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TRANSFORMATION OF QUININE INTO THE INDOLE ALKALOIDS—II

THE SYNTHESIS OF 10-METHOXYDIHYDROCORYNANTHEOL AND OCHROSANDWINE

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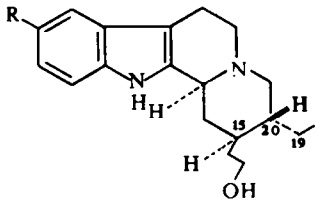
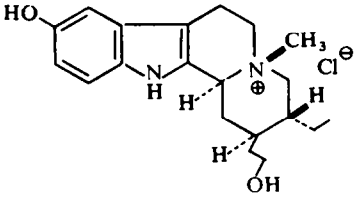
Abstract—10-Methoxydihydrocorynantheol (I) and ochrosandwine (III) were synthesized from quinine (VII) and the absolute configurations of these alkaloids was established. Dihydrocorynantheol (VI) was also obtained from 10-methoxydihydrocorynantheol (I).

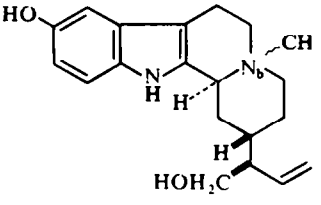
RECENTLY some new 10-substituted indole alkaloids of yohimbinoid variant, 10-methoxydihydrocorynantheol (I),[1] 10-methoxygeissoschizol (II),[1] ochrosandwine (III),[2] hunterburnine α-methochloride (IV)[3] and β-methochloride (V)[3] were isolated from the Apocinaceae and the structures of these alkaloids were elucidated. The



I: R = OCH_3
II: R = OCH_3, Δ^{19-20}
VI: R = H



III



IV + N_bCH_3 α
V + N_bCH_3 β

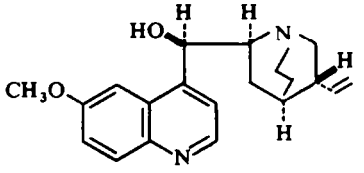
absolute configurations depicted for the two alkaloids IV and V were confirmed synthetically in a previous paper.[4]

This paper describes the synthesis of 10-methoxydihydrocorynantheol (I) and ochrosandwine (III) from quinine (VII) and confirms the absolute configurations of these alkaloids.

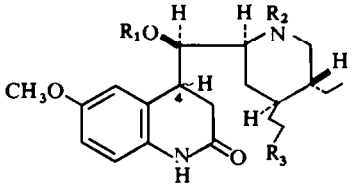
The normal and *allo*-N-cyanobromides (VIIIa and VIIIb),* the vital intermediates in the synthesis of 10-methoxydihydrocorynantheane from quinine,[5] were used as

* The tentative prefixes, normal and *allo*, have been used to distinguish between the epimers at the asymmetric centers $C_{4'}$, which were generated by reduction of the heterocyclic ring of the quinoline moiety of quinine.[5] The compounds of normal and *allo* types are denoted (a) and (b), respectively, throughout this paper.

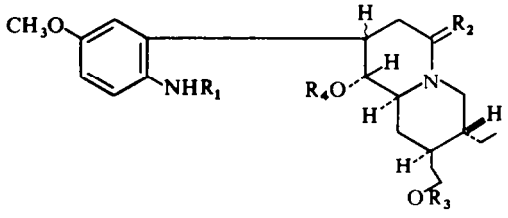
starting materials. Treatment of the N-cyanobromides (VIIIa and VIIIb) with silver acetate in pyridine gave the respective N-cyanoacetates, (IXa) m.p. 216–217°, $[\alpha]_D^{25.5}$ +55·9° and (IXb) m.p. 157–158°, $[\alpha]_D^{26.5}$ −55·3° in good yields. Removal of the acetyl and cyano groups from the *allo*-N-cyanoacetate (IXb) was readily accomplished by acid hydrolysis to give quantitative yields of the corresponding O-benzoylamino alcohol (Xb) whereas under the same conditions the hydrolysis of the normal N-cyanoacetate (IXa) was not so easy and prolonged hydrolysis of the latter afforded the O-benzoylamino alcohol (Xa), m.p. 213–214° (dec) [styphnate] in 55% yield and 19% yield of the desbenzoylamino alcohol (XIa), m.p. 185–187° (dec) [styphnate].



VII



	R_1	R_2	R_3
VIIIa, b:	COϕ	CN	Br
IXa, b:	COϕ	CN	OAc
Xa, b:	COϕ	H	OH
XIa:	H	H	OH
XIIa, b:	COϕ	H	O



	R_1	R_2	R_3	R_4
XIIIa, b:	H	O	THP	COϕ
XIVa, b:	H	H_2	THP	H
XVa, b:	$CH_2\phi$	H_2	THP	H

	R_1	R_2	R_3	R_4
XVIb:	H	O	THP	H
XVIIb:	H	H_2	H	H

The structures of Xa and Xb were established by the presence of their maximum UV absorption at 258 and 300 mμ due to the dihydrocarbostyril chromophore and 235 mμ due to the benzoyl groups. The structure of XIa was also proven by the UV spectrum which lacked the maximum absorption attributed to the benzoyl group. The compounds Xa and Xb were treated with dihydropyran in the presence of *p*-toluenesulfonic acid and then converted to the respective quinolizidones, XIIIa, m.p. 188–189°, $[\alpha]_D^{22}$ +173° and XIIIb, m.p. 169·171°, $[\alpha]_D^{24}$ +47·0°, by heating in one of the dipolar aprotic solvents such as acetone, acetonitrile and nitromethane. This conversion proceeded more easily in the normal series (XIIa → XIIIa) compared with that in the *allo* series (XIIb → XIIIb) as observed in the synthesis of dihydrohunterburnine α-methochloride.[4]

Reduction of the normal quinolizidone (XIIIa) with LAH gave the quinolizidine

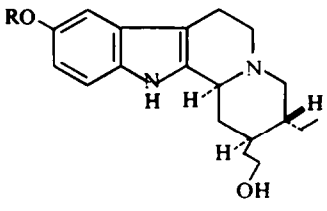
(XIVa) in 76% yield and a small amount of the N-benzylquinolizidine (XVa). The structure of the former was proven by the presence of its maximum UV absorption at 236 and 300 mμ due to the *p*-anisidyl chromophore and that of the latter was also proven by a UV absorption curve similar to that of N-benzyl-*p*-anisidine and the presence of the NMR signals at 2·67 and 5·75 τ which were comparable to the benzyl signals of N-benzyl-*p*-anisidine.

On the other hand, the same reduction of the *allo*-quinolizidone (XIIIb) gave a mixture of the desired quinolizidine (XIVb) and the N-benzyl-quinolizidine (XVb) in a ratio of 1 : 4. The quinolizidine (XIVb) was obtained in good yield by saponication of the quinolizidone (XIIIb) followed by reduction of the resulting desbenzoylquinolizidone (XVIb), m.p. 131–132°, with LAH.

An oppenauer oxidation of the normal quinolizidine (XIVa) followed by removal of the tetrahydropyranyl grouping with acid gave an indole compound (I), m.p. 163–164°, $[\alpha]_D^{23}$ −21·8° (pyridine), in 68% yield, while the *allo*-quinolizidine (XIVb) resisted this oxidation giving the quinolizidine (XVIIb) besides a trace of the indole compound (I).

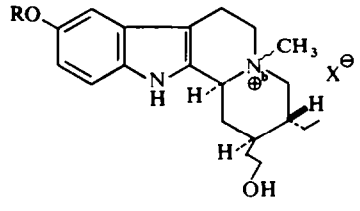
The identity of this compound (I) with 10-methoxyldihydrocorynantheol* was proven by comparison of their IR spectra and specific rotations and by the mixed m.p.d. The absolute configurations at C_{15} and C_{20} of 10-methoxydihydrocorynantheol were finely established, because these configurations must be retained throughout this procedure. Therefore, the absolute configuration of 10-methoxydihydrocorynantheol (I) illustrated by Schmid *et al.* was confirmed since the α-configuration of the C_3-hydrogen was already proven by means of the ORD.[7]

Furthermore, 10-methoxydihydrocorynantheol (I) was successfully converted to dihydrocorynantheol (VI)[1] by demethylation with borontribromide and successive elimination of the phenolic OH grouping from the resulting phenolic compound (XVIII), m.p. 225–226°, by Musliner's method[8] which involved the hydrogenolysis of the tetrazolyl ether (XIX), m.p. 265° (dec) [hydrochloride]. The identity of the



XVIII: R = H

XIX: R =



	R	$+N_bCH_3$
XX:	H	β
XXI:	H	α
XXII:	CH_3	β
XXIII:	CH_3	α

synthetic and the natural dihydrocorynantheol† was confirmed by comparison of their IR spectra and specific rotations and by the mixed m.p.

Quaternization reaction of the phenolic compound (XVIII) with methyliodide

* This sample was donated by the courtesy of Prof. H. Schmid.

† See footnote * on page 4.

gave two isomeric methiodides, XX (X = I, m.p. 276° dec) and XXI (X = I), an amorphous powder, in 31 and 50% yields, respectively. The latter (XXI) was characterized as its picrate, m.p. 193–194° (dec). Treatment uf the former (XX) with an anion exchanger containing Cl^- gave the corresponding methochloride, m.p. 288–289° (dec), $[\alpha]_D^{26}$ +94·9° (MeOH), which was identical with ochrosandwine (III)* by comparison of the IR spectra and by mixed m.p. The same quaternization reaction of 10-methoxydihydrocorynantheol (I) also gave two isomeric methiodides, XXII (X = I, m.p. 268–268·5° dec) and XXIII (X = I), an amorpyous powder, in 37·7 and 49·5% yields, respectively. The latter gave a crystalline picrate, m.p. 234–235° (dec). The stereochemistry of the above mentioned quaternary salts was determined by studies of the chemical shifts of the quaternary N-Me signals.

It is well known that, in a series of N-methylquinolizidimium cations, the quaternary N-Me protons resonate at higher fields in case of the *trans* fused system compared with the *cis* fused system.[9, 10] According to this correlation, the compounds XX and XXII were assigned the *trans*-N-methylquinolizidinium structure and the compounds XXI and XXIII were assigned the *cis* N-methylquinolizidinium structure, since the +N-Me signals of XX and XXII appeared at higher fields compared with the corresponding signals of XXI and XXIII as shown in Table 1.

TABLE 1. THE CHEMICAL SHIFTS OF THE QUATERNARY N-METHYL SIGNALS (τ)

Compounds	XX	XXI	XXII	XXIII
Iodide	6·97[a]	6·67[a]	6·90[a]	6·65[a]
Chloride	7·34[b]	6·93[b]		
Picrate			6·80[c]	6·54[c]

[a] in CF_3COOH, [b] in D_2O, [c] in d_6-acetone

Therefore, the quaternary N-Me groups of XX and XXII must be illustrated by the β-configuration and those of XXI and XXIII by the α-configuration because the tertiary alkaloids I and XVIII had the C_3-hydrogen in the α-orientation.

From these results, it is evident that ochrosandwine (III) is identical with 10-hydroxydihydrocorynantheol β-methochloride (XX, X = Cl).

EXPERIMENTAL

All m.ps are uncorrected. The NMR spectra were recorded on a Varian A-60 instrument. The chemical shifts are expressed as τ units and are referred to TMS as the internal reference. The CD curves were obtained with a JASCO ORD/UV-5 attached with CD. Kiesel gel G (Merck) plates were used for TLC and Kiesel gel GF (Merck) plates were used for preparative TLC. They were developed by $CHCl_3$-MeOH mixture.

Normal and allo-N-*cyanobromides* (VIIIa and VIIIb)

These compounds were prepared by the method of Ochiai *et al.*[5] VIIIa, m.p. 220–221° [lit. 218–219°], $[\alpha]_D^{24.5}$ +74·5° (*c*, 2·052, $CHCl_3$). (Found: C, 60·91; H, 5·68; N, 7·83; Br, 14·53. Calc. for $C_{28}H_{32}O_4N_3Br$: C, 60·65; H, 5·82; N, 7·58; Br, 14·41%). VIIIb, m.p. 206–207° [lit. 206–207°], $[\alpha]_D^{24.0}$ −38·5° (*c*, 2·097, $CHCl_3$). (Found: C, 60·40; H, 5·77; N, 7·64. Calc. for $C_{28}H_{32}O_4N_3Br$: C, 60·65; H, 5·82; N, 7·58%).

* This sample was donated by the courtesy of Prof. P. J. Scheuer.

Normal N-*cyanoacetate* (IXa)

A soln of VIIIa (16·65 g) and AcOAg (10·05 g) in pyridine (24 g) was heated at 130–135° for 10 min. After cooling, the mixture was stirred with NaCl aq to decompose the excess reagent. The ppts were filtered off and washed with CH_2Cl_2. The filtrate and the CH_2Cl_2 soln were combined and concentrated to dryness under reduced press. The residue was dissolved in CH_2Cl_2, washed with dil HCl and then with water, dried over K_2CO_3 and the solvent was removed. The residue was dissolved in CH_2Cl_2 and chromatographed on alumina (133 g). Elution with CH_2Cl_2 gave a crystalline material (13·79 g) which was recrystallized from MeOH to give IXa as colourless needles (12·94 g, 76%), m.p. 216–217°, $[\alpha]_D^{25.5}$ +55·9° (*c*, 2·018, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε): 233·5 (4·21), 257 (4·12), 298 (3·44), λ_{min}^{EtOH} mμ (log ε): 223 (4·10), 248 (4·08), 290 (3·42); IR $\lambda_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 2220 (CN), 1732 (OCOφ, OAc), 1682 (sec lactam); NMR ($CDCl_3$): τ 4·37 (d–d, *J* = 8·5 and 3 c/s, 1H, C<u>H</u>OCOφ), 6·05 (tr, *J* = 6 c/s, 2H, $CH_2C\underline{H}_2OAc$), 6·23 (s, $OC\underline{H}_3$), 8·12 (s, $OCOC\underline{H}_3$). (Found: C, 67·80; H, 6·72; N, 8·13. $C_{30}H_{35}O_6N_3$ requires: C, 67·52; H, 6·61; N, 7·88%).

allo-N-*Cyanoacetate* (IXb)

A soln of VIIIb (11·1 g) and AcOAg (6·70 g) in pyridine (18 g) was treated as above. The resulting material (8·8 g) was chromatographed on alumina (174 g). Elution with CH_2Cl_2 gave a crystalline material (8·6 g) which was recrystallized from MeOH to give IXb as colourless needles, m.p. 157–158°, $[\alpha]_D^{26.5}$ −55·3° (*c*, 2·114, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε): 234 (4·21), 258 (4·16), 299 (3·48); λ_{min}^{EtOH} mμ (log ε): 222·5 (4·12), 247·5 (4·21), 291 (3·46); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3386 (NH), 2225 (CN), 1732 (OCOφ, OAc), 1686 (sec lactam); NMR ($CDCl_3$): τ 4·39 (d–d, *J* = 8 and 5 c/s, 1H, C<u>H</u>OCOφ), 6·00 (tr, *J* = 6 c/s, 2H, $CH_2C\underline{H}_2OAc$), 6·34 (s, $OC\underline{H}_3$), 8·13 (s, $OCOC\underline{H}_3$). (Found: C, 67·44; H, 6·79; N, 7·93. $C_{30}H_{35}O_6N_3$ requires: C, 67·52; H, 6·61; N, 7·88%).

Hydrolysis of normal N-*cyanoacetate* (IXa)

A suspension of IXa (6 g) in 15% H_2SO_4 (100 ml) was refluxed for 11·5 hr. After washing with Et_2O, the soln was made alkaline with NH_4OH aq and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent was removed. The residue was dissolved in EtOH and treated with a soln of styphnic acid in EtOH to give Xa styphnate (4·4 g, 55%), m.p. 212–214° (dec) which was recrystallized from EtOH to give yellow needles, m.p. 213–214° (dec). (Found: C, 55·39; H, 5·44; N, 9·74. $C_{27}H_{34}O_5N_2$ $C_6H_3O_8N_3$ requires: C, 55·69; H, 5·24; N, 9·84%). The free base (Xa) was an amorphous powder, $[\alpha]_D^{21}$ +97·0° (*c*, 1·982, EtOH), UV λ_{max}^{EtOH} mμ (log ε): 232 (4·24), 258 (4·15), 298 (3·48); λ_{min}^{EtOH} mμ (log ε): 224 (4·17), 248 (4·10), 291 (3·45); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620 (OH), 3380 (NH), 1720 (OCOφ), 1670 (sec lactam). The mother liquor of Xa styphnate was concentrated to about one fifth of its original volume and allowed to stand for a long time. The separated crystals were collected and recrystallized from EtOH to give XIa styphnate as yellow needles (1·30 g, 19·2%), m.p. 185–187° (dec). (Found: C, 50·84; H, 5·69; N, 11·30; H_2O, 1·54. $C_{20}H_{30}O_4N_2$ $C_6H_3O_8N_3 \cdot \frac{1}{2}H_2O$ requires: C, 50·64; H, 5·56; N, 11·36; H_2O, 1·46%). The free base (XIa) was an amorphous powder, $[\alpha]_D^{22}$ −17·0° (*c*, 2·033, EtOH), UV λ_{max}^{EtOH} mμ (log ε): 258·5 (4·11), 298 (3·51); λ_{min}^{EtOH} mμ (log ε): 228 (3·51), 288 (3·45); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3528 (OH), 3328 (NH), 1666 (sec lactam).

allo-O-*Benzoylamino alcohol* (Xb)

A suspension of IXb (4·0 g) in 15% H_2SO_4 (200 ml) was refluxed for 3 hr. The clear soln was made alkaline with 28% NH_4OH under ice-cooling and extracted with CH_2Cl_2. The CH_2Cl_2 soln was washed with H_2O, dried over K_2CO_3 and the solvent was removed. The residue was dissolved in benzene and chromatographed on alumina (18 g). Elution with benzene gave an amorphous powder (3·5 g, 96%), $[\alpha]_D^{23}$ +53·0° (*c*, 1·916, EtOH); UV λ_{max}^{EtOH} mμ (log ε): 234 (4·20), 258·5 (4·15), 297·5 (3·49); λ_{min}^{EtOH} mμ (log ε): 223 (4·11), 247 (4·09), 292 (3·48); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3614 (OH), 3394 (NH), 1718 (OCOφ), 1678 (sec lactam). (Found: C, 67·99; H, 7·59; N, 5·84; H_2O, 2·01. $C_{27}H_{34}O_3N_2 \cdot \frac{1}{2}H_2O$ requires: C, 68·19; H, 7·42; N, 5·89; H_2O, 1·89%).

allo-*Tetrahydropyranyl ether* (XIIb)

To a soln of Xb (6·8 g) in $CHCl_3$ (130 ml) was added *p*-TsOH H_2O (3·0 g) and the water was removed azeotropically. After addition of dihydropyran (5·0 g), the soln was allowed to stand overnight at room temp, washed with 5% NH_4OH and then with water, dried over K_2CO_3 and the solvent was removed to give a crystalline residue (7·5 g) (94%), m.p. 178–181°. Recrystallization from EtOAc-CH_2Cl_2 (3:4) gave XIIb as colourless needles (6·8 g, 85·5%), m.p. 181–182°, $[\alpha]_D^{23.5}$ +68·5° (*c*, 1·741, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε):

233 (4·20), 258 (4·15), 296 (3·49); λ_{min}^{EtOH} mμ (log ε): 222·5 (4·12), 247·5 (4·09), 290 (3·47); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3403 (NH), 1719 (OCOφ), 1681 (sec lactam). (Found: C, 69·53; H, 7·67; N, 5·22. $C_{32}H_{42}O_6N_2$ requires: C, 69·79; H, 7·69; N, 5·09%).

Conversion of normal O-*benzoylaminoalcohol* (Xa) *to quinolizidone* (XIIIa)

To a soln of Xa (9·0 g) in $CHCl_3$ (56 ml) was added *p*-TsOH H_2O (3·6 g) and the water was removed azeotropucally. After addition of dihydropyran (4·9 g), the soln was allowed to stand for 1 hr at room temp, washed with 5% NH_4OH and then with water, dried over K_2CO_3 and the solvent was removed. The resulting crude XIIa (11·2 g) was dissolved in acetone (150 ml) and refluxed for 3·5 hr. Removal of the solvent and recrystallization from acetone-n-hexane (1 : 1) gave XIIIa as colourless pillars (6·6 g, 62·2%), m.p. 185–186° Further recrystallization from acetone-n-hexane raised its m.p. to 188–189°, $[\alpha]_D^{22}$ +173° (*c*, 2·057, $CHCl_3$); UV λ_{max}^{EtOH} mμ (log ε): 232·5 (4·33), 304 (3·53); λ_{min}^{EtOH} mμ (log ε): 265 (3·09); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440 (NH), 1720 (OCOφ), 1630 (tert lactam). (Found: C, 69·66; H, 7·75; N, 5·36. $C_{32}H_{42}O_6N_2$ requires: C, 69·79; H, 7·69; N, 5·09%). After removal of the solvent from the mother liquor of XIIIa, the residual material was dissolved in EtOH (20 ml) and treated with styphnic acid to recover the starting Xa as the styphnate (3·8 g, 27%), m.p. 212–214° (dec).

allo-*Quniolizidone* (XIIIb)

A soln of XIIb (2·0 g) in MeCN (60 ml) was refluxed for 36·5 hr. After removal of the solvent, the residue was treated with acetone to yield crystals (130 mg, 6·5%), m.p. 178–182°, which was identified as the starting XIIb by comparison of its IR spectra and R_f values on TLC and by mixed m.p. The material obtained from the mother liquor of XIIb was recrystallized from EtOAc to give XIIIb as colourless pillars (1·58 g, 79%), m.p. 165–167°, increasing to 169–171° upon recrystallization from acetone-n-hexane, $[\alpha]_D^{24}$ +47·0° (*c*, 2·074, EtOH); UV λ_{max}^{EtOH} mμ (log ε): 232·5 (4·32), 284·5 (3·29), 307 (3·50); λ_{min}^{EtOH} mμ (log ε): 267·5 (3·14), 287 (3·28); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3446, 3371 (NH), 1710 (OCOφ), 1634 (tert lactam). (Found: C, 69·93; H, 7·75; N, 5·09. $C_{32}H_{42}O_6N_2$ requires: C, 69·79; H, 7·69; N, 5·09%).

Lithium aluminum hydride reduction of normal quinolizidone (XIIIa)

A soln of XIIIa (1·0 g) in THF (20 ml) was added to a well stirred suspension of LAH (1·0 g) in THF (30 ml) under refluxing. The soln was refluxed for 1 hr, and the excess reagent was decomposed by addition of moist Et_2O under ice-cooling. The mixture was treated with 5% NaOH and the organic layer was evaporated under reduced press. The residue was taken in Et_2O, washed with water, dried over K_2CO_3 and the solvent was removed to give an oily residue which showed two spots on TLC. Preparative TLC ($CHCl_3$-MeOH = 4 : 1) gave the main product XIVa as an oil (577 mg, 76%), $[\alpha]_D^{22}$ +26·9° (*c*, 1·771, EtOH); UV λ_{max}^{EtOH} mμ (log ε): 236 (3·85), 300 (3·44); λ_{min}^{EtOH} mμ (log ε): 266 (2·73); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3564 (OH), 3414 (NH), 3344 (NH). A minor product (XVa) was obtained as an oil (133 mg, 17·5%) UV λ_{max}^{EtOH} mμ (log ε): 244 (4·00), 308 (3·50); λ_{min}^{EtOH} mμ (log ε): 226 (3·78), 280 (3·20); NMR ($CDCl_3$): τ 2·67 (s, 5H, $CH_2\phi$), 5·75 (s, 2H, —C<u>H</u>$_2\phi$).

Lithium aluminum hydride reduction of allo-*quinolizidone* (XIIIb)

Reduction of XIIIb (200 mg) with LAH (200 mg) by the above mentioned procedure gave an oily material (150 mg), which showed two spots on TLC. Preparative TLC ($CHCl_3$-MeOH = 4 : 1) gave the main product XVb as an oil (90 mg, 48%), $[\alpha]_D^{23}$ −9·3° (*c*, 1·067, EtOH); UV λ_{max}^{EtOH} mμ (log ε): 243 (4·03), 308 (3·50); λ_{min}^{EtOH} mμ (log ε): 225 (3·81), 279 (3·24); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640 (OH), 3360 (NH), 2780, 2720 (*trans*-quinolizidine); NMR ($CDCl_3$) τ 2·70 (s, 5H, $-CH_2\phi$), 5·77 (s, 2H, —C<u>H</u>$_2\phi$). A minor product (17 mg, 11%) was identified as *allo*-XIVb by TLC and IR and UV spectroscopy.

allo-*Desbenzoyl quinolizidone* (XVIb)

A soln of XIIIb (4·0 g) in MeOH (30 ml) was made alkaline by addition of 5% NaOH (6 ml) and heated for 5 min on a water bath. After removal of the solvent, the residue was extracted with CH_2Cl_2, washed with water, dried over K_2CO_3 and the solvent was removed. A crystalline residue (3·17 g, 97·3%), m.p. 128–130°, was recrystallized from EtOAc-n-hexane (3 : 2) to give XVIb as pillars (3·02 g, 93%), m.p. 131–132°, $[\alpha]_D^{24}$ 0° (*c*, 2·105, EtOH); UV λ_{max}^{EtOH} mμ (log ε): 235 (3·86), 302 (3·51); λ_{min}^{EtOH} mμ (log ε): 226 (3·86), 265 (2·72); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575 (OH), 3355 (NH). (Found: C, 67·38; H, 8·52; N, 6·57. $C_{25}H_{38}O_3N_2$ requires: C, 67·23; H, 8·53; N, 6·27%).

Lithium aluminum hydride reduction of allo-*desbenzoylquinolizidone* (XVIb).

Reduction of XVIb (1·8 g) with LAH (1·8 g) in the same manner as described in the reduction of XIIIb gave an oily product (1·7 g), which was dissolved in benzene and chromatographed over alumina (17 g). Elution with benzene, benzene-$CHCl_3$ (4:1) and benzene-$CHCl_3$ (1:1) gave XIVb as an oil (1·36 g, 78·2%). $[\alpha]_D^{24}$ +15·1° (*c*, 1·704, EtOH); UV λ_{max}^{EtOH} mμ (log ε): 234·5 (3·89), 300 (3·49); λ_{min}^{EtOH} mμ (log ε): 264 (2·59); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3578 (OH), 3403, 3343 (NH), 2822, 2778 (*trans*-quinolizidine); NMR ($CDCl_3$) τ 6·30 (s, $OC\underline{H}_3$), 9·07 (3H, CH_2—$C\underline{H}_3$).

10-*Methoxydihydrocorynantheol* (I)

(a) A mixture of XIVa (7·0 g), t-BuOLi (7·0 g) and benzophenone (25 g) in dry benzene (160 ml) was heated at 115° for 72 hr in a sealed tube under N_2. The reaction mixture was poured into ice-cooled 10% HCl (100 ml) under stirring. Separated crystals were collected and dissolved in MeOH. The solution was acidified with 10% HCl and the MeOH was removed.

After washing with Et_2O, the residue was made alkaline with NH_4OH aq and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent was removed. The residue (5·0 g) was crystallized from EtOAc to give brown crystals (3·0 g), m.p. 162–163°.

The acidic layer was washed with benzene and then made alkaline with NH_4OH aq and extracted with $CHCl_3$. The $CHCl_3$ soln was worked up as above to give a residue (300 mg) which was combined with the material (2·0 g) obtained from the above mentioned mother liquor and chromatographed on alumina (15 g) and developed with $CHCl_3$. Removal of the solvent and crystallization from EtOAc gave brown crystals (1·08 g), m.p. 162–163°. The crude product (4·08 g) was recrystallized from EtOAc to give pale brown needles (3·61 g, 68%), m.p. 163–164°, $[\alpha]_D^{22}$ +10·5° (*c*, 1·662, EtOH), $[\alpha]_D^{23}$ −21·8° (*c*, 2·000, pyridine) [lit.[1] $[\alpha]_D^{24}$ −16·3° (*c*, 1·55, pyridine)]; UV λ_{max}^{EtOH} mμ (log ε): 226·5 (4·46), 282 (3·95), 294 (sh) (3·90); λ_{min}^{EtOH} mμ (log ε): 251 (3·41); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3616 (OH), 3466 (NH), 2829, 2805, 2753 (*trans*-quinolizidine). (Found: C, 73·01; H, 8·68; N, 8·47. $C_{20}H_{28}O_2N_2$ requires: C, 73·13; H, 8·59; N, 8·53%). This product was identical with I given by courtesy of H. Schmid by comparison of their IR spectra and specific rotations and mixed m.p.

(b) An Oppenauer oxidation of XIVb (500 mg) with t-BuOLi (500 mg) and benzophenone (3·0 g) in dry benzene (10 ml) gave an oily material (328 mg) which was submitted to preparative TLC ($CHCl_3$-MeOH = 4:1). The extraction from the major band gave an oily material (256 mg, 64%) which was identified as XVIIb by TLC and IR spectroscopy. The minor band was treated as above to give a crystalline material (10 mg, 2·5%), m.p. 157–159°, which was recrystallized from EtOAc as brown needles, m.p. 162–163°. This product was identified as I by comparison of its IR spectra and mixed m.p.

allo-*Quinolizidine* (XVIIb)

A soln of XIVb (100 mg) in MeOH (2 ml) was acidified with 10% HCl (1 ml) and the MeOH was removed. after washing with Et_2O, the residue was made alkaline with NH_4OH aq and extracted with $CHCl_3$. The soln was washed with water, dried over K_2CO_3 and the solvent was removed to give an oily residue (83 mg), which was dissolved in benzene and chromatographed on alumina (400 mg). Elution with benzene gave XVIIb as an oil (80 mg), $[\alpha]_D^{23}$ −6·3° (*c*, 1·548, EtOH); UV λ_{max}^{EtOH} mμ (log ε): 234·5 (3·90), 299·5 (3·50); λ_{min}^{EtOH} mμ (log ε): 263 (2·67); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640 (OH), 3400 (NH), 2780, 2740 (*trans*-quinolizidine).

10-*Hydroxydihydrocorynantheol* (XVIII)

BBr_3 (2·6 g) was added to an ice cooled soln of I (800 mg) in $CHCl_3$ (30 ml). After standing for 15 min at room temp, the mixture was poured into ice water under stirring and made basic with NH_4OH aq. Separated crystals were collected and recrystallized from 50% MeOH to give XVIII as needles (714 mg, 93%), m.p. 225–226° (dec), $[\alpha]_D^{23}$ +6·4° (*c*, 2·061, EtOH); UV λ_{max}^{EtOH} mμ (log ε): 226 (4·44), 280 (3·96), 295·5 (sh) (3·86); λ_{min}^{EtOH} mμ (log ε): 251 (3·43); CD: $[\theta]_{310}$ −3400, $[\theta]_{275}$ +6700, $[\theta]_{244}$ +2500 (*c*, 0·0412, EtOH). (Found: C, 71·49; H, 8·46; N, 8·78. $C_{19}H_{26}O_2N_2 \cdot \frac{1}{2}H_2O$ requires: C, 71·55; H, 8·38; N, 8·79%).

Tetrazolyl ether (XIX)

Finely powdered K_2CO_3 (220 mg) and 1-phenyl-5-chlorotetrazole (174 mg) was added to a soln of XVIII (250 mg) in DMF (8 ml). After stirring overnight at room temp under an N_2 stream, the reaction mixture was poured into ice water (10 ml) and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with 5% KOH and then with water, dried over K_2CO_3, and the solvent was removed. The residue was dissolved in benzene and extracted with 10% HCl. The aqueous layer was made basic with aq 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 sol-

vent was removed. The residue was converted to the hydrochloride. Recrystallization from EtOH gave colourless needles (280 mg, 71%), m.p. 265° (dec). (Found: C, 62·96; H, 6·26; N, 16·99; Cl, 7·25. $C_{26}H_{30}O_2N_6$ HCl requires: C, 63·08; H, 6·31; N, 16·98; Cl, 7·16%).

Dihydrocorynantheol (VI)

A soln of XIX liberated from the hydrochloride (240 mg) in EtOH (13 ml) was hydrogenated on 5% Pd-C (220 mg) at room temp for 3 hr. After removal of the catalyst and the solvent, the residue was made alkaline with 5% NaOH and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent was removed to give a crystalline residue (142 mg) which was recrystallized from EtOAc to give VI as needles (99 mg, 62%), m.p. 184–185° (lit.[1] 185–187°), $[\alpha]_D^{25}$ −36·8° (*c*, 1·059, pyridine) (lit.[1] $[\alpha]_D^{23}$ −37° (*c*, 0·938, pyridine)); UV λ_{max}^{EtOH} mμ (log ε): 226 (4·57), 275 (sh) (3·85), 283 (3·87), 290·5 (3·8); λ_{min}^{EtOH} mμ (log ε): 247·5 (3·31), 288·5 (3·79); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3464 (NH), 2804, 2754 (*trans*-quinolizidine). (Found: C, 76·63; H, 8·90; N, 9·30. Calc. for $C_{19}H_{26}ON_2$: 76·47; H, 8·78; N, 9·39%). This product was identical with dihydrocorynantheol donated by the courtesy of H. Schmid by comparison of their IR spectra and specific rotations and the mixed m.p.

Quaternization of 10-*methoxydihydrocorynantheol* (I)

A soln of I (196 mg) and excess MeI (3 ml) in EtOH (5 ml) was allowed to stand overnight at room temp and the solvent was removed to give a crystalline residue which showed two +N-Me signals at 6·90 and 6·65 τ in the NMR spectrum (CF_3COOH). Recrystallization from EtOH gave XXII (X = I) as prisms (105 mg, 37·7%), m.p. 268–269° (dec). Further recrystallization from EtOH raised its m.p. to 270–272° (dec) [lit.[1] 263–266° (dec)], $[\alpha]_D^{23·5}$ + 81·6° (*c*, 0·515, 70% MeOH); UV λ_{max}^{EtOH} mμ (log ε): 275 (3·96), 296 (sh) (3·75), 309 (sh) (3·63); λ_{min}^{EtOH} mμ (log ε): 247 (3·44); NMR (CF_3OOH): τ 5·93 (s, $OC\underline{H}_3$), 690 (s, +N—$C\underline{H}_3$); CD: $[\theta]_{304}$ −4970, $[\theta]_{265}$ +8590 (*c*, 0·0515, 70% MeOH). (Found: C, 53·58; H, 6·77; N, 5·87; I, 26·73. Calc. for $C_{20}H_{28}O_2N_2MeI$: C, 53·62; H, 6·64; N, 5·96; I, 26·98%). The picrate was recrystallized from EtOH as orange-red needles, m.p. 222–223° (dec): NMR (d_6-acetone): τ 6·22 (s, $OC\underline{H}_3$), 6·80 (s, +N-$C\underline{H}_3$). (Found: C, 56·86; H, 6·02; N, 12·26. $C_{21}H_{31}O_2N_2$ $C_6H_2O_7N_3$ requires: C, 56·73; H, 5·82; N, 12·25%). The material obtained from the mother liquor of XXII (X = I) was dissolved in aq EtOH and treated with sodium picrate. Precipitated crystals were collected and recrystallized from EtOH-acetone to give XXIII as a picrate, yellow needles, (170 mg, 49·5%), m.p. 234–235° (dec); NMR (d_6-acetone): τ 6·20 (s, $OC\underline{H}_3$), 6·54 (s, +N-$C\underline{H}_3$). (Found: C, 56·83; H, 6·02; N, 12·26. $C_{21}H_{31}O_2N_2$ $C_6H_2O_7N_3$ requires: C, 56·73; H, 5·82; N, 12·25%).

The iodide XXIII (X = I). The picrate (170 mg) was dissolved in 50% acetone and passed through a column of Amberlite IRA-410 iodide form (95 ml). Removal of the solvent gave an amorphous powder (140 mg), $[\alpha]_D^{23·5}$ +36·7° (*c*, 0·534, 70% MeOH); UV λ_{max}^{EtOH} mμ (log ε): 272 (3·91), 295·5 (3·67), 307·5 (3·58); λ_{min}^{EtOH} mμ (log ε): 246·5 (3·44), 293 (3·66), 306 (3·58); NMR (CF_3COOH): τ 5·93 (s, $OC\underline{H}_3$), 6·65 (s, +N—$C\underline{H}_3$); CD: $[\theta]_{303}$ −6000, $[\theta]_{270}$ +4300 (*c*, 0·0534, 70% MeOH).

Quaternization of 10-*hydroxydihydrocorynantheol* (XVIII)

A soln of XVIII (440 mg) and excess MeI (3 ml) in EtOH (10 ml) was allowed to stand for 5 hr at room temp. Removal of the solvent gave a crystalline residue which showed two +NCH_3 signals at 6·97 and 6·67 τ in the NMR spectrum (CF_3COOH). Treatment of the residue with MeOH-acetone gave XX (X = I) as needles (200 mg, 31·5%), m.p. 272° (dec). Recrystallization from MeOH-acetone raised its m.p. to 275–276° (dec), $[\alpha]_D^{24}$ +71·8° (*c*, 1·535, 50% MeOH); UV λ_{max}^{EtOH} mμ (log ε): 275·5 (3·96), 300 (3·69), 310 (sh) (3·62); λ_{min}^{EtOH} mμ (log ε): 248 (3·45), 297 (3·69; NMR (CF_3COOH): τ 6·97 (s, +$NC\underline{H}_3$); CD: $[\theta]_{270}$ +11,500 (*c*, 0·0768, 50% MeOH). (Found: C, 51·86; H, 6·51; N, 5·67; I, 27·11. $C_{20}H_{29}O_2N_2I\cdot\frac{1}{2}H_2O$ requires: C, 51·61; H, 6·50; N, 6·02; I, 27·27%). The picrate was recrystallized from EtOH as orange-red needles, m.p. 261–262° (dec). (Found: C, 54·78; H, 5·48; N, 12·29. $C_{20}H_{29}O_2N_2$ $C_6H_2O_7N_3\cdot\frac{1}{2}H_2O$ requires: C, 55·12; H, 5·69; N, 12·36%).

The chloride. A soln of the iodide in 50% MeOH was passed through a column of Amberlite IRA 410 (Cl^-) and the solvent was removed. The residue was recrystallized from EtOAc-MeOH to give prisms, m.p. 288–289° (dec) (in evacuated tube) [lit.[2] m.p. 288–289° (dec) (in evacuated tube)], $[\alpha]_D^{26}$ +94·9° (*c*, 1·778, MeOH) [lit. $[\alpha]_D^{23}$ +85·3° (MeOH)]; λ_{max}^{MeOH} mμ (log ε): 267 (sh) (3·92), 275·5 (3·95), 299 (3·69), 309 (sh) (3·63); λ_{min}^{MeOH} mμ (log ε): 246·5 (3·40), 297 (3·69); NMR (D_2O): τ 2·4–3·2 (3H, aromatic $\underline{H}$), 7·34 (s, +$NC\underline{H}_3$); CD: $[\theta]_{308}$ −4300, $[\theta]_{265}$ +10,400 (*c*, 0·0445, MeOH). (Found: C, 65·64; H, 7·84; N, 7·65; Cl, 9·66. Calc. for $C_{20}H_{29}O_2N_2Cl$ C, 65·83; H, 8·01; N, 7·68; Cl, 9·72%). This compound was identical with III donated

by the courtesy of P. J. Scheuer by comparison of their IR spectra, m.ps and specific rotations. The material obtained from the mother liquor of XX (X = I) was dissolved in aqueous EtOH and treated with sodium picrated to give XXI as a picrate, yellow needles (500 mg, 50%), m.p. 191–193° (dec). Recrystallization from EtOH-acetone raised its m.p. to 193–194° (dec). (Found: C, 55·31; H, 5·53; N, 12·34. $C_{20}H_{29}O_2N_2$ $C_6H_2O_7N_3 \cdot \frac{1}{2} H_2O$ requires: C, 55·12; H, 5·69; 12·36%). The iodide, prepared from the picrate by the use of anion exchanger, Amberlite IRA 410 (I^-), was an amorphous powder, $[\alpha]_D^{24}$ +29·8° (*c*, 0·590, 50% MeOH); Uv λ_{max}^{EtOH} mμ (log ε): 272·5 (3·84), 300 (3·56), 308 (sh) (3·52); λ_{min}^{EtOH} mμ (log ε): 247 (3·41), 294·5 (3·54); CD: $[\theta]_{304}$ −4000, $[\theta]_{264}$ +3600 (*c*, 0·0590, 50% MeOH); NMR (CF_3COOH): τ 6·67 (s, $+NC\underline{H}_3$). The chloride, prepared from the picrate by the use of an anion exchanger, Amberlite IRA 410 (Cl^-), was an amorphous powder, $[\alpha]_D^{24}$ +47·3° (*c*, 0·660, MeOH); UV λ_{max}^{MeOH}mμ (log ε): 245·5 (3·42), 294 (3·61); CD: $[\theta]_{306}$ −4100, $[\theta]_{260}$ +5600 (*c*, 0·0466, MeOH); NMR (D_2O): τ 6·93 (s, $+NC\underline{H}_3$).

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