, CH_3 in butyl), 1·99–3·06 (br m 8H, *N*-substit. and H-5eq,ax), 3·5 (m, 4H, H-2ax,eq, H-6ax,eq) 5·08 (s, 1H, 4OH), 5·72 (dd, 1H J 12·1,4, H-3ax) (Found: C, 70·8; H, 7·5; N, 3·6. $C_{22}H_{27}NO_2$.HCl requires C, 70·7; H, 7·5; N, 3·8%).

*2-Benzyl-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-c]-pyridine HBr* ***10***

3-Benzoyl-1-benzyl-4-hydroxy-4-phenylpiperidine HCl **4** (3·32 g, 0·008 mol) was stirred with hydrobromic acid (48% w/v, 10 mL) for 2 h at room temperature, and then heated under reflux for 2 h. The cooled mixture was diluted with water (50 mL), extracted with chloroform (3 × 50 mL), dried ($MgSO_4$), and evaporated in-vacuo to give a yellow solid which was recrystallized from ethanol to give **10** (2·39 g, 73%) as yellow prisms, mp 196–197°C.

The same procedure was adopted for the synthesis of the dienes **9** and **11–14**; analytical and experimental data are summarized in Tables 1 and 2.

*2-(2,2,2-Trichloroethoxycarbonyl)-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-c]pyridine* ***23***

2-Benzyl-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-*c*]-pyridine HBr **10** (16·64 g, 40 mmol) was made alkaline with ammonia solution and the green mixture was extracted with ether (4 × 50 mL), washed with brine (50 mL), dried, and the ethereal extract was evaporated to give a dark green oil (12·60 g, 94%). The oil (12·60 g, 38 mmol) was dissolved in dry toluene (150 mL) and to this was added 2,2,2-trichloroethyl chloroformate (8·0 g, 38 mmol) dropwise. Stirring was continued for 5 days. The solution was then washed with HCl (6 M, 2 × 50 mL) and water (50 mL), dried, and evaporated in-vacuo to give a yellow solid which was recrystallized from absolute ethanol to give **23** (12·81 g, 80%) as yellow crystals, mp 110–111°C. δ_H ($CDCl_3$): 7·61 (9H, m, Ar-H), 6·82 (1H, dt, H-4a), 4·80 (4H, m, H_2-1, $CO_2CH_2CCl_3$), 4·55 (2H, dd, J_{gem} 15·8 Hz, H_2-3). δ_C ($CDCl_3$): 133·83, 133·66 (2 × Cq), 128·77–122·31 (7 × Ar-CH), 119·94, 119·78 (2 × C-4), 75·22 ($CO_2CH_2CCl_3$), 44·01, 43·07 (3 × CH_2).

*9-Phenyl-2,3-dihydro-1*H*-indeno[2,1-c]pyridine hydrochloride* ***24***

Zinc dust (10·92 g, 170 mmol) was added to the carbamate **23** (9·0 g, 12 mmol) in acetic acid

Table 1. ^{1}H NMR (270MHz) characteristics of 2-alkyl-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-*c*]pyridine hydrobromides and other experimental data.

Compound	R	H_2-1	H_2-3	H_1-4	Ar-H	N-R	Yield (%)	Mp (°C)
9[a]	Ethyl	4·46, br s	4·16, br s	6·63, t 4·0Hz	7·62, m	3·62, q, 7·3 Hz CH_2; 1·40, t, 7·3 Hz	68	194–195
10[b]	Benzyl	3·6–4·1, m	eq 3·52 dd 13·6, < 3Hz ax 3·6–4·1 m	6·2, dd 3·1, 5·0 Hz	7·68, m	3·6–4·1, m CH_2Ph	78	196–197
11	Phenethyl	4·59, br s	4·41, br s	6·57, br s	7·89, m	3·62, m, CH_2CH_2Ph 3·13, m, CH_2CH_2Ph	65	201–202
12[b]	Butyl	eq: 4·56, dd, 1·7, 13·1Hz; ax: 4·30, dd, 1·7, 15·6Hz	eq: 4·40, dt ax: 4·36, dt	6·60, t 3·7, 7·9Hz	7·61, m	3·11, 1·76, 1·31, m 3 × CH_2; 0·86, t, 7·3Hz CH_3	87	198–199
13[b]	Hexyl	eq: 4·60, m ax: 4·80, m	eq: 4·47, dt ax: 4·32, dt	6·62, t	7·65, m	3·12, 2·04, m, 5 × CH_2; 0·83, t, CH_3	84	196–197
14[b]	Cyclohexyl	4·4, m	eq 4·3, dt 18, 3·7Hz, ax 4·16 dt, 18, 4Hz	6·65, t 3·2Hz	7·4, m	3·18, m, NCH; 1·15–2·19, m, 5 × CH_2	61	218–219

[a]Deuterated salts unless otherwise stated. The NH proton resonates typically between 11·6 and 13ppm. [b]The non-deuterated HBr salts are included to illustrate their complexity.

Table 2. ^{13}C NMR chemical shifts of 2-alkyl-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-*c*]pyridine hydrobromides.

Compound	C-1	C-3	C-4	C-4a	C-9	C-9a	Ar-C[a]	N-R
9	47·81	49·01	115·47	120·89	133·11	131·91	129·03–120·66 (6) 142·45–139·24 (3)	48·55, CH_2; 10·05, CH_3
10	47·00	48·91	114·88	120·30	133·18	131·82	131·01–120·72 (8) 143·14–139·37 (3)	55·89, CH_2Ph
11	49·33	49·82	120·23	124·55	133·31	131·33	129·22–121·14 (9) 141·87–136·94 (4)	56·14, CH_2CH_2Ph 29·81, CH_2CH_2Ph
12	48·59	49·43	115·14	120·56	133·05	131·85	128·99–120·69 (4) 142·65–139·18 (3)	53·32, 26·43, 19·85 3 × CH_2; 13·36, CH_3
13	48·46	49·50	115·08	120·46	133·05	131·83	129·01–120·72 (4) 142·59–139·20 (3)	53·42, 30·81, 26·12, 24·49, 22·09 5 × CH_2; 13·65 CH_3
14	46·06	46·80	115·73	121·31	133·08	131·91	129·06–120·72 (6) 142·55–139·92 (4)	61·98, NCH; 28·32, 27·93, 24·81, 24·29 4 × CH_2

All compounds had a satisfactory elemental analysis, ±0·4% of theoretical values, except **11** for which EIMS showed m/z 349 (24%, M^+), 258 (100%, M − 91), HRMS EI $C_{26}H_{23}N$ Found 349·1818 (M^+ calc. 349·1831). [a]The figure in parentheses indicates the number of signals seen.

(150mL) at 0°C. The reaction was stirred at room temperature for 2h, heated under reflux for 2h, cooled to room temperature and stirred for 16h. The zinc was removed by filtration and the solvent removed. Water (50mL) and ammonia solution (50mL, pH > 10) were added and the aqueous solution was extracted with ether (4 × 75mL). The ethereal extract was washed with brine (2 × 50mL), dried, and concentrated in-vacuo to a small volume. Ethereal HCl was then added in portions to precipitate the solid, which was recrystallized from ethanol–ether to give **24** (2·90g, 49%), mp 222–223°C. (Found: C, 72·5; H, 5·58; N, 4·64. $C_{18}H_{16}ClN.H_2O$ requires C, 72·1; H, 6·01; N, 4·67%). δ_H (DMSO-d_6): 9·92 (2H, s, NH_2), 7·86 (9H, m, Ar-H), 7·11 (1H, t, J 4·0, H-4), 4·40 (2H, s, H_2-1), 4·15 (2H, d, J 4·0, H_2-3). δ_C (DMSO-d_6): 141·67–137·55 (3 × Ar-Cq), 129·12–120·85 (6 × Ar-CH), 133·60 (C-9), 132·62 (C-9a), 124·68 (C-4a), 119·94 (C-4), 41·61, 40·51 (C-1, C-3).

The dienes were hydrogenated as described below; experimental and analytical data are given in Table 3.

2-Phenethyl-9-phenyl-2,3,4,4a-tetrahydro-1H-indeno[2,1-c]pyridine hydrobromide **17**

A solution of 2-phenethyl-9-phenyl-2,3-dihydro-1*H*-indeno[2,1-*c*]pyridine hydrobromide **11** (4·30g, 0·01mol) in ethanol (250mL) was hydrogenated over palladium (0·4g, 10% on activated charcoal), at a pressure of 100psig for 6h at room temperature. The catalyst was removed by filtration through celite and the residual ethanolic solution was concentrated in-vacuo. The product was recrystallized from ethanol–ether to give **17** (2·98g, 69%) as a colourless solid, mp 122–123°C.

Table 3. ^{13}C NMR chemical shifts of 2-alkyl-9-phenyl-2,3,4,4a- and 2,3,4,9-tetrahydro-1*H*-indeno[2,1-*c*]pyridines.

Compound	R	CH (non-Ar)	CH_2	Ar-CH	Ar-Cq	N-R	Yield (%)	Mp (°C)
15	Ethyl	45·67	50·83, 27·05	120·36–128·83 (6)	132·27–145·50 (4 signals)	9·02, CH_3 49·85, CH_2	66	182–184
16[a]	Benzyl	45·90	49·85, 49·59 47·78, 35·42 29·09	123·58–133·11[b] (9 signals)	134·41–143·27[b] (3 signals)	56·89, 56·05 2 × CH_2	67	185–187
17[a]	Phenethyl	45·82	50·79, 50·60 36·38	119·06–128·98[b] (6 pairs)	132·43–145·72[b] (6 signals)	56·47, 55·79 2 × CH_2	69	122–123
18	Butyl	45·90, 55·85	65·55, 49·90 47·48, 47·16 46·90, 46·38	118·68–128·96 (16 signals)	131·04–145·41 (10 signals)	69·05, 59·49, 2 × NCH 27·02–19·20, 6 × CH_2 15·02–8·11, 6 × CH_3		
19	Cyclohexyl	45·93, 55·21	47·10, 46·84 26·69, 26·11 25·92, 25·52 24·65, 24·49	120·17–128·83 (8 signals)	132·53–145·50 (5 signals)	64·25, NCH		
20	Hexyl	55·17	54·87, 49·33 30·68	119·00–128·93 (8 signals)	134·83–147·80 (5 signals)	48·64–19·56 5 × CH_2; 13·85, CH_3	78	176–177
21[a]	Benzyl	55·85, 56·05	48·81, 48·33 47·68, 47·10 18·75, 18·39	118·68–131·01[b] (6 pairs)	128·25–147·51[b] (6 pairs)	57·31, 57·07 2 × CH_2Ph	92	188–189
22[a]	Phenethyl	54·72, 55·14	49·07, 48·88 48·49, 47·91 29·48, 29·32	118·81–128·80[b] (7 pairs)	134·57–147·74[b] (5 pairs)	55·59, 55·50 2 × CH_2CH_2Ph	89	140–141

[a]Spectrum contains some duplication of signals owing to epimeric pairs. [b]Includes signals from *N*-R. Elemental (CHN) analysis was satisfactory for compounds **15–17** and **20–22**.

*2-Benzyl-9-phenyl-2,3,4,4a- **16** and 2,3,4,9-tetrahydro-1*H*-indeno[2,1-c]pyridine **21***

Palladium catalyst (10mg, 5% Pd on C) was added to a solution of 2-benzyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-*c*]pyridine **16** (50mg) in absolute ethanol (10mL) and stirred for 3 weeks at room temperature. The catalyst and then solvent were removed and the product shown to be a mixture of the title enes by ^{13}C NMR.

Results and Discussion

The piperidines **3–8** were used to prepare the novel 2,3-dihydroindenopyridines **9–14** as outlined in Figure 2; the analytical data for **9–14** are presented in Tables 1 and 2. Three novel piperidines (**4**, **6** and **7**) were prepared for this work and their conformational disposition determined from their proton NMR spectra; the *N*-benzylpiperidine **4** is discussed in detail.

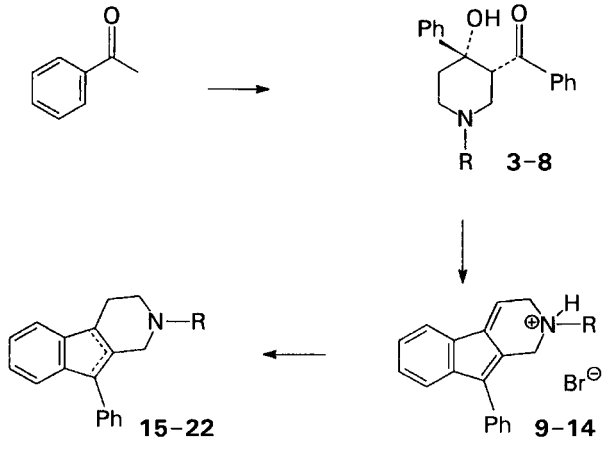

Figure 2. Preparation of the 2,3-dihydroindenopyridines **9–14** from piperidines **3–8**.

The purified base from the reaction was examined in $CDCl_3$. The most shielded protons, at C-5, resonated at δ 1·76 (5-H_{eq}) and 2·01 (5-H_{ax}) respectively; the 5-H_{eq} signal was a geminally-coupled doublet of triplets (J 13·8, 2·6) whereas the axial proton appeared as a broadened triplet of doublets with J of about 13Hz (gem and ax/ax with 6-H_{ax}) and J ~3Hz for ax/eq (at 6-H_{eq}). These assignments run contrary to the expected behaviour in six-membered rings where equatorial protons normally appear at lower field than their axial neighbours (Casy et al 1989; Upton & Jaffar 1996). This atypical feature is maintained in the salts of these bases. A multiplet centred on δ 2·85 integrated for the 6-H_{ax}, 6-H_{eq} and 2-H_{ax}, whereas the 2-H_{eq} appeared as a doublet of doublets (J 13·5, 3·5; gem and eq/ax with 3H_{ax}). The *N*-benzyl methylene resonated as a geminally coupled doublet (J 15)-evidence of a diastereotopic environment. The 3-H_{ax}, the most deshielded of the aliphatic protons, appeared as a doublet of doublets (J 12·1, 4·1); this ax/ax coupling was seen for all the piperidines prepared and confirmed this configuration at 3-C. The reaction produced only one diastereoisomer, as evidenced by the very broad absorption of the 4-OH group in the infra-red spectrum; this occurred because of intramolecular hydrogen-bonding with

the 3-benzoyl substituent and could only happen if the 4-OH was in an axial position. Further evidence of this conformation was provided by the coupling of the 4-OH to the 5-H_{ax} (J 2·3), which arises from the restricted rotation of this OH as a result of the 3-benzoyl group and so enables the formation of a near-planar W-pathway to 5-H_{ax} (Sternhell 1969). Finally, these assignments were confirmed by a two dimensional correlation spectroscopy (COSY) ^1H-^1H spectrum. The spectrum of the hydrochloride salt of **4** was similar to that of the base but with general deshielding of most signals because of the quaternary nitrogen, coupling of 2- and 6-H with the protonated nitrogen and the loss of the long-range coupling in the hydroxyl group.

N-Debenzylation (Abdel-Monem & Portoghese 1972; Rozwadowska et al 1980) of the *N*-benzyl-2,3-dihydroindenopyridine **10** with 2,2,2-trichloroethyl chloroformate via its trichloroethyl carbamate **23** with Zn in acetic acid gave the required secondary amine **24** (Figure 3). Debenzylation of the diene was also achieved catalytically (70°C, 100psig with Pd for 6h or Pt for 2h) but this was accompanied by concomitant reduction of the diene to the *cis*-2,3,4,4a,9,9a-hexahydroindenopyridine. *N*-Alkylation of the secondary amine was effected with the appropriate alkyl bromide in acetonitrile.

The outcome of the reduction of the dienes described by Plati & Wenner (1949) was affected by the anion used to isolate the proton salts, but not in a predictable way. We have sought to rationalize this outcome by examining the reduction of a series of novel dienes. The results of a series of reductions of the various dienes are summarized in Table 3 and represent the generalized outcome for these compounds when hydrogenated for different times. When hydrogenated for 6h the major products were the 9,9a-enes. These appeared within the first

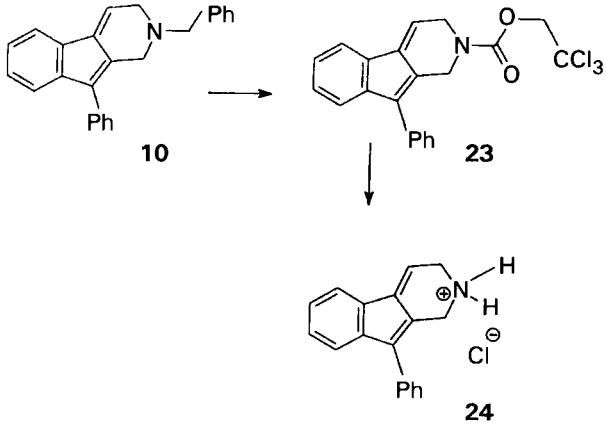

Figure 3. The preparation of the secondary amine **24**.

20min of the reduction. This 1,2-addition represents the kinetic outcome of this reaction, reflecting the ease with which the 4,4a-ene is reduced, because of its accessibility to the catalyst; it is preferred to the sterically less favourable 1,4-addition, which would lead directly to the thermodynamic product, the 4a,9a-ene. An alternative 1,2-addition to the 9,9a-ene in the diene, leading directly to the 4a,9a-ene, was never observed. Increasing the reaction time led to complete loss of starting material by 3h and the 9,9a-enes were isolable in good yield after 6h. During the next 10h a second major component was produced; this was shown to be the 4a,9a-ene. Products isolated at this stage had the characteristics of both enes; the representative ^{13}C data given in Table 3 illustrate this. When the hydrogenation was extended to more than 48h the product isolated was the pure 4a,9a-ene; this represents the thermodynamic outcome for the reaction.

The behaviour of 2-methyl-9-phenyl-2,3,4,9-tetrahydro-1*H*-indeno[2,1-*c*]pyridine hydrobromide, reported by Plati & Wenner (1955) to isomerize with the formation of different salts, was apparent in these analogues also. For example, when the *N*-phenethyl hydrobromide **17** (9,9a-ene) was converted to its hydrochloride, the 4a,9a-ene was obtained. With the *N*-ethyl 9,9a-ene HBr **15**, a mixture of the two enes was afforded and these co-crystallized on repeated recrystallization, in a similar way to that described for the salicylate salt (Branch et al 1987).

Pd-C-catalysed reductions

These results indicate that the reduction products of the dienes are susceptible to isomerization by the palladium catalyst via metal-alkyl or metal-allyl intermediates (Becconsall et al 1967; Cruikshank & Davies 1973). The hydrogen required for the isomerization process can either be from the hydrogen in the hydrogenation environment or abstracted from the substrate. That it originates from the substrate is supported by the observation that a solution of 2-benzyl-9-phenyl-2,3,4,4a-tetrahydro-1*H*-indeno[2,1-*c*]pyridine **16** in ethanol was isomerized to a mixture of the 2,3,4,4a- and 2,3,4,9-indenopyridines in the presence of palladium. The initial outcome of the reduction represents the kinetic product which slowly gives its thermodynamic counterpart.

Base-catalysed isomerization

When the 9,9a-enes were made alkaline with ammonia and subsequently re-acidified to give the salts, the result was either a mixture of the two enes (4a,9a- and 9,9a-) or the 4a,9a-ene alone. These

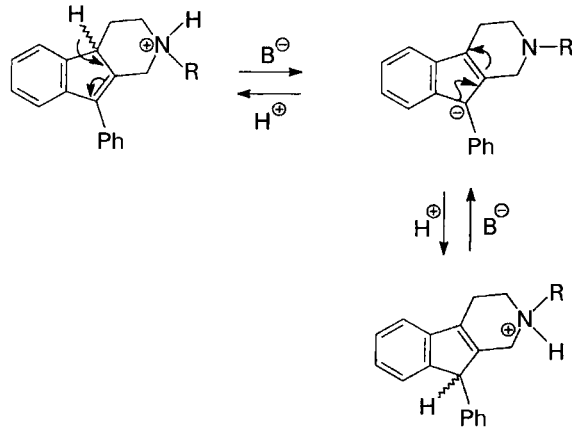

Figure 4. Base-catalysed isomerization of the 9,9a-enes by Michael-type addition.

results indicate that isomerization of the indene double bond had taken place via a Michael-type addition process (Figure 4). The proton at C-4a was abstracted by the base, leading to the formation of a carbanion at C-9, mesomerically stabilized at C-4a by an energetically less favourable, and so less predominant, carbanion. The stabilized anion at C-9 was then reprotonated at this position to give the 4a,9a- isomer.

^1H and ^{13}C NMR studies

The features of the NMR spectra of the dienes **9**–**14** are listed in Tables 1 and 2. The hydrobromide salts used to isolate these products showed much conformational preference when examined in $CDCl_3$.

The ^{13}C spectrum of the *N*-benzyl diene **10** is described. The three up-field signals (47·0, 48·91 and 55·89 ppm) are assigned to the two endocyclic and benzylic methylene groups, respectively. The alkenic C-4 resonates at 114·88 ppm and in the aromatic region of the spectrum the seven quaternary carbons are clearly identified in the 135 DEPT (distortionless enhancement by polarization transfer) spectrum. In the proton spectrum the chiral, protonated nitrogen caused the pseudo-axial and pseudo-equatorial protons at C-1 and C-3 to appear as geminally-coupled doublets, each of which in turn showed fine coupling to the protonated nitrogen. The rate of deprotonation and reprotonation is sufficiently slow for this to occur and this effect is abolished on deuteration of the sample, when these two sets of protons appear as broadened singlets (Table 2; compounds **9** and **11**). This behaviour is common to all dienes examined in this work.

The outcome of the catalytic reductions used to obtain the tetrahydroindenopyridines were monitored by observation of the resonance signals of the methine at position C-4a or C-9 (in the appropriate isomer) assigned from the proton-coupled ^{13}C spectrum (Branch et al 1987). Compounds isolated after a short hydrogenation time (e.g. the *N*-ethyl-9,9a-ene **15**, Table 3) gave a single set of signals readily assigned to the 9,9a-ene structure (and confirmed by the most up-field aliphatic signal at 45·67 ppm) but spectra of others, **16** and **17**, contained a duplication of many signals which did not differ markedly from one another in their chemical shifts. This is ascribed to the presence of significant proportions of the two epimeric species and not a mixture of two geometric alkenes. Two examples of mixtures of geometric isomers are presented in Table 3 for **18** and **19**, isolated after 16 h hydrogenation. Here, two up-field signals are present at 45·9 and 55·2 ppm indicating that a mixture of both 9,9a- and 4a,9a-enes is present. Reaction products which contain only the 4a,9a-ene (e.g. *N*-hexyl **20**, isolated after 48 h) give a single high-field signal at 55·17 ppm, although evidence of epimeric mixtures in these enes is evident in the spectrum of the *N*-benzyl-4a,9a-ene **21** and *N*-phenythethyl-4a,9a-ene **22**, where duplication of some signals is again present. Complete assignment of the ^1H spectra of these enes was hampered by the multiplicity of overlapping epimeric signals but the 4a,9a- and 9,9a-enes could be identified by the resonances of the H-9 (δ 4·4–4·6, br s) or H-4ax (δ 1·3–1·8, dq); (where epimerization was apparent, the H-9 signal appeared as two br s and the H-4ax as overlapping dq or m). For example, the spectrum of the *N*-phenethyl-4a,9a-ene **22** indicated the loss of the signal from the vinyl proton of the starting material (δ 6·6), lacked the characteristic doublet of quartets for the H-4ax of the 9,9a-ene at δ 1-2 and showed a pair of broadened singlets associated with the epimeric H-9 (δ 4·62). Further evidence of epimeric products was seen as two broadened singlets for the *N*-H which disappeared on deuteration.

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