

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

By Y. K. SAWA* and H. MATSUMURA

(Shionogi Research Laboratory, Shionogi & Co., Ltd., Fukushima-ku, Osaka, Japan)

OCHIAI *et al.* reported the synthesis of 5'-methoxydihydrocinchonamine^{1,2} and 10-methoxydihydrocorynantheane³ from quinine and dihydrocinchonamine² and dihydrocorynantheane⁴ from cinchonine.

We describe the synthesis of dihydroantirhine

(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.

Treatment of the normal and *allo-N*-cyano-bromides⁹ (VIa, VIIa, VIb, and VIIb)[†] with silver

[†]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°.

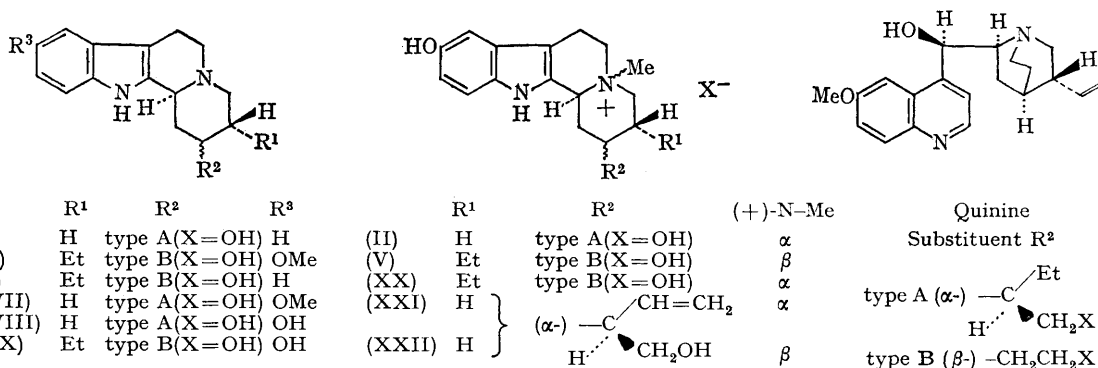
Reduction of (XVa) and (XVb) with LiAlH₄ gave the quinolizidines (XVIa) (76%) and (XVIb), (86%) m.p. 102—103°, respectively.

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.

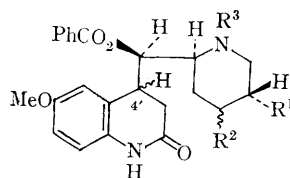
Oppenauer oxidation of (XIIIa) and (XVIa) with Bu⁴OLi and benzophenone followed by hydrolysis with acid gave the indoles (III), (68%) m.p. 163—164°, [α]_D²⁵ - 21.8° (pyridine), and (XVII) (70%) m.p. 242—243° (decomp.) (hydrochloride), respectively. The former was identical with a sample of 10-methoxydihydrocorynantheol (III).⁷

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), [α]_D²⁵ + 23.6° (CHCl₃), and (IV), m.p. 185—187°, [α]_D²⁵ - 36.8° (pyridine). These compounds were identical with samples of dihydroantirrhine⁵ 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.), [α]_D^{24.5} + 13.4° (50% MeOH), was proved to be identical with a sample of dihydrohunnerburnine α -methochloride (II; X = Cl).⁶ The same quaternization of (XIX) gave two methiodides, (XX; X = I), [α]_D²⁴ + 29.8° (50% MeOH) [m.p. 193—194° (X = picrate)], and (V, X = I), m.p. 275—276° (decomp.), [α]_D²⁴ + 71.8° (50% MeOH). The methochloride, m.p. 288—289° (decomp.), [α]_D²⁶ + 96.9° (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), τ 6.67† (X = I), τ 6.93‡ (X = Cl); V, τ 6.97† (X = I), τ 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

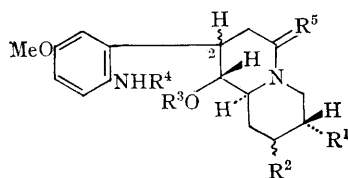


† In CF₃CO₂H. § In D₂O. All the spectra were determined at 60 Mc. on a Varian Model A-60 spectrometer with tetramethylsilane as internal reference.



(a) normal $C_4-H \alpha$
 (b) *allo* $C_4'-H \beta$

| | R ¹ | R ² | R ³ |
|------------|----------------|----------------|----------------|
| (VIa, b) | H | type A(X=Br) | CN |
| (VIIa, b) | Et | type B(X=Br) | CN |
| (VIIIa, b) | H | type A(X=OAc) | CN |
| (IXa, b) | Et | type B(X=OAc) | CN |
| (Xa, b) | H | type A(X=OH) | H |
| (XIa, b) | Et | type B(X=OH) | H |



(a) normal $C_2-H \beta$
 (b) *allo* $C_2-H \alpha$

| | R ¹ | R ² | R ³ | R ⁴ | R ⁵ |
|------------|----------------|----------------|----------------|--------------------|----------------|
| (XIIa, b) | Et | type B(X=OTHP) | COPh | H | O |
| (XIIIa, b) | Et | type B(X=OTHP) | H | H | H ₂ |
| (XIVb) | Et | type B(X=OTHP) | H | CH ₂ Ph | H ₂ |
| (XVa, b) | H | type A(X=OTHP) | H | H | O |
| (XVIa, b) | H | type A(X=OTHP) | H | H | H ₂ |

depicted by the α - and β -configurations, respectively.

It is evident that the absolute configurations of ochrosandwine,⁶ hunterburnine α -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.

We thank Professor Emeritus E. Ochiai and Dr. K. Takeda, for valuable suggestions and Professor H. Schmid of Zurich University, Professor P. J. Scheuer of Hawaii University, and Dr. S. R. Johns of CSIRO Chemical Research Laboratories for samples.

(Received, March 15th, 1968; Com. 323.)

- ¹ M. Ishikawa, *Chem. and Pharm. Bull. (Japan)*, 1958, **6**, 71.
- ² E. Ochiai, H. Kataoka, T. Dodo, and M. Takahashi, *Ann. Report ITSUU Lab.*, 1962, **12**, 11.
- ³ E. Ochiai and M. Ishikawa, *Chem. and Pharm. Bull. (Japan)*, 1959, **7**, 559.
- ⁴ E. Ochiai and M. Ishikawa, *Tetrahedron*, 1959, **7**, 228.
- ⁵ S. R. Johns, J. A. Lamberton, and J. L. Occolowitz, *Austral. J. Chem.*, 1967, **20**, 1463.
- ⁶ W. Jordan and P. J. Scheuer, *Tetrahedron*, 1965, **21**, 3731.
- ⁷ N. J. Dastoor, A. A. Gorman, and H. Schmid, *Helv. Chim. Acta*, 1967, **50**, 213.
- ⁸ B. Gilbert, L. D. Antonaccio, and C. Djerassi, *J. Org. Chem.*, 1962, **27**, 4702.
- ⁹ F. Bohlmann, *Angew. Chem.*, 1957, **69**, 641; *Chem. Ber.*, 1958, **91**, 2157.
- ¹⁰ W. J. Musliner and J. W. Gates, jun., *J. Amer. Chem. Soc.*, 1966, **88**, 4272.
- ¹¹ T. M. Moynihan, K. Schofield, R. A. Jones, and A. R. Katritzky, *J. Chem. Soc.*, 1962, 2637.