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TRANSFORMATION OF QUININE INTO THE INDOLE ALKALOIDS—III

CONFIGURATION AT $C^{4'}$ OF NORMAL AND ALLOHEXAHYDROQUININE

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Abstract—The configurations at $C_{4'}$ of normal and allo hexahydroquinine (IIIa and IIIb) obtained by catalytic hydrogenation of dihydroquinine (II) were proven to be α and β, respectively.

ALTHOUGH a considerable number of reports[1-6] on the reduction of the quinoline moiety of cinchona alkaloids have been published, the structures of the hydrogenated products have remained unsolved. Skita reported that the reduction of quinine (I) with sodium and amyl alcohol gave a hexahydroquinine, m.p. 271–273° (hydrochloride), $[\alpha]_D$ −36·5°[5] and the reduction of quinine sulfate with colloidal platinum in diluted hydrochloric acid gave another hexahydroquinine, m.p. 94°, $[\alpha]_D$ −23°.[6] The former product was considered to be a *trans* isomer and the latter product was considered to be a *cis* isomer judging from Auer's rule.[5] But this assignment is not considered significant nowadays.

Recently, Ochiai *et al.*[7] reexamined the catalytic hydrogenation of dihydroquinine (II) in acetic acid and obtained two isomers of hexahydroquinine, one, m.p. 80–81° and the other, m.p. 272–273° (hydrochloride), $[\alpha]_D$ −36°. The latter product was considered to be the same compound as Skita's *trans* isomer, the reduction product in the alkali medium. These two isomers were proven[7] to be identical with normal and allo-hexahydroquinine (IIIa and IIIb)* respectively, prepared by LAH reduction of the corresponding 2'-oxo-hexahydroquinine derivatives (IVa and IVb).[8]

Thus, it was made clear that the catalytic hydrogenation of dihydroquinine (II) gave two isomers at $C_{4'}$ of hexahydroquinine (IIIa and IIIb) regardless of the character of the medium.

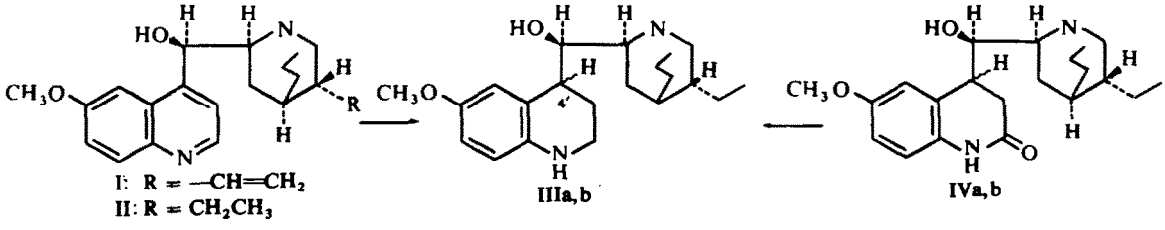
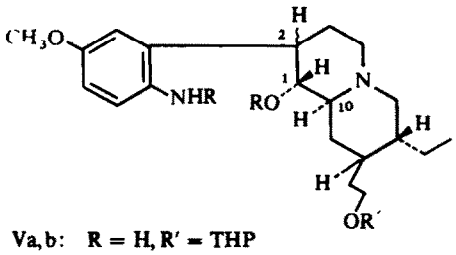


FIG 1.

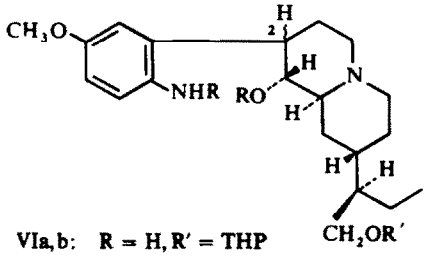
* The compounds of the normal and allo series are denoted by (a) and (b) respectively, throughout this paper.

In this paper we wish to report on the configuration at $C_{4'}$ of normal and allo-hexahydroquinine.

The quinolizidine derivatives (Va, b and VIa, b)[10–11] were used for this purpose since the three adjacent asymmetric centers, *i.e.*, C_2, C_1 and C_{10} corresponding to $C_{4'}$, C_9 and C_8 in the flexible systems (IIIa, b and IVa, b) were fixed in a ring system and hence this problem could be elucidated without difficulty. In the IR spectra the



Va, b: R = H, R′ = THP
VIIa, b: R = COϕ, R′ = H
IXb: R = COϕ, R′ = THP

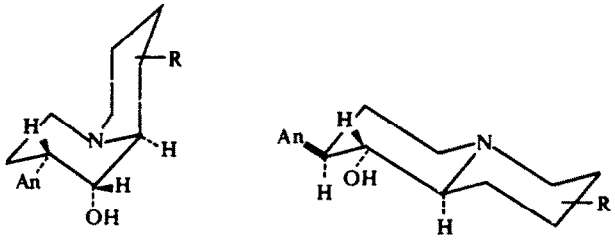


VIa, b: R = H, R′ = THP
VIIIa, b: R = COϕ, R′ = H
Xa, b. R = $COCH_3$, R′ = H

THP = Tetrahydropyranyl group

FIG 2.

alloquinolizidines (Vb and VIb) derived from IVb show Bohlmann bands,[12] whereas the normal quinolizidines (Va and VIa) derived from IVa do not show these bands. The former compounds must have a *trans* quinolizidine system and the latter compounds must be *cis* fused. When the bulky anisidyl groups (An) at C_2 exist in the more stable equatorial orientation, the quinolizidine derivatives will be shown by the following structures. It is expected from the Karplus equation[13] that the C_1-protons



normal quinolizidines allo quinolizidines

FIG 3.

of the normal quinolizidines (Va and VIa) will show narrow triplet signals (J = 4–5 c/s) and those of the alloquinolizidines (Vb and VIb) will show broad triplet signals (J = 10 c/s). The signals of the C_1-protons of quinolizidine derivatives (Va, b and VIa, b) could not be distinguished from the other methylene proton signals, while in the corresponding O,N-diacyl derivatives (VIIa, b–IXa, b) these signals were observed in the expected patterns in the 4·5–5·1 τ region (Table 1).

The above results revealed the configuration at C_2 of the quinolizidine derivatives. Hence normal hexahydroquinine (IIIa) and 2′-oxohexahydroquinine (IVa) must have α-hydrogens and allohexahydroquinine (IIIb) and 2′-oxo-hexahydroquinine (IVb) must have β-hydrogens at $C_{4'}$.

TABLE 1. THE C_1-PROTON SIGNALS AND THE BOHLMANN BANDS OF THE QUINOLIZIDINE DERIVATIVES

Compounds	Series	C_1-Proton (τ)	Bohlmann bands (cm^{-1})
Va	normal	———[a]	absent
VIa	normal	———[a]	absent
VIIa	normal	4·78 (t. J = 4 c/s)	absent
VIIIa	normal	4·73 (t. J = 5 c/s)	absent
Xa	normal	5·10 (t. J = 4 c/s)	absent
Vb	allo	———[a]	2788, 2822
VIb	allo	———[a]	2768, 2813
VIIb	allo	4·80 (t. J = 10 c/s)	2765, 2810, 2835
VIIIb	allo	4·55 (t. J = 10 c/s)	2771, 2816, 2836
IXb	allo	4·78 (t. J = 10 c/s)	2759, 2814
Xb	allo	4·97 (t. J = 10 c/s)	2766, 2816

[a] This proton signal could not be distinguished from the other methylene proton signals.

NMR spectra were measured in $CDCl_3$ solution on a Varian A-60 spectrometer. The chemical shifts are expressed as τ units, and are referred to TMS as the internal reference.

IR spectra were obtained in $CHCl_3$ with the Nihon Bunko DS-201 spectrometer.

EXPERIMENTAL*

Quinolizidine derivatives (Va, b *and* VIa, b). Preparation of these compounds have been reported in previous papers.[10–11]

Normal O,N-*Dibenzoylquinolizidine* (VIIa). To a well stirred soln of normal quinolizidine (Va) (370 mg) in $CHCl_3$ (10 ml) was added a soln of KOH (300 mg) in water (3 ml) and then benzoylchloride (300 mg) at room temp. After stirring for 2·5 h, the $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent was removed to give an oily residue. The residue was dissolved in MeOH (5 ml), acidified with 10% HCl and the solvent removed. After washing with Et_2O, the residue was made basic with NH_4OH aq under ice-cooling and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent removed under reduced pressure. The residue (500 mg) was dissolved in MeOH and treated with a soln of ammonium thiocyanate in water. The separated crystals (290 mg, 69%), m.p. 280–281° (dec), were collected and recrystallized from MeOH—$CHCl_3$ to give needles (200 mg), m.p. 284–285° (dec); IR ν_{max}^{Nujol} cm^{-1}: 3580 (OH), 3340 (NH), 1725 (—OCOφ), 1665 (NHCOφ). (Found: C, 67·96; H, 6·72; N, 6·74; S, 5·28. $C_{35}H_{41}O_5N_3S$ requires: C, 68·26; H, 6·71; N, 6·83; S, 5·21%). The free base was an amorphous powder $[\alpha]_D^{23}$ +166·5° (c, 2·029, EtOH); UV λ_{max} mμ (log ε): 230 (4·49), 270 (sh) (3·87); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3418 (NH), 1709 (OCOφ), 1670 (NHCOφ).

allo-O,N-*Dibenzoylquinolizidine* (IXb). A soln of alloquinolizidine (Vb) (385 mg) and benzoyl chloride (150 mg) in pyridine (5 ml) was allowed to stand overnight under ice-cooling. The reaction mixture was poured into ice-cooled NH_4OH aq and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent removed under reduced pressure. The residue was crystallized from EtOAc:n-hexane (1:1) to give IXb (500 mg, 87·5%), m.p. 150°. Recrystallization from EtOAc:n-hexane gave prisms (480 mg, 84·5%), m.p. 152°, $[\alpha]_D^{24}$ −10·0° (c, 1·015, EtOH); UV λ_{max} mμ (log ε): 228 (4·46), 259–272 (sh) (3·85); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3430 (NH), 2814, 2759 (*trans* quinolizidine), 1727 (OCOφ), 1670 (NHCOφ). (Found: C, 72·90; H, 7·45; N, 4·37. $C_{39}H_{48}O_6N_2$ requires: C, 73·10; H, 7·55; N, 4·37%).

allo-O,N-*Dibenzoylquinolizidine* (VIIb). A soln of IXb (340 mg) in MeOH (5 ml) was acidified with 10% HCl (3 ml) and the solvent removed. After washing with Et_2O, the residue was made basic with NH_4OH aq and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent removed. The residue was crystallized from EtOAc as needles (223 mg, 78%), m.p. 192–193°, $[\alpha]_D^{24}$ −25·5° (c, 2·028, EtOH); UV λ_{max} mμ (log ε): 228 (4·45), 259–272 (sh) (3·85); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3615 (OH), 3420 (NH), 2835, 2810, 2765 (*trans*-quinolizidine), 1728 (OCOφ), 1670 (NHCOφ). (Found: C, 73·45; H, 7·21; N, 4·86. $C_{34}H_{40}O_5N_2$ requires: C, 73·35; H, 7·24; N, 5·03%).

normal O,N-*Dibenzoyl quinolizidine* (VIIIa). Treatment of a soln of VIa[10] (433 mg) in $CHCl_3$ (5 ml) with

* All m.ps. are uncorrected. UV spectra were measured in EtOH.

benzoylchloride (480 mg) as described in the case of VIIa gave an amorphous powder (570 mg), which was dissolved in EtOAc and treated with a soln of ammonium thiocyanate in water. The separated crystals (520 mg), m.p. 236–237° (dec), were recrystallized from EtOH to give needles (460 mg, 74·7%), m.p. 236–237° (dec). (Found: C, 68·25; H, 6·74; N, 6·71; S, 5·41. $C_{35}H_{41}O_5N_3S$ requires: C, 68·26; H, 6·71; N, 6·83; S, 5·21%). The free base was an amorphous powder, $[\alpha]_D^{24}$ +140·3° (*c*, 1·957, EtOH) UV λ_{max} mμ (log ε): 229 (4·46), 273 (sh) (3·83); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3410 (NH), 1704 (OCOϕ), 1668 (NHCOϕ).

allo-O,N-*Dibenzoyl quinolizidine* (VIIIb). Treatment of a soln of VIb[10] (433 mg) in pyridine (5 ml) with benzoylchloride (420 mg) in the same way as described in the case of IXb and VIIb gave a reddish-brown amorphous powder (560 mg) which was dissolved in MeOH (10 ml) and treated with picric acid. The separated crystals (610 mg, 77%), m.p. 241–242° (dec), were recrystallized from MeOH to give yellow needles, m.p. 241–242° (dec). (Found: C, 59·99; H, 5·62; N, 8·46; H_2O, 1·20. $C_{40}H_{43}O_{12}N_5H_2O$ requires: C, 59·77; H, 5·64; N, 8·71; H_2O, 2·24%). The free base was an amorphous powder, UV λ_{max} mμ (log ε): 228 (4·45), 270 (sh) (3·85); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3621 (OH), 3416 (NH), 2836, 2816, 2771, (*trans*-quinolizidine), 1725 (OCOϕ), 1672 (NHCOϕ).

normal O-N-*Diacetyl quinolizidine* (Xa). To a well stirred soln of VIa[10] (433 mg) in $CHCl_3$ (10 ml) was added 10% K_2CO_3 (10 ml) and then a solution of acetylchloride (620 mg) in $CHCl_3$ (2 ml) under ice-cooling. Stirring was continued for 30 min. The $CHCl_3$ layer was washed with K_2CO_3 aq, dried over K_2CO_3 and the solvent removed. The residue was treated as described for the preparation of VIIb to yield an amorphous powder (356 mg) which was recrystallized from $CHCl_3$—EtOAc to give needles (225 mg, 52%), m.p. 212–213°, $[\alpha]_D^{24}$ +31·0° (*c*, 1·042, EtOH); UV λ_{max} mμ (log ε): 228·5 (4·00), 276 (3·34), 280 (sh) (3·30), λ_{min} mμ (log ε): 264·5 (3·25); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3410 (NH), 1704 ($OCOCH_3$), 1668 ($NHCOCH_3$). (Found: C, 66·90; H, 8·47; N, 6·48. $C_{24}H_{36}O_5N_2$ requires: C, 66·64; H, 8·39; N, 6·48%).

allo-O,N-*Diacetyl quinolizidine* (Xb). Treatment of a soln of VIb[10] (433 mg) in pyridine (5 ml) with acetic anhydride (404 mg) as described for the preparation of IXb and VIIb gave an amorphous powder (430 mg), which was purified by chromatography on alumina (6·0 g) developing with benzene to give Xb as an amorphous powder (300 mg, 69·5%), $[\alpha]_D^{24}$ +45·9° (*c*, 1·148, EtOH); UV λ_{max} mμ (log ε): 229·5 (3·94), 276–278 (3·29), 281·5 (3·29). λ_{max} mμ (log ε): 266 (3·19), 279·5 (3·28); IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 3615 (OH), 3416, 3366 (NH), 2816, 2766 (*trans*-quinolizidine), 1736 ($OCOCH_3$), 1678 ($NHCOCH_3$). (Found: C, 65·29; H, 8·60; N, 6·21. $C_{24}H_{36}O_5N_2 \cdot 1/2\ H_2O$ requires: C, 65·28; H, 8·45; N, 6·34%).

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