Tetrahedron. Vol. 26, pp. 2923 to 2929. Pergamon Press 1970. Printed in Great Britain

TRANSFORMATION OF QUININE INTO THE INDOLE ALKALOIDS—IV

CONFIGURATION AT C_8 OF CINCHONAMINE

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(*Received in Japan* 25 *September* 1969; *Received in the UK for publication* 24 *February* 1970)

Abstract—Dihydrocinchonamine (IV) was synthesized from quinine (II) and the configuration at C_8 which heretofore had been ambiguous was clarified.

CINCHONAMINE, one of the minor cinchona alkaloids, was shown to have the structure I by Prelog *et al.*,[1] who considered that this alkaloid and cinchonine (II) could be biogenetically synthesized from the same precursor. Ochiai *et al.*[2,3] carried out the conversion of cinchonine (II) and cinchonidine (III) into dihydrocinchonamine (IV) showing the relationship between these alkaloids and further established the stereochemistry at C_3 and C_4 of cinchonamine (I). However, no definite conclusion could be reached concerning the stereochemistry at C_8 of cinchonamine because cinchonine (II) and cinchonidine (III) gave the same dihydrocinchonamine (IV). In this connection, Wenkert and Bringi[4] have successfully converted dihydrocinchonamine (IV) and dihydrocorynantheol (V), which has an α-hydrogen at C_3 in the molecule, into the

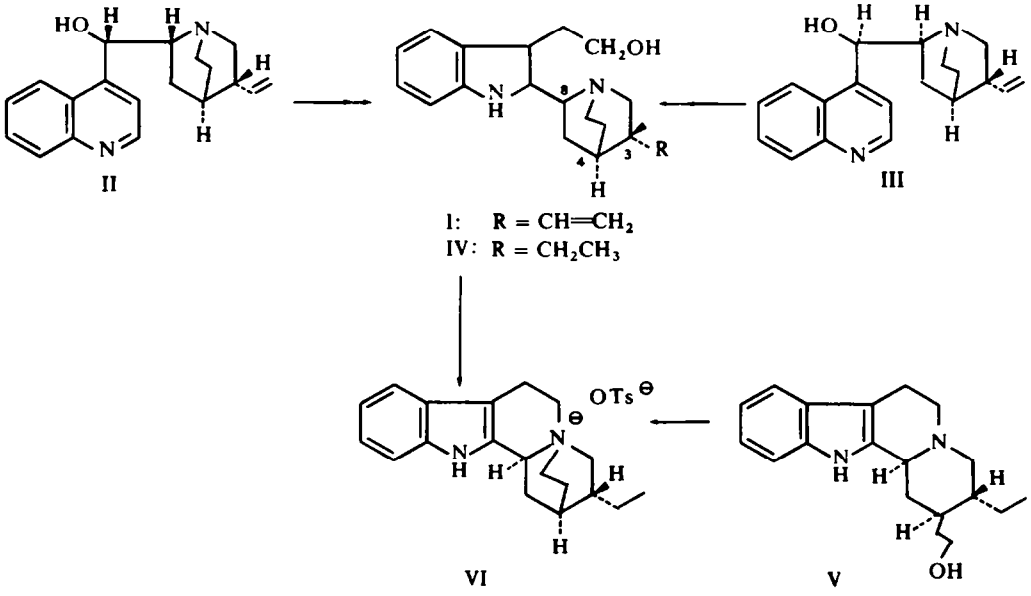

FIG 1

same quaternary tosylate (VI) and assigned the α-configuration to the C_8-hydrogen of cinchonamine (I). Later, Augustine[5] gave the β-configuration to this hydrogen after investigating the molecular rotation, pointing out that during or after the formation of the quaternary tosylate, the hydrogen at C_8 of dihydrocinchonamine must reverse to the more stable α-configuration presumably through the influence of a positive charge on the nitrogen. Thus, the configuration at C_8 remains unsolved.

During the reexamination of the synthesis of 5'-methoxydihydrocinchonamine (XIIIa) according to Ochiai *et al.*,[3,6] we had an opportunity to solve this problem.

The starting material, 2'-oxo-hexahydroquininone (IX), had been prepared from normal and *allo*-2'-oxo-hexahydroquinine (VIIa, b) by modified Oppenauer oxidation.[7] This compound was also obtained from normal and *allo*-2'-oxo-hexahydroquinidine (VIIIa, b). This showed that not only epimerization at C_4, but also that at C_8 had occurred. Treatment of the oxo-compound (IX) with ethanolic hydrochloric acid gave two isomeric indole esters, Xa, m.p. 140–141° and Xb, m.p. 247° (dec) (perchlorate) and two isomeric indole carboxylic acids, XIa, m.p. 195–196°, and XIb, m.p. 200°. Of these four compounds, the indole ester (Xa) has already been reported by Ochiai *et al.*, but the others were newly isolated from this reaction mixture.

It is evident that the indole esters (Xa, b) are the C_8-epimers because the CD curves of these compounds showed opposite Cotton effects and the acid catalyzed epimerization of each isomer gave a mixture of these two isomers in about equal amount. Saponification of the indole esters (Xa, b) gave the respective indole carboxylic acids (XIa, b), and the esterification of the indole carboxylic acids (XIa, b) gave the respective indole esters (Xa, b). Reduction of the indole esters (Xa, b) with LAH gave the corresponding indole alcohols, XIIIa, m.p. 180–181°, $[\alpha]_D$ +143·4°, and XIIIb, m.p. 148–149°, $[\alpha]_D$ −16·5°, the former of which was identical with 5'-methoxydihydrocinchonamine reported by Ochiai *et al.*[3,6] in every respect. When the indole alcohols (XIIIa, b) were subjected to the quaternization reaction by the action of tosylchloride, the corresponding quaternary tosylates, XIVa, m.p. 315–316° (dec) and XIVb, an amorphous powder, were obtained in good yields. The latter was characterized as the quaternary picrate, m.p. 221–222° (dec). This showed that the quaternization reaction caused no epimerization at C_8 of the indole alcohols (XIIIa, b), whereas the configuration at C_8 of the indole alcohols was convertible on treatment with acid to give a mixture of these two compounds. In the same quaternization reaction, 10-methoxydihydrocorynantheol (XVa) (C_3—H α) gave the quaternary tosylate (XIVa) and 3-epi-10-methoxydihydrocorynantheol (XVb) (C_3—H β) gave XIVb.

These results revealed that the hydrogen at C_8 had the α-configuration in the case of the indole derivatives, Xa–XIVa and the β-configuration in the case of the indole derivatives, Xb–XIVb. Furthermore, the experimental results of the quaternization reaction proved clearly that the hydrogen at C_8 of cinchonamine (I) must be represented by the α-configuration as assigned by Wenkert *et al.*[4] These results were further confirmed by conversion of 5'-methoxydihydrocinchonamine (XIIIa) into dihydrocinchonamine (IV). Demethylation of the indole alcohol (XIIIa) by the action of BBr_3 gave the phenolic compound, XVI, m.p. 133–134°, in good yield. Elimination of the phenolic hydroxyl group of XVI was successfully achieved by the Ullmann reaction with 1-phenyl-5-chlorotetrazole followed by hydrogenolysis with Pd—C to yield dihydrocinchonamine (IV), m.p. 163–164°, $[\alpha]_D^{25}$ +109·7°, which was identical with

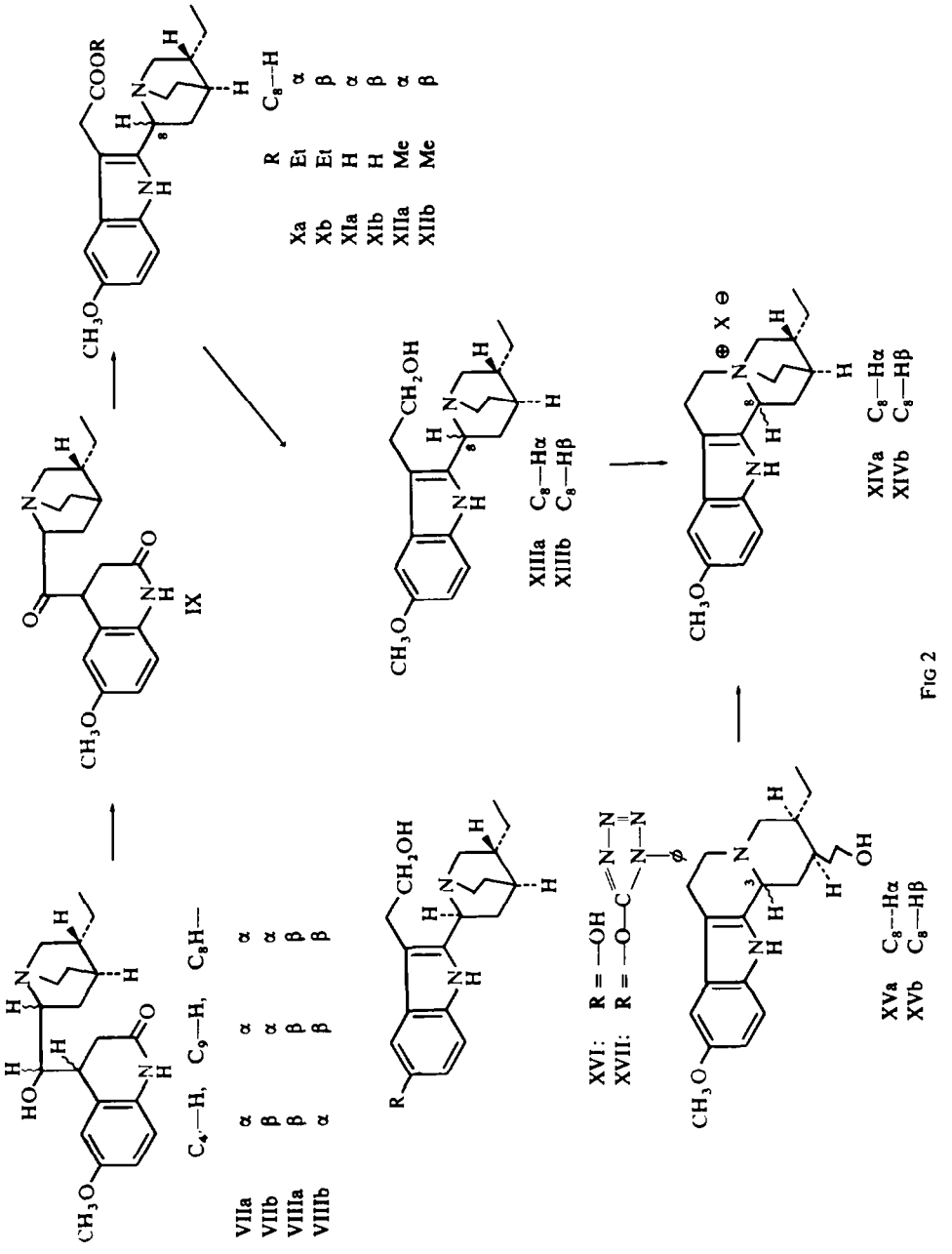
VIIa α α α
VIIb β α α
VIIIa β β β
VIIIb α β β
IX
Xa Et α
Xb Et β
XIa H α
XIb H β
XIIa Me α
XIIb Me β
XIIIa Hα
XIIIb Hβ
XIVa Hα
XIVb Hβ
XV: R = —OH
XVI: R = —O—C(=N—N=N—)—N—φ
XVa Hα
XVb Hβ

FIG 2

an authentic sample donated by E. Ochiai. The CD curve of dihydrocinchonamine (IV) is very similar to that of the indole alcohol XIIIa and almost a mirror image of that of the indole alcohol XIIIb as shown in Table 1.

TABLE 1. CIRCULAR DICHROISM OF DIHYDROCINCHONAMINE AND RELATED COMPOUNDS

Compounds		Cotton effects [mμ([θ])]	
	C_8—H	First	Second
IV	α	274 (+4000)	226 (−40000)
XIIIa	α	273 (+5700)	231·5 (−46000)
XIIIb	β	289 (−5800)	228 (+33200)

CD curves were obtained in MeOH with a JASCO ORD/UV-5 with CD attachment.

In NMR spectra, the terminal methyl protons at C_3 of the indole derivatives Xb-XIVb were all observed at a little higher field compared with those of the corresponding C_8-epimers (Xa-XIVa), as shown in Table 2.
This shielding effect is due to the anisotropic effect of the indole ring, which is on the same side as the ethyl group at C_3 in compounds Xb–XIVb.

TABLE 2. THE CHEMICAL SHIFTS OF THE TERMINAL METHYL PROTONS AT C_3

Compounds	C_8—H	Methyl proton signal	Solvent
Xa	α	9·03 (t. J = 6 c/s)	$CDCl_3$
Xb	β	9·22 (t. J = 6 c/s)	$CDCl_3$
XIa	α	9·18 (t. J = 6 c/s)	pyridine
XIb	β	9·36 (t. J = 6 c/s)	pyridine
XIIa	α	9·07 (t. J = 6 c/s)	$CDCl_3$
XIIb	β	9·25 (t. J = 6 c/s)	$CDCl_3$
XIIIa	α	9·08 (t. J = 6 c/s)	$CDCl_3$
XIIIb	β	9·17 (t. J = 6 c/s)	$CDCl_3$
IV	α	9·08 (t. J = 6 c/s)	$CDCl_3$
XIVa	α	9·00 (t. J = 7 c/s)	d_6-acetone
XIVb	β	9·14 (t. J = 7 c/s)	d_6-acetone

NMR spectra were taken with a Varian A-60 spectrometer. Chemical shifts are expressed in τ unit from TMS used as internal reference.

EXPERIMENTAL*

2'-Oxo-hexahydroquininone (IX). Preparation of this compd was carried out in accordance with Ishikawa's method.[7] Normal 2'-oxo-hexahydroquinine (VIIa) gave IX, m.p. 163–164°, in 46·5% yield and was recovered unchanged in 42% yield. Recrystallization from benzene gave prisms, m.p. 164° (lit 160–162°), $[\alpha]_D^{23\cdot5}$ +79·8° (*c*, 2·093, $CHCl_3$) (lit +79° ($CHCl_3$)). *allo*-2'-Oxo-hexahydroquinine (VIIb) gave IX, m.p. 163–164°, in 48% yield and was recovered unchanged in 31% yield. The same oxidation of normal 2'-oxo-hexahydroquinidine (VIIIa)[8] gave IX, m.p. 163°, $[\alpha]_D^{26}$ +80·5° (*c*, 2·021, $CHCl_3$), in 39% yield and the unchanged starting material (VIIIa) was recovered in 42% yield. *allo*-2'-Oxo-hexahydroquinidine (VIIIb)[8] also gave

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

IX, m.p. 163–164°, $[\alpha]_D^{27}$ +79·8° (*c*, 2009, $CHCl_3$), in 50% yield and was recovered unchanged in 29% yield.

Conversion of 2'-oxo-hexahydroquininone (IX) *into the indole derivatives* (Xa, b *and* XIa, b). In accordance with Ochiai's method,[3] a soln of IX (25 g) in dry EtOH (500 ml) saturated with HCl gas was refluxed for 22 h. The solvent was removed under reduced pressure. The residue was made basic with aq NH_4OH and extracted with CH_2Cl_2. Undissolved crystals (4·20 g) (17%), m.p. 188°, were collected and recrystallized from MeOH-EtOAc to give XIa as colourless needles (4·0 g), m.p. 195–196°, $[\alpha]_D^{25}$ − 11·5° (*c*, 2·093, EtOH); IR ν_{max}^{Nujol} cm^{-1}: 2184 (NH^+), 1593 (COO^-); UV λ_{max} mμ (log ε): 280 (4·02), 300 (sh) (3·76), 310 (sh) (3·67), λ_{min} mμ (log ε): 247·5 (3·27). (Found: C, 70·02; H, 7·82; N, 7·92. $C_{20}H_{26}O_3N_2$ requires: C, 70·15; H, 7·65; N, 8·18%). The aqueous layer was evaporated to dryness under reduced pressure. The residue was taken up in MeOH-CH_2Cl_2 (1:1) and the solvent removed. The resulting material was dissolved in MeOH and treated with 60% $HClO_4$. The separated crystals (2·93 g, 8·8%), m.p. 188° (dec) were recrystallized from MeOH to give XIIb perchlorate as colourless prisms (1·98 g) m.p. 249° (dec), $[\alpha]_D^{24.5}$ +115·7° (*c*, 1·283, pyridine); IR ν_{max}^{Nujol} cm^{-1}: 3329 (NH), 1692 ($COOCH_3$). (Found: C, 55·20; H, 6·57; N, 6·13; Cl, 7·76%). The CH_2Cl_2 layer was washed with water, dried over K_2CO_3 and the solvent removed. The residue (20·55 g) was crystallized from EtOAc to give Xa as prisms (11·08 g, 41%), m.p. 139–140°. Recrystallization from EtOAc raised its melting point to 140–141° (lit[3,6] 139–140°), $[\alpha]_D^{25.5}$ +14·5° (*c*, 1·148, EtOH); UV λ_{max} mμ (log ε): 280 (4·04), 297 (sh) (3·99), 310 (sh) (3·69), λ_{min} mμ (log ε): 250 (3·53): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3439 (NH), 1726 (COOEt). (Found: C, 71·15; H, 8·09; N, 7·67. Calc for $C_{22}H_{30}O_3N_2$: C, 71·32; H, 8·16; N, 7·56%). The perchlorate was recrystallized from EtOH as colourless prisms, m.p. 216–217° (dec): IR ν_{max}^{Nujol} cm^{-1}: 3334 (NH), 1723 (COOEt); CD $[\theta]_{280}$ +4310, $[\theta]_{226}$ −18000 (*c*, 0·0414, MeOH). (Found: C, 55·87; H, 6·76; N, 6·21; Cl, 7·72. $C_{22}H_{30}O_3N_2 \cdot HClO_4$ requires: C, 56·10; H, 6·64; N, 5·95; Cl, 7·53%). The mother liquor of Xa was evaporated and the residue (9·08 g) was chromatographed on alumina (150 g). Elution with benzene and CH_2Cl_2 gave a pale brown oil (6·46 g) which was dissolved in MeOH and treated with 60% $HClO_4$ to give Xb as a perchlorate (6·91 g) (20%), m.p. 242° (dec). Recrystallization from MeOH gave colourless prisms (6·53 g), m.p. 247° (dec); IR ν_{max}^{Nujol} cm^{-1}: 3340 (NH), 1685 (COOEt); CD $[\theta]_{277}$ −4970, $[\theta]_{225.5}$ +23 300 (*c*, 0·0500, MeOH). (Found: C, 56·14; H, 6·82; N, 6·14; Cl, 7·63. $C_{22}H_{30}O_3N_2 \cdot HClO_4$ requires: C, 56·10; H, 6·64; N, 5·95; Cl, 7·53%). The free base was an oily material, $[\alpha]_D^{24.5}$ +77·4° (*c*, 2·131, EtOH); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3435 (NH), 1728 (COOEt); UV λ_{max} mμ (log ε): 279 (3·99), 294 (sh), (3·87), 308 (sh) (3·68), λ_{min} mμ (log ε): 250 (3·52).

Saponification of the indole ester (Xa). A soln of Xa (300 mg) in 5% KOH-EtOH (20 ml) was stirred for 2 h at room temp and saturated with CO_2. The precipitated K_2CO_3 was filtered off and the filtrate evaporated under reduced pressure to dryness. The residue was treated with CH_2Cl_2 and water and the undissolved crystals (280 mg), m.p. 186°, were collected. Recrystallization from MeOH gave colourless needles, m.p. 195–196°. The mixed melting point determination and the comparison of IR spectra showed that this product was identical with XIa.

Indole carboxylic acid (XIb). Saponification of Xb (perchlorate 400 mg) was carried out in the same way as described above. The product was crystallized from water (5 ml) to give XIb (320 mg), m.p. 200° (with foaming) (sintered at 177°). Recrystallization from MeOH-EtOAc gave colourless needles (290 mg), m.p. 200° (with foaming) (sintered at 179°), $[\alpha]_D^{23.5}$ +111·2° (*c*, 2·000, EtOH); UV λ_{max} mμ (log ε): 280 (4·04), 300 (sh) (3·80), 310 (sh) (3·68), λ_{min} mμ (log ε): 247·5 (3·32); IR ν_{max}^{Nujol} cm^{-1}: 2246 (NH^+), 1596 (COO^-). (Found: C, 63·69; H, 8·26; N, 7·43; H_2O, 9·47. $C_{20}H_{26}O_3N_2 \cdot 2H_2O$ requires: C, 63·47; H, 7·99; N, 7·40; H_2O, 9·52%).

Esterification of the indole carboxylic acid (XIa). 1 *Ethyl ester* (Xa). A soln of XIa (100 mg) in EtOH (5 ml) was acidified with 60% $HClO_4$ and refluxed for 30 min. Concentration gave colourless prisms (115 mg, 84%), m.p. 216–217° (dec). This compound was identified as Xa perchlorate by comparison of IR spectra and the mixed melting point determination.

2 *Methyl ester* (XIIa). A soln of XIa (300 mg) in MeOH (5 ml) was treated with 60% $HClO_4$ as described above to give XIIa as a perchlorate (390 mg), m.p. 239° (dec), which was recrystallized from MeOH as colourless prisms (310 mg), m.p. 246° (dec), $[\alpha]_D^{25.5}$ −41·4° (*c*, 1·151, pyridine). IR ν_{max}^{Nujol} cm^{-1}: 3332 (NH), 1693 ($COOCH_3$). The free base was recrystallized from MeOH as colourless needles, m.p. 126–127°, $[\alpha]_D^{23.5}$ +19·8° (*c*, 2·003, EtOH); UV λ_{max} mμ (log ε): 280 (4·01), 296 (sh) (3·88), 308 (sh) (3·66), λ_{min} mμ (log ε): 251 (3·49); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3426 (NH), 1727 ($COOCH_3$). (Found: C, 71·11; H, 8·05; N, 7·78. $C_{21}H_{28}O_3N_2$ requires: C, 70·76; H, 7·92; N, 7·86%). Saponification of this ester as described for Xa gave XIa, m.p. 195–196°.

Esterification of the indole carboxylic acid (XIb). 1 *Ethyl ester* (Xb). A soln of XIb (30 mg) in EtOH (1 ml) was treated with 60% $HClO_4$ as described above to give colourless prisms (36 mg), m.p. 234° (dec). Re-

crystallization from EtOH raised its melting point to 247° (dec). The mixed melting point determination and comparison of the IR spectra showed that this compound was identical with Xb perchlorate.

2 *Methylester* (XIIb). A solution of XIb (30 g) in MeOH (1 ml) was treated with 60% $HClO_4$ as described above to give colourless prisms (34 mg), m.p. 245° (dec) which were identical with XIIb perchlorate by the mixed melting point determination and comparison of the IR spectra.

5'-Methoxydihydrocinchonamine (XIIIa). Following the known method,[3] reduction of Xa with LAH was carried out to yield XIIIa (88%), m.p. 180–181° (lit 180–181°), $[\alpha]_D^{25.0}$ +143·4° (*c*, 1·917, EtOH) (lit +136° (EtOH)). (Found: C, 73·04; H, 8·79; N, 8·30. Calc for $C_{20}H_{28}O_2N_2$: C, 73·13; G, 8·59; N, 8·53%).

5'-Methoxydihydro-epi-cinchonamine (XIIIb). A soln of the ethyl ester (Xb) (583 mg) in dry Et_2O (30 ml) was reduced with LAH (300 mg) to give an amorphous powder (490 mg), the rhodanate of which was recrystallized from MeOH-acetone to give colourless needles (474 mg), m.p. 203–204° (dec). (Found: C, 65·32; H, 7·69; N, 11·06; S, 8·49. $C_{21}H_{29}O_2N_3S$ requires: C, 65·08; H, 7·54; N, 10·84; S, 8·27%). The free base was recrystallized from acetone as colourless needles, m.p. 148–149°, $[\alpha]_D^{24.5}$ −16·5° (*c*, 2·046, EtOH); UV λ_{max} mμ (log ε): 287 (3·97), 294 (sh) (3·85), λ_{min} mμ (log ε): 250 (3·36); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3487 (NH). (Found: C, 73·09; H, 8·75; N, 8·45. $C_{20}H_{28}O_2N_2$ requires: C, 73·13; H, 8·59; N, 8·53%).

Equilibration reaction of the indole esters (Xa *and* Xb). 1 A soln of Xa (300 mg) in dry EtOH (10 ml) saturated with HCl gas was refluxed for 4 h. After removal of the solvent, the residue was made basic with NH_4OH aq and extracted with CH_2Cl_2. The CH_2Cl_2 layer was dried over K_2CO_3 and the solvent removed. The residue was decolourized by activated charcoal to give a pale brown amorphous powder (250 mg).

This product showed two spots, attributed to Xa and Xb, on TLC. The value of the specific rotation, $[\alpha]_D^{24}$ +41·4° (*c*, 2·080, EtOH), showed that this product contained Xa (57%) and Xb (43%).

2 The same reaction of Xb perchlorate (300 mg) gave a pale brown amorphous powder (190 mg), which showed two spots on TLC that were attributed to Xa and Xb. The specific rotation value, $[\alpha]_D^{24}$ +44·9 (*c*, 2·015, EtOH) showed that this product contained Xa (51%) and Xb (49%).

Equilibration reaction of 5'-methoxydihydrocinchonamine (XIIIa) *and 5'-methoxydihydro-epi-cinchonamine* (XIIIb). 1 A soln of XIIIa (100 mg) in dry EtOH (5 ml) saturated with HCl was refluxed for 22 h and the solvent removed. The residue was made basic with NH_4OH aq and extracted with CH_2Cl_2. The solution was dried over K_2CO_3 and the solvent removed to give an amorphous powder showing two spots, due to XIIIa and XIIIb, on TLC. The residue was converted to the rhodanate (66 mg), m.p. 172–184°, $[\alpha]_D^{25}$ +58·6° (*c*, 1·956, EtOH). The specific rotation value showed the existence of XIIIa (63%) and XIIIb (37%).

2 The same reaction of XIIIb (83 mg) gave an amorphous powder which showed two spots, due to XIIIa and XIIIb, on TLC. The residue was converted to the rhodanate (70 mg), m.p. 152–158° $[\alpha]_D^{25}$ +39·6° (*c*, 2·026, EtOH). The specific rotational value showed the existence of XIIIa (51%) and XIIIb (49%).

Quaternary tosylate (XIVa). 1 A soln of XIIIa (150 mg) and tosylchloride (250 mg) in pyridine was allowed to stand overnight at room temp and then evaporated to dryness. The last traces of pyridine were removed by distillation of added water. The crystalline residue was washed with water and benzene and recrystallized from MeOH-acetone to give XIVa as colourless needles (200 mg) 91%), m.p. 315–316° (dec). IR ν_{max}^{Nujol} cm^{-1}: 1171, 1032, 1009 (OTs^-). (Found: C, 66·96; H, 7·34; N, 6·01: S, 6·65. $C_{20}H_{27}ON_2{\cdot}C_7H_7O_3S$ requires: C, 67·18; H, 7·10; N, 5·80; S, 6·64%). The picrate was prepared by treatment of the tosylate (XIVa) with sodium picrate in MeOH and recrystallized from MeOH-acetone as reddish orange needles, m.p. 216–217° (dec) (sintered at 212°). (Found: C, 58·04; H, 5·44; N, 13·00. $C_{20}H_{27}ON_2{\cdot}C_6H_2O_7N_3$ requires: C, 57·88; H, 5·42; N, 12·98%).

2 Treatment of XVa (97 mg) in pyridine (5 ml) with tosylchloride (165 mg) as described above gave a crystalline material (123 mg, 86%), which was dissolved in DMF (2 ml) and refluxed for 30 min. Evaporation and recrystallization from EtOH gave colourless needles (85 mg), m.p. 315–316° (dec). This compd was identical with the quaternary tosylate (XIVa) obtained from 5'-methoxyldihydrocinchonamine (XIIIa) by comparison of the IR spectra and the mixed melting point determination.

Quaternary tosylate (XIVb). 1 Quaternization of XIIIb (88 mg) was carried out in the same way as described for XIIIa to yield XIVb as an amorphous powder (120 mg, 93%) [IR ν_{max}^{Nujol} cm^{-1}: 1170, 1120, 1030, and 1007 (OTs^-)]. The product was dissolved in MeOH (1 ml) and treated with sodium picrate. The precipitated oily material was crystallized from acetone-EtOAc to give yellow needles (71 mg, 91%), m.p. 215° (dec). Recrystallization from EtOAc-acetone raised its melting point to 221–222° (dec). (Found: C, 58·05; H, 5·50; N, 13·06. $C_{20}H_{27}ON_2{\cdot}C_6H_2O_7N_2$ requires: C, 57·88; H, 5·42; N, 12·98%).

2 The same reaction of XVb (100 mg) gave an amorphous powder (137 mg, 93%). The picrate was prepared

in EtOH and recrystallized from EtOAc-acetone as yellow needles (128 mg), m.p. 223–224° (dec). Comparison of IR spectra and the mixed melting point determination showed that this compd was identical with the quarternary picrate obtained from 5'-methoxydihydro-epi-cinchonamine (XIIIb).

5'-Hydroxydihydrocinchonamine (XVI). A solution of BBr_3 (2·5 g) in $CHCl_3$ (10 ml) was added to an ice-cooled solution of XIIIa (636 mg) in $CHCl_3$ (20 ml). After shaking for 30 min at room temp, the mixture was poured into dil NH_4OH under ice-cooling and extracted with $CHCl_3$-EtOH (9:1). The organic layer was dried over K_2CO_3 and the solvent removed. The residue (405 mg) was recrystallized from EtOH to give XVI as needles (310 mg, 51·5%), m.p. 133–134° (with foaming), $[\alpha]_D^{23}$ +122·4° (*c*, 0·998, EtOH); CD: $[\theta]_{270}$ +3790, $[\theta]_{226}$ −31560 (*c*, 0·0414, EtOH); UV λ_{max} mμ (log ε): 215 (4·53), 273 (sh) (3·98), 280 (4·02), 300 (sh) (3·72), λ_{min} mμ (log ε): 248 (3·37). (Found: C, 69·88; H, 8·95; N, 7·69. $C_{19}H_{26}O_2N_2 \cdot C_2H_5OH$ requires: C, 69·97; H, 8·95; N, 7·77%). The hydrobromide was recrystallized from MeOH as colourless needles, m.p. 242–244° (dec). (Found: C, 56·35; H, 7·32; N, 6·34; Br, 18·44; CH_3OH, 6·96. $C_{19}H_{26}O_2N_2 \cdot HBr \cdot CH_3OH$ requires: C, 56·20; H, 7·31; N, 6·56; Br, 18·70; CH_3OH, 7·50%).

Tetrazolyl ether (XVII). To a soln of XVI (500 mg) in DMF (10 ml) was added finely powdered K_2CO_3 (440 mg) and 1-phenyl-5-chlorotetrazole (350 mg). After stirring for 56 h at 50° under N_2 stream, the reaction mixture was poured into ice water and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with 5% KOH and with water, dried over K_2CO_3 and the solvent removed. The residue was dissolved in benzene and extracted with 10% HCl. The aqueous layer 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. The residue (780 mg) was recrystallized from EtOH to give XVII as colourless needles (640 mg, 81%), m.p. 203–205°, $[\alpha]_D^{23}$ +112·1° (*c*, 1·007, EtOH); UV λ_{max} mμ (log ε): 227·5 (4·68), 287·5 (3·99), λ_{min} mμ (log ε): 212·5 (4·48), 260 (3·84). (Found: C, 67·90; H, 6·57; N, 18·33. $C_{26}H_{30}O_2N_6$ requires: C, 68·10; H, 6·59; N, 18·33%).

Dihydrocinchonamine (IV). A soln of XVII (700 mg) in EtOH (20 ml) was hydrogenated on 5% Pd-C (700 mg) at room temp for 50 h. After removal of the catalyst and the solvent, the residue was made alkaline with 5% NaOH and extracted with $CHCl_3$ soln. It was then washed with water, dried over K_2CO_3 and the solvent removed to give a crystalline residue (390 mg, 86%), recrystallized from EtOH to give IV as colourless needles, m.p. 163–164° (lit[2] 162–163°), $[\alpha]_D^{25}$ +109·7° (*c*, 0·936, EtOH) [lit[2] +106° (EtOH)]. CD: $[\theta]_{280}$ +1150, $[\theta]_{228}$ −5000. (Found: C, 75·14; H, 8·81; N, 9·17; H_2O, 2·12. Calc for: $C_{19}H_{26}ON_2$ 1/3H_2O: C, 74·96; H, 8·83; N, 9·20; H_2O, 1·97%). This compound was identical with dihydrocinchonamine donated by E. Ochiai from a comparison of their IR and NMR spectra and the mixed melting point determination.

Acknowledgement—We wish to express our appreciation to Prof. Emeritus E. Ochiai of Tokyo University and Dr. K. Takeda, Director of this Laboratory for their valuable suggestions. We also thank Mr. K. Fujimori and Mr. T. Fujioka for their technical assistance.

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