Transformation of Quinine into Indole Alkaloids Synthesis of Dihydroantirhine, Dihydrohunterburnine α-Methochloride, 10-Methoxydihydrocoryantheol, Dihydrocorynantheol, and Ochrosandwine

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OCHIAI *et al.* reported the synthesis of 5'-methoxydihydrocinchonamine^{1,2} and 10-methoxydihydrocorynantheane³ from quinine and dihydrocinchonamine² and dihydrocorynantheane⁴ from cinchonine. (I),⁵ dihydrohunterburnine α -methochloride (II; X = Cl),⁶ 10-methoxydihydrocorynantheol (III),⁷ dihydrocorynantheol (IV),^{7,8} and ochrosandwine (V; X = Cl)⁶ from quinine.

We describe the synthesis of dihydroantirhine

Treatment of the normal and *allo-N*-cyanobromides³ (VIa, VIIa, VIb, and VIIb)[†] with silver

 \dagger The compounds of the normal and *allo*-types are denoted by (a) and (b). Determination of the configuration at C-4' of these compounds will be reported elsewhere.

acetate in pyridine afforded the corresponding N-cyano-acetates (VIIIa), m.p. 158—159°, (IXa), m.p. 217—218°, (VIIIb), m.p. 200—201°, and (IXb), m.p. 157—158°, in about 75% yields. Each N-cyanoacetate was hydrolyzed with acid to give O-benzoyl amino-alcohols (Xa), m.p. 181° (perchlorate), (XIa), m.p. 213—214° (styphnate), (Xb), m.p. 201°, and (XIb), an amorphous powder.

Treatment of (XIa) and (XIb) with dihydropyran and dipolar aprotic solvent (MeCN) afforded the benzoyl quinolizidones (XIIa), (71%) m.p. 189-190°, and (XIIb), (73.5%) m.p. 169-170°.

Reduction of (XIIa) with LiAlH₄ gave the quinolizidine (XIIIa) (76%), whereas the same reduction of (XIIb) afforded mainly the benzyl quinolizidine (XIVb). Therefore, (XIIb) was saponified with dilute alkali, followed by reduction with LiAlH₄, to give the quinolizidine (XIIIb) (78%). However, methanolysis of the tetrahydropyranyl (THP) ethers of (Xa) and (Xb) followed by treatment with dipolar aprotic solvent afforded the quinolizidones (XVa), (70%) m.p. 195-196°, and (XVb) (60.5%) m.p. 149-150°.

Reduction of (XVa) and (XVb) with LiAlH₄ gave the quinolizidines (XVIa) (76%) and (XVIb), (86%) m.p. 102—103°, respectively.

Compounds of the *allo*-type, (XIIIb) and (XVIb), show the Bohlmann band⁹ in the i.r. spectra, whereas those of the normal type, (XIIIa) and (XVIa), do not.

Oppenauer oxidation of (XIIIa) and (XVIa) with Bu^tOLi and benzophenone followed by hydrolysis with acid gave the indoles (III), (68%) m.p. 163—164°, $[\alpha]_{23}^{23} - 21 \cdot 8^{\circ}$ (pyridine), and (XVII) (70%) m.p. 242—243° (decomp.) (hydrochloride), respectively. The former was identical with a sample of 10-methoxydihydrocorynantheol (III).⁷

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However, (XIIIb) and (XVb) resisted oxidation to give only the starting materials. Demethylation of (XVII) and (III) was effected by the action of BBr₃ to give the phenols, (XVIII), m.p. 226-227° (decomp.), and (XIX) m.p. 224-225° (decomp), in high yields. Ullmann reaction of (XVIII) and (XIX) with 5-chloro-1-phenyltetrazole¹⁰ followed by hydrogenolysis afforded (I), m.p. 130° (foaming), $[\alpha]_{D}^{23} + 23.6°$ (CHCl₃), and (IV), m.p. 185–187°, $[\alpha]_{D}^{25} - 36.8°$ (pyridine). These compounds were identical with samples of dihydroantirhine⁵ and dihydrocorynantheol.⁷ Quaternization of (XVIII) with methyl iodide gave a single methiodide (II; X = I), m.p. 272-273° (decomp.). The corresponding methochloride, m.p. 317-318° (decomp.), $[\alpha]_{D}^{24.5} + 13.4^{\circ}$ (50% MeOH), was proved to be identical with a sample of dihydrohunterburnine α -methochloride (II; X = Cl).⁶ The same quaternization of (XIX) gave two methiodides, (XX; X = I), $[\alpha]_{\rm D}^{24} + 29.8^{\circ}$ (50% MeOH) [m.p. 193—194° (X = picrate)], and (V, X = I), m.p. 275-276° (decomp.), $[\alpha]_{D}^{24}$ + 71.8° (50% MeOH). The methochloride, m.p. 288–289° (decomp.), $[\alpha]_{D}^{26} + 96.9^{\circ}$ (MeOH), prepared from the latter, was proved to be identical with a sample of ochrosandwine⁶ (V; X = Cl).

The configuration of the quaternary N-methyls of (V) and (XX) was based on n.m.r. studies. It is known that in a series of N-methylquinolizidinium cations, the (+)-N-methyl protons with *cis*-fused rings resonate at lower fields than those with *trans*-fused rings.¹¹ In the n.m.r. spectra, the (+)-N-methyl signals of (XX) were observed at lower fields than those of (V) [(XX), $\tau 6.67$ [‡] (X = I), $\tau 6.93$ [§] (X = Cl); V, $\tau 6.97$ [‡] (X = I), $\tau 7.34$ [‡] (X = Cl)]. Since the α -configuration was assigned to the C₃-hydrogen of those alkaloids, the quaternary N-methyl groupings of (XX) and (V) must be



 $1 \text{ In CF}_3\text{CO}_2\text{H}$. $1 \text{ In D}_2\text{O}$. All the spectra were determined at 60 Mc. on a Varian Model A-60 spectrometer with tetramethylsilane as internal reference.



depicted by \mathbf{the} and β -configurations. αrespectively.

It is evident that the absolute configurations of ochrosandwine,⁶ hunterburnine *a*-methochloride,^{6,9,12} and β -methochloride^{9,12} are represented as (V), (XXI), and (XXII, X = Cl), respectively and that the absolute configuration of 10-methoxydihydrocorynantheol (III)⁷ assigned by H. Schmid was correct.



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