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SYNTHESIS OF 3-EPI-10-METHOXYDIHYDROCORYNANTHEOL FROM QUINIDINE

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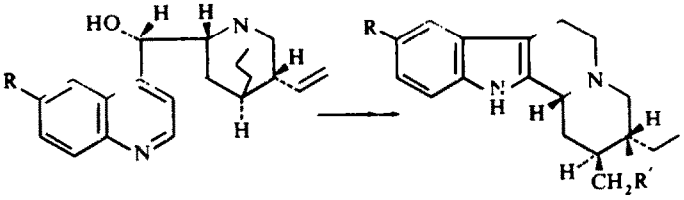
Abstract—3-epi-10-Methoxydihydrocorynantheol (I) was synthesized from quinidine (II). The elimination of the methoxyl group from this compound is also described.

AS DESCRIBED in a previous paper,[1] 3-epi-10-methoxydihydrocorynantheol (I) is required for the determination of the configuration at C_8 of 5'-methoxydihydrocinchonamine and its epimer. Our goal in this experiment was to synthesize 3-epi-10-methoxydihydrocorynantheol (I) from quinidine (II), since the corresponding methoxy-free cinchona alkaloid, cinchonine (III), had been successfully converted to 3-epi-dihydrocorynantheane (IV) by Ochiai *et al.*[2] In accordance with the methods



II: R = OCH_3 I: R = OCH_3, R' = CH_2OH

III: R = H IV: R = H, R' = CH_3

FIG 1

used by Ochiai for the preparation of 2'-oxo-tetrahydroquinine[3] and 2'-oxo-tetrahydrocinchonine,[4] quinidine (II) was transformed into 2'-oxo-tetrahydroquinidine (IX), m.p. 203–204°, through V, m.p. 167–168°, VI, m.p. 156°, VII, m.p. 190–191°, and VIII, m.p. 203–205°, as shown in Fig 2. Catalytic hydrogenation of IX gave two $C_{4'}$-isomers of 2'-oxo-hexahydroquinidine, Xa, m.p. 226–227°, and Xb, m.p. 120° (with foaming), of which the latter was isolated as its benzoate (XIIb), m.p. 230–231°. The configuration at $C_{4'}$ was determined by a comparison of the CD curves of these compounds, Xa and Xb, with those of the corresponding quinine derivatives, XIa and XIb. The configuration at $C_{4'}$ of the latter two compounds was determined by NMR study described in a previous paper.[5]

As shown in Table 1 the compound, Xa has a CD curve which is the mirror image of XIa; the compounds Xb and XIb also exhibit almost exact mirror image curves. This indicates that the compounds Xa and XIa as well as the compounds Xb and XIb have opposite sterochemistries from each other at the asymmetric center C_4.

The von Braun reaction of the benzoates XIIa and XIIb gave the corresponding N-cyanobromides, XIIIa, m.p. 183–184°, and XIIIb, m.p. 232–233° (dec), in good

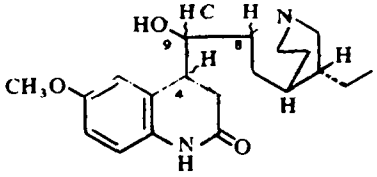
II
Pd/c
V
H_2O_2
AcOH
VI
SO_2
VII
Raney Ni
H_2
IX: R = OH
VIII: R = Cl
Xa, b: R = H
XIIa, b: R = COφ

FIG 2

TABLE 1. CIRCULAR DICHROISM OF 2'-OXO-HEXAHYDROQUINIDINES (Xa AND Xb) AND 2'-OXO-HEXAHYDROQUININES (XIa AND Xb)

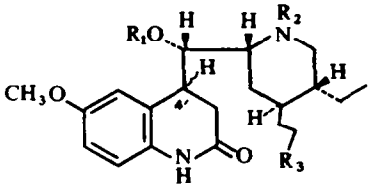
Compound	Configurations C_8H	C_9H	C_4·H	Cotton effects $m_\mu([\theta])$	$m\mu([\theta])$
Xa	β	β	β	300 (+ 10700)	262 (− 14400)
Xb	β	β	α	301 (− 15200)	261 (+ 15800)
XIa	α	α	α	301 (− 12400)	262 (+ 17500)
XIb	α	α	β	301 (+ 15000)	262 (− 20000)

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

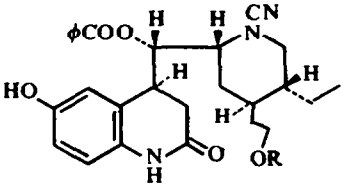


Xa, b and XIa, b

yields. The structures of XIIIa and XIIIb were based on NMR studies of the corresponding N-cyanoacetates, XIVa, m.p. 226·5–227·5° and XIVb, m.p. 178–179°, both of which were prepared in good yields by treatment of the N-cyanobromides, XIIIa and XIIIb, with silver acetate in pyridine solution. In the NMR spectra, the N-cyanoacetate XIVa clearly showed the signal due to the methylene protons adjacent to the O-acetyl grouping as a triplet centered at 6·12 τ (J = 6 c/s) and the corresponding signal of XIVb appeared at 6·15 τ, although the triplet structure was partly masked by the signal due to the methoxy group. However, in the demethylated compound XVb, m.p. 215–216°, which was derived from XIVb by the action of BBr_3 along with the compound XVIb, m.p. 223–224°, the signal appeared clearly as a triplet centered at 6·12 τ with J = 6 c/s. Acid hydrolysis of the N-cyanoacetates, XIVa and XIVb, gave the corresponding O-benzoylaminoalcohols, XVIIIa, m.p. 170–171°, and XVIIIb, m.p. 159–160°, via the N-amides, XVIIa, m.p. 148–150°, and XVIIb, m.p. 236–238° (dec), respectively.



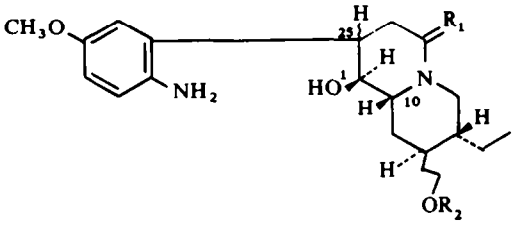
XIIIa, b: R_1 = COϕ, R_2 = CN, R_3 = Br
XIVa, b: R_1 = COϕ, R_2 = CN, R_3 = OAc
XVIIa, b: R_1 = COϕ, R_2 = $CONH_2$, R_3 = OH
XVIIIa, b: R_1 = COϕ, R_2 = H, R_3 = OH
XIXa, b: R_1 = COϕ, R_2 = H, R_3 = OTHP
XXa, b: R_1 = H, R_2 = H, R_3 = OTHP
XXIa, b: R_1 = H, R_2 = H, R_3 = OH



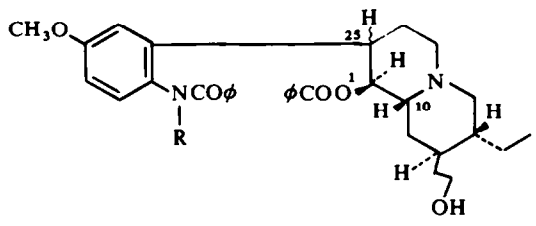
XVb: R = Ac
XVIb: R = H

FIG 3

The conversion of the O-benzoylaminoalcohols, XVIIIa and XVIIIb, into the corresponding quinolizidones, XXIIa, m.p. 138·5–140·5°, and XXIIb, an amorphous powder, was carried out in the same way as used in the synthesis of dihydrohunterburnine,[6] *i.e.*, protection of the primary alcohol groups with dihydropyran, methanolysis of the benzoyl groups and then recyclization of the lactam rings in a dipolar aprotic solvent. In the last step, the conversion, XXa → XXIIa, proceeded easily compared with another case, XXb → XXIIb. The quinolizidone XXIIa was



	R_1	R_2
XXIIa, b	O	THP
XXIIIb	O	H
XXIVa, b	H_2	THP
XXVb	H_2	H

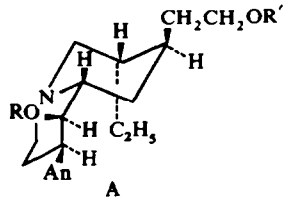


XXVIa, b: R = H
XXVIIa: R = COϕ

FIG 4

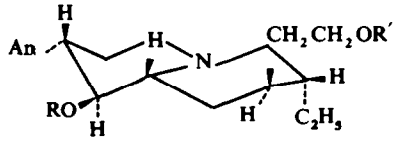
readily reconverted into the dihydrocarbostyril derivative XXIa, m.p. 231–232° (dec) (picrate) by the action of picric acid in ethanol, whereas treatment of the other quinolizidone XXIIb under the similar mild conditions merely caused the hydrolysis of the tetrahydropyranyl group to give XXIIIb, m.p. 253–254° (dec) (hydrochloride). LAH reduction of the quinolizidones XXIIa and XXIIb gave the corresponding quinolizidine derivatives, XXIVa and XXIVb, which were characterized as O,N-dibenzoates, XXVIa, m.p. 178–179° (picrate) and XXVIb, m.p. 242° (dec) (styphnate), respectively. In the IR spectra, the compounds XXIVb and XXVIb showed Bohlmann bands,[7] whereas the compounds XXIVa and XXVIa did not.

This indicated that the former compounds had a *trans*-fused quinolizidine system and the latter compounds a *cis*-fused system. In the NMR spectra, the benzoate XXVIb showed the signal of the C_1-proton as a triplet centered at 4·09 τ with J = 10 c/s and the corresponding signal of XXVIa was observed as a triplet centered at 4·92 τ with J = 3 c/s. These results showed that these compounds have the conformations A and B, respectively, so the hydrogen at C_2 must be represented by the α-configuration in XXIVa and XXVIa and by the β-configuration in XXIVb and XXVIb. Furthermore, the hydrogen at C_4· of the dihydrocarbostyril derivatives must be represented by the



A

XXIVa: R = H, R′ = THP
XXVIa: R = COϕ, R′ = H



B

XXIVb: R = H, R′ = THP
XXVIb: R = COϕ, R′ = H

FIG 5

β-configuration in Xa and XIIa—XXIa and by the α-configuration in Xb and XIIb—XXIb, since the configuration at $C_{4'}$ of the dihydrocarbostyril derivatives is identical with that at C_2 of the quinolizidine derivatives. This result is consistent with that obtained by comparison of the CD curves of Xa and Xb with those of XIa and XIb. The modified Oppenauer oxidation of XXIVa gave an indole compound, m.p. 216–217° (dec) (picrate), in 75·5% yield, while the compound XXIVb resisted the oxidation, the quinolizidine XXVb, m.p. 235° (dec) (hydrochloride) being recovered, given by the elimination of the tetrahydropyranyl group by the action of acid. The physical constants of this indole compound were consistent with those of 3-epi-10-methoxydihydrocorynantheol (I) reported by H. Schmid *et al.*[8] and its dehydrogenation with mercuric acetate gave the dehydro-compound (XXVIII), m.p. 223–225° (dec) (perchlorate), which was prepared by the similar dehydrogenation of 10-methoxydihydrocorynantheol (XXIX).[6]

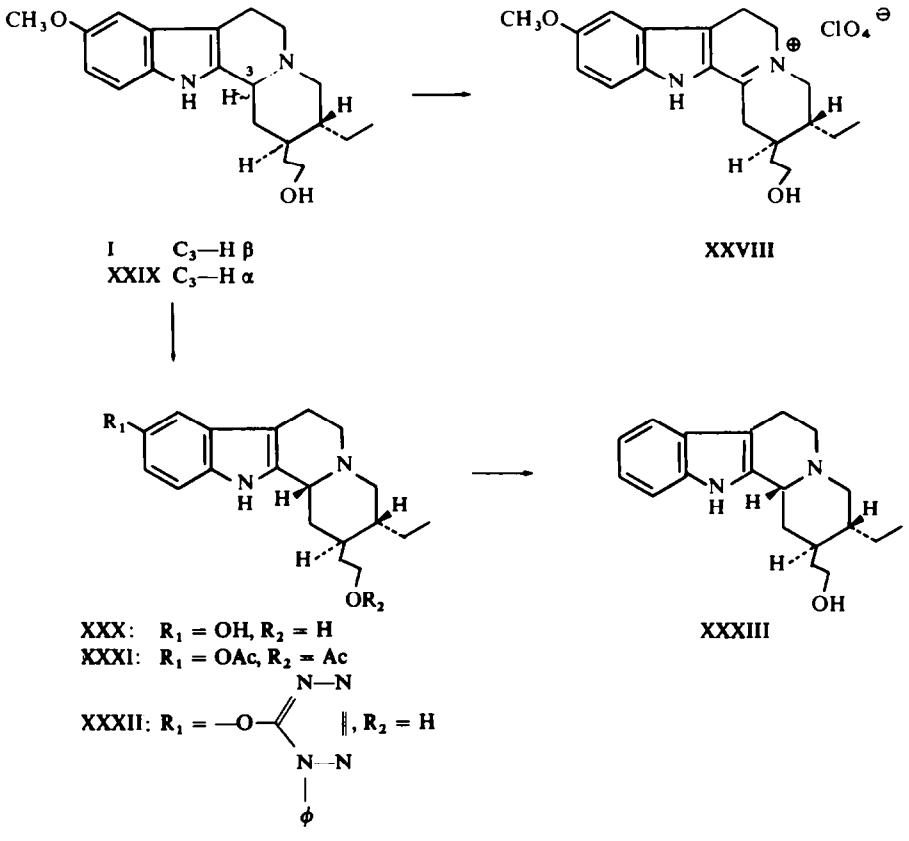


FIG 6

From these results, this indole compound was shown to be 3-epi-10-methoxydihydrocorynantheol (I). Conversion of I into 3-epi-dihydrocorynantheol (XXXIII) was also successfully achieved in the same way as previously described.[6] The methyl group of I was readily cleaved with BBr_3 giving the phenolic compound XXX as an amorphous powder which was purified by recrystallization of its diacetate (XXXI),

m.p. 153°. The phenolic compound (XXX) was subjected to Ullmann reaction with 1-phenyl-5-chlorotetrazole,[9] followed by hydrogenolysis of the resulting tetrazolyl ether (XXXII) to yield 3-epi-dihydrocorynantheol (XXXIII), m.p. 171–173°, $[\alpha]_D^{25}$ + 155·8° (pyridine), the physical constants of which were in good agreement with those of the same compound reported by H. Schmid.[8]

EXPERIMENTAL

All m.ps. are uncorrected. NMR spectra were recorded on a Varian A-60 instrument. The chemical shifts are exposed as τ units and are referred to TMS as the internal reference. CD curves were obtained with a JASCO ORD/UV-5 with CD attachment. UV spectra were measured in EtOH.

Dihydroquinidine (V)

Catalytic hydrogenation of I sulfate was carried out by known procedures.[10,11] Recrystallization from MeOH gave pillars, m.p. 167–168° (lit 169°), $[\alpha]_D^2$ +205·4° (c, 2·066, EtOH) (lit +231° (EtOH)). (Found: C, 70·32; H, 8·48; N, 7·83; CH_3O, 16·40. Calc for $C_{20}H_{26}O_2N_2.CH_3OH$: C, 70·36; H, 8·44; N, 7·82; CH_3O, 17·32%).

Dihydroquinidine di-N-oxide (VI)

To a soln of V (175 g) in AcOH (1350 ml) was added 30% H_2O_2 (175 ml) and the mixture heated at 65° under stirring. After 3·5 h more 30% H_2O_2 (175 ml) was added and the mixture was maintained at the same temp for an additional 5·5 h. The excess reagent was decomposed with SO_2 gas (81 g) under ice-cooling. The reaction mixture was concentrated under reduced press below 65°. The residue was made basic with NH_4OH aq under ice-cooling and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over K_2CO_3 and the solvent removed. The residue was dissolved in MeOH (300 ml) and treated with 60% $HClO_4$ to give colourless needles (118·1 g, 47·3%), m.p. 186–187° (dec). Recrystallization from EtOH raised its m.p. to 192–193° (dec). (Found: C, 51·49; H, 6·05; N, 6·03; Cl, 7·95; H_2O, 1·67. $C_{20}H_{26}O_4N_2.HClO_4.1/2H_2O$ requires: C, 51·34; H, 6·03; N, 5·99; Cl, 7·58; H_2O, 1·92%). The free base was recrystallized from acetone as needles, m.p. 156° (with foaming); UV λ_{max} mμ (log ε): 240 (4·66), 275 (3·80), 326 (4·08); λ_{min} mμ (log ε): 261 (3·67), 294·5 (3·62). (Found: C, 63·14; H, 7·66; N, 7·10; H_2O, 6·02. $C_{20}H_{26}O_4N_2.5/4H_2O$ requires: C, 63·05; H, 7·54; N, 7·35; H_2O, 5·91%).

Dihydroquinidine ar-N-oxide (VII)

A soln of VI liberated from its perchlorate (100 g) in 20% AcOH (450 ml) was saturated with SO_2 gas under ice-cooling. The ppts were filtered off and the filtrate was evaporated to dryness under reduced press. The residue was made alkaline with NH_4OH aq and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over K_2CO_3 and the solvent removed. The residue was dissolved in MeOH and treated with 60% $HClO_4$ to give VII perchlorate (23·3 g), m.p. 258° (dec). Recrystallization from MeOH gave colourless needles, m.p. 262° (dec). (Found: C, 52·83; H, 6·35; N, 6·22; Cl, 7·89. $C_{20}H_{26}O_3N_2.HClO_4.1/2H_2O$ requires: C, 53·15; H, 6·25; N, 6·20; Cl, 7·85%). The free base recrystallized from acetone as needles, m.p. 190–191°, $[\alpha]_D^{27.5}$ + 212·4° (c, 2·112, EtOH). UV λ_{max} mμ (log ε): 240 (4·65), 274 (3·81), 326 (4·06), λ_{min} mμ (log ε): 259·5 (3·69), 293 (3·59). (Found: C, 69·81; H, 7·88; N, 8·14. $C_{20}H_{26}O_3N_2$ requires: C, 70·15; H, 7·65; N, 8·18%). The ppts were dissolved in AcOH (150 ml) and the AcOH was removed under reduced pressure. The residue was made alkaline with aq NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was dried over K_2CO_3 and the solvent removed. The residue was dissolved in MeOH and treated with 60% $HClO_4$ to give VII perchlorate (74·1 g), m.p. 262° (dec). Total yield was 97·4 g (quantitative).

2'-Chloro-dihydroquinidine (VIII)

The ar-N-oxide VII (11·49 g) was dissolved in $CHCl_3$ (110 ml) and the water of crystallization was removed azeotropically. After the addition of $POCl_3$ (11 ml) under ice-cooling, the mixture was refluxed for 1·5 h, poured into ice water (100 ml) and made alkaline with 20% NaOH under stirring. The $CHCl_3$ layer was separated and the aqueous layer washed with $CHCl_3$. The $CHCl_3$ washing was combined with the $CHCl_3$ layer, washed with water, dried over K_2CO_3 and the solvent removed to give a solid material. Recrystallization from MeOH gave VIII as felts (11·17 g, 92%), m.p. 203–205°, $[\alpha]_D^{27.5}$ + 190·2° (c, 2·092, EtOH); UV λ_{max} mμ (log ε): 212 (4·50), 224 (sh) (4·46), 240 (4·55), 278 (3·59), 328 (sh) (3·68), 339 (3·71), λ_{min} mμ (log ε): 229 (4·45), 263·5 (3·57), 302 (3·20). (Found: C, 66·51; H, 7·17; N, 7·56; Cl, 9·83. $C_{20}H_{25}O_2N_2Cl$ requires: C, 66·65; H, 7·22; N, 7·67; Cl, 10·01%).

2'-Oxo-tetrahydroquinidine (IX)

A suspension of VIII (11·17 g) in 15% H_2SO_4 (120 ml) was refluxed for 5 h. The clear soln was poured into ice-cooled 28% NH_4OH (50 ml) with stirring. Precipitated crystals were collected and washed with water to give IX (11·18 g, 96%), m.p. 203–204° (dec). Recrystallization from MeOH gave colourless needles, m.p. 203–204° (dec), $[\alpha]_D^{24.5}$ + 145·7° (*c*, 2·079, EtOH); UV λ_{max} mμ (log ε): 235 (4·56), 350 (3·81), λ_{min} mμ (log ε): 298 (2·71); IR ν_{max}^{Nujol} cm^{-1}: 3330 (broad) (OH, NH), 1662 (C = O). (Found: C, 67·33; H, 8·19; N, 7·47; CH_3O, 15·39; CH_3OH, 8·14. $C_{20}H_{26}O_3N_2.CH_3OH$ requires: C, 67·35; H, 8·08; N, 7·48; CH_3O, 16·58; CH_3OH, 8·56%).

Reduction of 2'-oxo-tetrahydroquinidine (IX)

The reduction of IX (20 g) in EtOH (250 ml) was carried out at 120–130° for 15 h in the presence of Raney Ni (10 g) and H_2 at an initial pressure of 100 atm. After removal of the catalyst and the solvent, the residue was crystallized from acetone (100 ml) to give Xa (7·95 g), m.p. 222–224°. Recrystallization from EtOH gave colourless needles (7·40 g, 37%), m.p. 226–227°, $[\alpha]_D^{22.5}$ + 93·9° (*c*, 2·068, EtOH): UV λ_{max} mμ (log ε): 258·5 (4·13), 297 (3·46), λ_{min} mμ (log ε): 230·5 (3·64), 286·5 (3·41); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3330 (OH, NH), 1668 (C = O). (Found: C, 69·79: H. 8·30: N, 8·20. $C_{20}H_{28}O_3N_2$ requires: C, 69·74; H, 8·19; N, 8·13%). The acetone solution from Xa was evaporated to give an oily material (7·25 g). To a well stirred soln of the residue in $CHCl_3$ (40 ml) was added a soln of benzoylchloride (5·05 g) in $CHCl_3$ (10 ml) in the presence of 10% NaOH (20 ml) at room temp. After 2·5 h, the $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent was removed to give a solid material. Recrystallization from EtOH gave XIIb as colourless needles (5·99 g, 21%), m.p. 230–231°, $[\alpha]_D^{24}$ + 130·5° (*c*, 1·007, $CHCl_3$); UV λ_{max} mμ (log ε): 233·5 (4·26), 258 (4·20), 298 (3·53), λ_{min} mμ (log ε): 222·5 (4·18), 247 (4·15), 291 (3·50); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3411 (NH), 1718 (OCOφ), 1680 (C = 0). (Found: C, 72·50; H. 7·39; N, 6·50. $C_{27}H_{32}O_4N_2$ requires: C, 72·29; H, 7·19; N, 6·25%).

2'-Oxo-hexahydroquinidine (Xb)

A soln of XIIb (3·78 g) in 3% KOH-EtOH (75 ml) was refluxed for 1·5 h and the solvent removed to dryness. The residue was dissolved in 10% HCl and washed with Et_2O. The aqueous layer was made basic with conc NH_4OH under ice-cooling and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent removed to give a crystalline residue. Recrystallization from MeOH gave Xb as colourless needles (2·75 g, 95%), m.p. 120° (with foaming), $[\alpha]_D^{25}$ + 71·5° (*c*, 2·062, EtOH); UV λ_{max} mμ (log ε): 259 (4·12), 297 (3·48), λ_{min} mμ (log ε): 229 (3·50), 287 (3·43); IR ν_{max}^{Nujol} cm^{-1}: 3218 (OH, NH), 1673 (C = 0). (Found: C, 66·78; H, 8·72; N, 7·39; CH_3O, 16·54. $C_{20}H_{28}O_3N_2.CH_3OH$ requires: C, 66·99; H, 8·57; N. 7·44; CH_3O, 16·49%).

9-Benzoyl-2'-oxo-hexahydroquinidine (XIIa)

Benzoylation of Xa (48·16 g) as described above gave an oily material (70 g), which was dissolved in MeOH (120 ml) and treated with conc HCl. After removal of the solvent, the residue was crystallized from EtOAc to give XIIa as its hydrochloride (66·8 g, 97%), m.p. 284–285° (dec). Recrystallization from MeOH-EtOAc gave colourless needles, m.p. 284–285° (dec), $[\alpha]_D^{24.5}$ − 30·6° (*c*, 2·057, EtOH). (Found: C, 66·86; H, 6·94; N, 5·94; Cl, 7·59. $C_{27}H_{32}O_4N_2.HCl$ requires: C, 66·86; H. 6·86; N, 5·78; Cl, 7·31%). The free base was recrystallized from MeOH-Et_2O as colourless needles, m.p. 164°, $[\alpha]_D^{25}$ − 18·0° (*c*, 2·066, $CHCl_3$): UV λ_{max} mμ (log ε): 236 (4·25), 257 (4·13), 299 (3·44). λ_{min} mμ (log ε): 222·5 (4·07), 250 (4·11), 293 (3·43): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3414 (NH), 1720 (OCOφ), 1680 (C = 0). (Found: C, 72·47: H, 7·57: N, 6·30. $C_{27}H_{32}O_4N_2$ requires: C, 72·29; H, 7·19; N, 6·25%).

N-Cyanobromide (XIIIa)

To a well stirred soln of XIIa (3·0 g) in $CHCl_3$ (10 ml) was added a soln of BrCN (85 mg) in $CHCl_3$ (5 ml) and the mixture was refluxed for 2 h. After cooling, the soln was washed with 10% NaOH and then with water, dried over K_2CO_3 and the solvent removed. The crystalline residue was recrystallized from MeOH to give XIIIa as needles (3·35 g, 91%), 183–184°, $[\alpha]_D^{25}$ − 65·7° (*c*, 2·076, $CHCl_3$): UV λ_{max} mμ (log ε): 235 (4·25), 258 (4·16), 299 (3·52), λ_{min} mμ (log ε): 223 (4·14), 248 (4·13), 291 (3·50): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420 (NH), 2200 (CN), 1725 (OCOφ), 1680 (C = 0). (Found: C, 60·80; H, 5·92; N, 7·75; Br, 14·80. $C_{28}H_{32}O_4N_3Br$ requires: C, 60·65; H, 5·82; N, 7·58; Br, 14·41%).

N-Cyanobromide (XIIIb)

A von Braun reaction on XIIb (21·40 g) was carried out in the same way as described above. The crystalline product was recrystallized from $CHCl_3$-MeOH to give XIIIb as colourless needles (25·18 g, quantitative

yield), m.p. 232–233° (dec), $[\alpha]_D^{24.5}$ + 17·5° (*c*, 1·993, $CHCl_3$): UV λ_{max} mμ (log ε): 235 (4·23), 259 (4·16), 300 (3·49), λ_{min} mμ (log ε): 223 (4·10), 249·5 (4·13), 292 (3·47): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH), 2214 (CN), 1730 ($OCO\phi$), 1685 (C = 0). (Found: C, 60·86; H. 5·84; N, 7·78; $C_{28}H_{32}O_4N_3Br$ requires: C, 60·65; H, 5·82; N, 7·58%).

N-Cyanoacetate (XIVa)

A soln of XIIIa (22·20 g) and AgOAc (13·40 g) in pyridine (32 ml) was heated for 10 min at 130–135°. The excess reagent was decomposed by addition of aq NaCl. The ppts were filtered off and washed with CH_2Cl_2. The filtrate combined with the washings was evaporated to dryness and the residue was taken up in CH_2Cl_2. The CH_2Cl_2 soln was washed with dilute HCl and then with water, dried over K_2CO_3 and the solvent removed. The crystalline residue was recrystallized from MeOH to give XIVa as colourless needles (17·45 g, 81·8%), m.p. 226·6–227·5°, $[\alpha]_D^{26.5}$ − 87·9° (*c*, 2·020, $CHCl_3$): UV λ_{max} mμ (log ε): 233·5 (4·36), 257·5 (4·24), 299 (3·54), λ_{min} mμ (log ε): 223 (4·21), 249 (4·21), 294 (3·53): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 2230 (CN), 1730 (ester), 1685 (C = 0): NMR ($CDCl_3$) τ: 6·12 (t. J = 6 c/s, $-C\underline{H}_2OAc$), 6·24 (s. $OC\underline{H}_3$), 8·14 (s. $COC\underline{H}_3$). (Found: C, 67·76; H, 6·84; N, 7·93. $C_{30}H_{35}O_6N_3$ requires: C, 67·52; H, 6·61; N, 7·88%).

N-Cyanoacetate (XIVb)

Treatment of XIIIb (16·1 g) with AgOAc (9·7 g) as described above gave a dark brown oil (15 g), which was dissolved in CH_2Cl_2 and chromatographed on alumina (300 g). Elution with CH_2Cl_2 gave a crystalline residue (13·6 g). Recrystallization from MeOH gave XIVb as colourless needles (12·84 g, 83%), m.p. 178–179°, $[\alpha]_D^{26.5}$ + 6·0° (*c*, 2·105, $CHCl_3$): UV λ_{max} mμ (log ε): 234·5 (4·22), 258·5 (4·15), 300 (3·46). λ_{min} mμ (log ε): 222·5 (4·10), 249 (4·11), 290 (3·44): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3405 (NH), 2221 (CN), 1730 (ester), 1687 (C = 0): NMR ($CDCl_3$) τ; 6·15 (t., *J* = 5 c/s, $C\underline{H}_2OAc$), 6·22 (s., $OC\underline{H}_3$), 8·17 (s., $COC\underline{H}_3$). (Found: C, 67·67; H, 6·55; N, 7·77. $C_{30}H_{35}O_6N_3$ requires: C, 67·52; H, 6·61; N, 7·88%).

Demethylation of the N-cyanoacetate (XIVb)

A soln of BBr_3 (1 ml) in benzene (3 ml) was added to a soln of XIVb (1·0 g) in benzene (35 ml) at room temp. After being kept standing overnight at room temp, the mixture was poured into ice-water with stirring and made basic with conc NH_4OH. The ppts were collected and dissolved in CH_2Cl_2-MeOH (6:1). The soln was washed with aq NaCl and the solvent removed to give an amorphous powder (780 mg), which showed two spots on thin layer chromatography (TLC). Preparative TLC on silica gel KGF (Merck), developing with $CHCl_3$-MeOH (6:1), gave XVb as crystals (294 mg), m.p. 213–214°. Recrystallization from $CHCl_3$-n-hexane gave colourless needles, m.p. 215–216°, $[\alpha]_D^{24}$ + 25·7° (*c*, 0·922, EtOH); UV λ_{max} mμ (log ε): 235 (4·22), 259 (4·13), 302 (3·50), λ_{min} mμ (log ε): 222·5 (4·11), 250 (4·10), 291·5 (3·46); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3250 (OH, NH), 2211 (CN), 1729 (ester, 1679 (C = 0); NMR (d_6-acetone): τ 4·26 (1H, d-d, *J* = 10, 4 c/s, $\phi COOC\underline{H}$), 6·12 (2H, t, *J* = 6 c/s, $CH_2C\underline{H}_2OAc$), 8·17 (s, $COC\underline{H}_3$). (Found: C, 66·73; H, 6·51; N. 8·21. $C_{29}H_{33}O_6N_3$ requires: C, 67·03; H, 6·40; N, 8·09%). Another crystalline product (280 mg) isolated by preparative TLC was recrystallized from aqueous MeOH to give XVIb as colourless needles, m.p. 223–224°, $[\alpha]_D^{22}$ + 29·6° (*c*, 1·034, EtOH); UV λ_{max} mμ (log ε); 234·5 (4·23), 259 (4·13), 302 (3·49), λ_{min} mμ (log ε): 222 (4·11), 249 (4·10), 291 (3·45); IR ν_{max}^{Nujol} cm^{-1}: 3250 (OH, NH), 2220 (CN), 1728 (— $CO\phi$), 1690 (C = 0). (Found: C, 65·46; H, 7·02; N, 8·54; H_2O, 2·63. $C_{27}H_{31}O_5N_3 \cdot H_2O$ Requires: C, 65·44; H, 6·71; N, 8·48; H_2O, 3·64%).

Hydrolysis of N-*cyanoacetate* (XIVa)

1 *Formation of N-amide* (XVIIa). To a soln of XIVa (3·0 g) in MeOH (40 ml) was added 10% HCl (10 ml). The soln was refluxed for 12 h and the MeOH removed. The separated crystals were washed with dil NH_4OH and with water to give XIVa (3·3 g) m.p. 135° (with foaming), which was recrystallized from MeOH as pillars (2·8 g, 95%), m.p. 148–150°, $[\alpha]_D^{24}$ − 94·3° (*c*, 2·153, EtOH); UV λ_{max} mμ (log ε): 235 (4·24), 257 (4·16), 299 (3·46), λ_{min} mμ (log ε): 225 (4·17), 249 (4·14), 292 (3·43); IR ν_{max}^{Nujol} cm^{-1}: 3463, 3353, 3203 (OH, NH), 1723 ($OCO\phi$), 1645 (C═O), 1581 ($NCONH_2$). (Found: C, 64·03; H, 7·33; N, 7·88. $C_{28}H_{35}O_6N_3 \cdot H_2O$ requires: C, 63·74; H, 7·07; N, 7·97%).

2 *Formation of O-benzoylaminoalcohol* (XVIIIa). A soln of XIVa (11 g) in EtOH (240 ml) containing 15% H_2SO_4 (360 ml) was refluxed for 49 h and the solvent removed under reduced pressure. The residue was made basic with conc NH_4OH and extracted with $CHCl_3$. The soln was washed with water, dried over K_2CO_3 and the solvent removed to give a crystalline residue (9·3 g). Recrystallization from acetone gave XVIIIa as colourless needles (7·0 g, 73%), m.p. 171°, $[\alpha]_D^{23.5}$ − 49·9° (*c*, 1·991, EtOH); UV λ_{max} mμ (log ε): 233 (4·27), 258 (4·19), 298 (3·51), λ_{min} mμ (log ε): 224 (4·22), 248 (4·14), 291 (3·49); IR ν_{max}^{Nujol} cm^{-1}:

3533, 3288 (OH, NH), 1705 (OCOϕ), 1670 (C=O). (Found: C, 69·41; H, 7·37; N, 6·11. $C_{27}H_{34}O_5N_2$ requires: C, 69·50; H, 7·35; N, 6·00%). The material obtained from the mother liquor was dissolved in EtOH and treated with picric acid. The separated crystals (980 mg, 8%), m.p. 230–231° (dec), were collected and recrystallized from EtOH to give XXIa picrate as yellow needles (920 mg), m.p. 231–232° (dec). (Found: C, 52·53; H, 5·85; N, 11·70. $C_{20}H_{30}O_4N_2.C_6H_3O_7N_3$ requires: C, 52·79; H, 5·62; N, 11·84%). The free base was an amorphous powder, $[\alpha]_D^{23}$ + 61·3° (*c*, 1·950, EtOH); UV λ_{max} mμ (log ε): 258 (4·05), 297 (3·42), λ_{min} mμ (log ε): 228·5 (3·49), 287 (3·37): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3600 (OH), 3400 (NH), 1665 (C=O).

Hydrolysis of N-cyanoacetate (XIVb)

1 *Formation of N-amide* (XVIIb). A soln of XIVb (1·0 g) in MeOH (12 ml) containing 10% HCl (3 ml) was refluxed for 15·5 h and treated as described for the preparation of the N-amide XVIIa to give XVIIb (832 mg, 87·2%), m.p. 234–236° (dec). Recrystallization from acetone gave pillars, m.p. 236–238° (dec), $[\alpha]_D^{24}$ + 6·3° (*c*, 0·978, EtOH); UV λ_{max} mμ (log ε): 234 (4·20), 258 (4·13), 297 (3·48), λ_{min} mμ (log ε): 223 (4·15), 248 (4·10), 290 (3·47); IR ν_{max}^{Nujol} cm^{-1}: 3540, 3220 (OH, NH), 1701 (OCOϕ), 1659 (C=O), 1584 (N-CONH$_2$). (Found: C, 66·22; H, 7·19; N, 8·18. $C_{28}H_{35}O_6N_3$ requires: C, 65·99; H, 6·92; N, 8·25%).

2 *Formation of O-benzoylaminoalcohol* (XVIIIb). To a soln of XVIIb (200 mg) in EtOH (20 ml) was added 15% H_2SO_4 (30 ml). The mixture was refluxed for 23 h and the EtOH removed. The residue was made basic with aq NH_4OH and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried over K_2CO_3 and the solvent removed to give a crystalline residue (177 mg) which was recrystallized from EtOAc as colourless needles (130 mg, 71%), m.p. 159–160°, $[\alpha]_D^{20}$ + 44·7° (*c*, 1·036, EtOH); UV λ_{max} mμ (log ε): 233 (4·20), 259 (4·15), 297 (3·46), λ_{min} mμ (log ε): 222·5 (4·13), 247·5 (4·10), 291 (3·46); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3390 (OH, NH), 1710 (COϕ), 1675 (C=O). (Found: C, 69·38; H, 7·36; N, 5·96. $C_{27}H_{34}O_5N_2$ requires: C, 69·50; H, 7·35; N, 6·00%).

Tetrahydropyranyl ether (XIXb)

To a soln of XVIIIb (11·6 g) in $CHCl_3$ (500 ml) was added *p*-TsOH.H_2O (6·15 g). After azeotropic removal of the water, dihydropyran (2·3 g) was added to the mixture at room temp. After standing for 30 min a further 2·3 g of dihydropyran was added to the mixture and the soln allowed to stand for an additional 30 min at room temp. The reaction mixture was treated with dilute NH_4OH and washed with water, dried over K_2CO_3 and the solvent removed under reduced pressure. The residue (13·6 g) was crystallized from EtOAc-n-hexane to give XIXb (7·31 g, 53·5%), m.p. 153°. Recrystallization from EtOAc gave needles, m.p. 155·5–157°, $(\alpha]_D^{21}$ + 64·8° (*c*, 1·027, EtOH); UV λ_{max} mμ (log ε): 233 (4·20), 258 (4·15), 298 (3·51), λ_{min} mμ (log ε): 222·5 (4·13), 247 (4·10), 292 (3·49); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH), 1720 (COϕ), 1682 (C=O). (Found: C, 69·89; H, 7·67; N, 5·27. $C_{32}H_{42}O_6N_2$ requires: C, 69·79; H, 7·69; N, 5·09%). The mother liquor from the crude XIXb was evaporated and the residue dissolved in MeOH (25 ml). This soln was acidified with 10% HCl (25 ml) and the MeOH removed. After washing with Et_2O, the residue was made basic with conc NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent removed to give an amorphous powder (5·4 g), which was dissolved in $CHCl_3$ and chromatographed on alumina (50 g). Elution with $CHCl_3$ gave the starting material (XVIIIb) (4·5 g, 39%), m.p. 159–160°.

Desbenzoyl aminoalcohol (XXb)

A soln of XIXb (4·0 g) in 70% MeOH (120 ml) was refluxed for 3 h and the MeOH was removed under reduced pressure. The residue was made basic with dil NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent removed to give an amorphous powder (3·53 g). A small sample (320 mg) was purified by preparative TLC on silica gel KGF (Merck), developing with $CHCl_3$-MeOH (6:1), to give XXb as an amorphous powder (285 mg, 96%), $[\alpha]_D^{22}$ +44·7° (*c*, 1·008, EtOH): UV λ_{max} mμ (log ε): 259 (4·10), 294 (3·46), λ_{min} mμ (log ε): 227·5 (3·46), 288 (3·45); IR $\nu_{max}^{CHCl_3}$ cm^{-1}; 3650, 3386, 3226 (OH, NH), 1678 (C=O).

Quinolizidone derivative (XXIIb)

A soln of XXb (3·2 g) in CH_3NO_2 (200 ml) was refluxed for 15 h and the solvent evaporated to dryness. The residue was dissolved in benzene and chromatographed on alumina (60 g). Elution with $CHCl_3$ gave a pale brown amorphous powder (2·37 g) which showed one spot on TLC. A portion (300 mg) was purified by preparative TLC on silica gel KGF (Merck), developing with $CHCl_3$-MeOH (6:1), to give XXIIb as an amorphous powder (295 mg), $[\alpha]_D^{23}$ + 72·9° (*c*, 1·074, EtOH); UV λ_{max} mμ (log ε): 235 (3·90), 302 (3·51), λ_{min} mμ (log ε): 265 (2·69); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3640 (OH), 3400 (broad) (NH_2), 1630 (tert lactam). A soln of

XXIIb (530 mg) in EtOH (2 ml) was acidified with conc HCl and warmed for a while on a water bath. The separated crystals were collected and recrystallized from EtOH to give XXIIIb as its hydrochloride (463 mg, 98%), m.p. 253–254° (dec). UV: λ_{max} mμ (log ε): 277 (3·24), 283 (3·24), 302 (2·88), λ_{min} mμ (log ε): 257 (2·76), 280·5 (3·22), 292·5 (2·83). (Found: C, 60·36; H, 7·83; N, 7·09; Cl, 8·97. $C_{20}H_{30}O_4N_2$ HCl requires: C, 60·21; H, 7·83; N, 7·02; Cl, 8·89%). The free base was recrystallized from EtOH as needles, m.p. 173°, $[\alpha]_D^{23}$ +79·7° (c, 0·660, EtOH); UV λ_{max} mμ (log ε): 235 (3·93), 302 (3·53), λ_{min} mμ (log ε): 266 (2·75); IR ν_{max}^{Nujol} cm^{-1}: 3336, 3266, 3200 (OH, NH), 1630 (tert lactam). (Found: C, 66·22; H, 8·44; N, 7·92. $C_{20}H_{30}O_4N_2$ requires: C, 66·27; H, 8·34; N, 7·73%).

Quinilizidone derivative (XXIIa)

Treatment of XVIIIa (12·7 g) with dihydropyran (5·0 g) as described for XIXb gave XIXa as an oil (14·8 g). Without further purification, the crude product was refluxed with 70% MeOH (500 ml) for 7 h and worked up in the same way as described for XXb to give XXa as an amorphous powder (11·7 g), which showed no absorption band due to the benzoyl group. The residue was dissolved in CH_3NO_2 (150 ml) and refluxed for 2 h. After removal of the solvent, the residue was crystallized from EtOAc to give XXIIa (10·23 g, 86%), m.p. 135–137°. Recrystallization from EtOAc gave colourless needles, m.p. 138·5–140°, $[\alpha]_D^{20}$ − 60·8° (c, 1·001, EtOH), UV λ_{max} mμ (log ε): 235·5 (3·92), 301 (3·51), λ_{min} mμ (log ε): 225 (3·84), 266·5 (2·73); IR ν_{max}^{Nujol} cm^{-1}: 3340, 3226 (OH, NH), 1595 (tert lactam). (Found: C, 67·21; H, 8·27; N, 6·30. $C_{25}H_{38}O_5N_2$ requires: C, 67·23; H, 8·53; N, 6·27%). Treatment of a soln of XXIIa (200 mg) in EtOH (2 ml) with picric acid gave yellow needles (200 mg), m.p. 231–232° (dec). Comparison of the IR spectra and the mixed melting point determination showed that this product was identical with XXIa picrate.

Quinolizidine derivative (XXIVa)

A soln of XXIIa (2·0 g) in THF (35 ml) was added to a well stirred suspension of LAH (2·0 g) in THF (70 ml) under refluxing. The mixture was refluxed for 1 h and the excess reagent decomposed with EtOAc (15 ml) under ice-cooling. After addition of 10% NaOH (30 ml), the soln was separated from the ppt and the solvent removed under reduced pressure. The residue was dissolved in $CHCl_3$, washed with water, dried over K_2CO_3 and the solvent removed to give an oily material (2 g). Purification by alumina chromatography gave XXIVa as an oil (1·71 g, 88%), which showed one spot on TLC. $[\alpha]_D^{20}$ + 3·7° (c, 0·872, EtOH); UV λ_{max} mμ (log ε): 236 (3·88), 300 (3·47), λ_{min} mμ (log ε): 221·5 (3·74), 265 (2·63); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3570 (OH), 3410, 3330 (NH); NMR ($CDCl_3$) τ: 2·87–3·35 (3H, aromatic H), 5·48 (1H, broad, O—C<u>H</u>—O), 6·25 (s, OC<u>H</u>$_3$), 9·10 (3H, t, J = 7 c/s, —CH_2 —C<u>H</u>$_3$).

Quinolizidine derivative (XXIVb)

Reduction of XXIIb (1·5 g) with LAH (1·5 g) was carried out in the same way as above to give XXIVb as a reddish oil (1·45 g), which was decolourised by activated charcoal to give a pale brown oil (1·32 g, 90·5%). A sample was purified by preparative TLC on silica gel KGF (Merck), developing with $CHCl_3$-MeOH (4:1), $[\alpha]_D^{22}$ + 76·7° (c, 1·086, EtOH); UV λ_{max} mμ (log ε): 234·5 (3·90), 300 (3·49), λ_{min} mμ (log ε): 222 (3·78), 264 (2·68); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584 (OH), 3400, 3336 (NH), 2804, 2764 (*trans*-quinilizidine). A soln of XXIVb (290 mg) in MeOH (2 ml) was acidified with conc HCl and the solvent evaporated to dryness. The residue was washed with Et_2O and recrystallized from EtOAc-EtOH to give XXVb hydrochloride as needles (260 mg), m.p. 235° (dec) (sintered at 90°) (Found: C, 52·23; H, 8·33; N, 6·22; Cl, 15·65; H_2O, 8·58. $C_{20}H_{32}O_3N_2.2HCl.2H_2O$ requires: C, 52·51; H, 8·37; N, 6·12; Cl, 15·50; H_2O, 7·88%). The free base was an amorphous powder, $[\alpha]_D^{22}$ + 79·3° (c, 1·020, EtOH), UV λ_{max} mμ (log ε): 234 (3·90), 300 (3·50), λ_{min} mμ (log ε): 263 (2·62); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3618 (OH), 3400 (NH), 2840, 2820, 2780 (*trans*-quinolizidine).

Benzoylation of quinolizidine derivative (XXIVa)

A soln of XXIVa (370 mg) and benzoylchloride (600 mg) in pyridine (6 ml) was allowed to stand overnight at room temp, poured into ice-cooled aq NH_4OH under stirring and extracted with $CHCl_3$. The solution was washed with water, dried over K_2CO_3 and the solvent removed. The residue, taken up in MeOH, was acidified with 10% HCl and the MeOH evaporated. The residue was washed with Et_2O, made basic with NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent removed to give an amorphous powder (480 mg) which showed two spots on TLC. Preparative TLC on silica gel KGF, developing with $CHCl_3$-MeOH (9:1), gave O,N-dibenzoate (XXVIa) as an amorphous powder (245 mg, 50%), $[\alpha]_D^{21}$ − 72·7° (c, 1·081, EtOH); UV λ_{max} mμ (log ε): 228·5 (4·71), 260–270 (sh) (3·83); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 3410 (NH), 1710 (OCOϕ), 1667 (NHCOϕ); NMR ($CDCl_3$)

τ: 1·8–3·4 (13 H, aromatic H), 4·92 (1H, t, J = 3 c/s, ϕCOOCH), 6·50 (s, OCH$_3$), 9·20 (3H, t, J = 6 c/s, CH$_2$CH$_3$). The picrate was recrystallized from EtOH as yellow needles, m.p. 178–179°. (Found: C, 61·15; H, 5·47; N, 8·91. $C_{34}H_{40}O_5N_2.C_6H_3O_7N_3$ requires: C, 61·14; H, 5·52; N, 8·91%). Another product (XXIIa) isolated by preparative TLC was an amorphous powder (210 mg, 36·5%), $[\alpha]_D^{20}$ − 124·7° (*c*, 1·018, EtOH): UV λ_{max} mμ (log ε): 231 (4·51): IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3606 (OH), 1710 (OCOϕ), 1688, 1666 (NCOϕ); NMR ($CDCl_3$) τ: 2·0–3·5 (18H, aromatic H), 4·87 (1H, t, J = 5 c/s, ϕCOOCH), 6·28 (s, OCH$_3$), 9·17 (3H, t, J = 7 c/s, CH$_2$CH$_3$).

Benzoylation of quinolizidine derivative (XXIVb)

To a soln of XXIVb (290 mg) in pyridine (3 ml) was added a soln of benzoylchloride (300 mg) in pyridine (1 ml) with ice-cooling. The mixture was allowed to stand for 40 h in a refrigerator and worked up as above to give an amorphous powder (365 mg), which was dissolved in EtOH (3 ml) and treated with styphnic acid (160 mg). The separated crystals (495 mg, 87%), m.p. 242° (dec) were collected and recrystallized from EtOH to give the O,N-dibenzoate (XXVIb) styphnate as yellow needles (420 mg), m.p. 242° (dec). (Found: C, 59·73; H, 5·87; N, 8·31. $C_{34}H_{40}O_5N_2.C_6H_3O_8N_3.C_2H_5OH$ requires: C, 59·49; H, 5·83; N, 8·26%). The free base was an amorphous powder, $[\alpha]_D^{22}$ + 79·0° (*c*, 0·980, EtOH): UV λ_{max} mμ (log ε): 228 (4·46), 263–272 (sh) (3·84); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3618 (OH), 3400 (NH), 2834, 2809, 2764 (*trans*-quinolizidine), 1720 (OCOϕ), 1665 (NHCOϕ); NMR ($CDCl_3$) τ: 2·0–3·5 (13H, aromatic H), 4·09 (1H, t, J = 10 c/s, ϕCOOCH), 6·28 (s, OCH$_3$), 6·50 (t, —CH$_2$CH$_2$OH), 9·15 (3H, t, J = 7 c/s, CH$_2$CH$_3$).

Oppenauer oxidation of quinolizidine (XXIVa)

A mixture of XXIVa (950 mg), t-BuOLi (1·16 g) and benzophenone (6·8 g) in anhydrous benzene (15 ml) was heated at 115° in a sealed tube for 72 h under N_2 and then poured into ice water. The mixture was acidified with conc HCl with stirring. The aqueous layer was washed with Et_2O, made basic with conc NH_4OH and then extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent removed to give an amorphous powder (815 mg), which was dissolved in EtOH (10 ml) and treated with picric acid (500 mg). The separated crystals (980 mg), m.p. 154° (dec), were collected and recrystallized from EtOH to give 3-epi-10-methoxydihydrocorynantheol (I) picrate as orange-red needles (920 mg, 75·5%), m.p. 216–217° (dec) (sintered at 156–157°), (lit[8] 214–215° (dec)). (Found: C, 54·25; H, 5·72; N, 12·04; H_2O, 3·38. $C_{20}H_{28}O_2N_2.C_6H_3O_7N_3.H_2O$ requires: C, 54·25; H, 5·78; N, 12·17: H_2O, 3·13%). The free base was an amorphous powder, $[\alpha]_D^{24}$ + 128·4° (*c*, 0·605, pyridine) (lit[8] + 115° (pyridine)), $[\alpha]_D^{23}$ + 29·0° (*c*, 1·065, EtOH) UV λ_{max} mμ (log ε): 225 (4·42), 283·5 (3·93), 295 (sh) (3·89), λ_{min} mμ (log ε), 251·5 (3·37); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3593 (OH), 3465 (NH), CD: $[\theta]_{279}$ − 11000, $[\theta]_{250}$ − 3450, $[\theta]_{237}$ − 19500 (*c*, 0·1192, EtOH).

Oppenauer oxidation of quinolizidine (XXIVb)

Oppenauer oxidation of XXIVb (500 mg) was carried out in the same way as above to yield an amorphous powder (370 mg), which was converted to a crystalline hydrochloride (277 mg, 52%), m.p. 160° (with foaming). Recrystallization from EtOH-EtOAc gave colourless needles, m.p. 235° (dec). This compound was identified as XXVb hydrochloride by comparison of the IR spectra and by the mixed melting point method.

Dehydro-10-methoxydihydrocorynantheol (XXVIII) *perchlorate*

Following the method of H. Schmid et al., 10-methoxydihydrocorynantheol (XXIX) (200 mg) was dehydrogenated with Hg $(OAc)_2$ (770 mg) to give XXVIII perchlorate (83 mg, 33%), m.p. 222–225° (dec). Recrystallization from EtOH gave pale brown needles m.p. 224–226° (dec); UV λ_{max} mμ (log ε): 213·5 (4·51), 234 (sh) (3·98), 367 (4·41), λ_{min} mμ (log ε): 283 (2·98); IR ν_{max}^{KBr} cm^{-1}: 1635, 1625 (aromatic C—H). (Found: C, 55·95; H, 6·30; N, 6·55; Cl, 8·37. Calc for $C_{20}H_{27}O_2N_2.ClO_4$: C, 56·27; H, 6·38; N, 6·56; Cl, 8·31%). The mother liquor of XXVIII was evaporated. The residue was made alkaline with aq NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent removed to give a crystalline residue (64 mg, 32%), m.p. 154–156°, which was recrystallized from EtOAc as colourless needles (33 mg), m.p. 162–163°. This compd was identical with the starting material (XXIX) in every respect.

Dehydrogenation of 3-epi-10-methoxydihydrocorynantheol (I)

A soln of I (200 mg) and Hg $(OAc)_2$ (770 mg) in 5% AcOH (12 ml) was heated at 120° in a sealed tube

for 3 h under N_2 and treated as above to give pale brown needles (31 mg, 12%), m.p. 223–225° (dec). Comparison of the IR spectra and the mixed melting point showed that this compd was identical with XXVIII.

Reduction of XXVIII *with* $NaBH_4$

To a soln of XXVIII (50 mg) in MeOH (4 ml) was added $NaBH_4$ (125 mg) and the mixture refluxed for 3 h. After decomposition of the excess reagent with acetone, the solvent was removed. The residue was made basic with conc NH_4OH and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent removed. The crystalline residue (38 mg) was recrystallized from EtOAc to give colourless needles (23 mg), m.p. 162–163°. The comparison of the IR spectra and the mixed melting point showed that this product was identical with 10-methoxydihydrocorynantheol (XXIX).

3-*epi*-10-*Hydroxydihydrocorynantheol* (XXX) *and its diacetate* (XXXI)

To an ice-cooled soln of I (600 mg) in $CHCl_3$ (40 ml) was added with stirring a soln of BBr_3 (1·5 g) in $CHCl_3$ (5 ml). After standing for 15 min at room temp, the mixture was poured into ice-cooled aq NH_4OH and the ppts (574 mg) were collected. After washing with water and drying, the crude product (XXX) (400 mg) was dissolved in pyridine (10 ml) and allowed to stand overnight with Ac_2O (1 ml) under ice-cooling. To the soln was added water (approx 10 ml) and the solvent was evaporated to dryness. The residue was made basic with dil NH_4OH 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 isopropanol to give XXXI as colourless needles (375 mg), m.p. 153°, $[\alpha]_D^{23}$ + 41·4° (*c*, 0·691, EtOH), UV λ_{max} mμ (log ε): 230 (4·51), 280 (sh) (3·87), 287 (3·91), 293 (sh) (3·86), λ_{min} mμ (log ε): 255 (3·51); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3460, 3376 (NH), 1740, 1727 ($OCOCH_3$). (Found: C, 69·45; H, 7·80; N, 7·07. $C_{23}H_{30}O_4N_2$ requires: C, 69·32; H, 7·59; N, 7·03%). A soln of XXXI (300 mg) in 1/2N methanolic NaOH (3 ml) was stirred for 45 min under N_2 at room temp. The soln was evaporated under reduced pressure and the residue treated with aq NH_4Cl. The ppts were collected, washed with water and dissolved in MeOH. After treatment with activated charcoal, the solvent was removed to give XXX as a white amorphous powder (210 mg), $[\alpha]_D^{23}$ + 30·9° (*c*, 0·356, EtOH); UV λ_{max} mμ (log ε): 223 (4·33), 282 (3·88), 299 (sh) (3·77), 310 (sh) (3·47), λ_{min} mμ (log ε): 253 (3·43); CD: $[\theta]_{308}$ +1450. $[\theta]_{275}$ −7250, $[\theta]_{236}$ −16900. (*c*, 0·089, EtOH).

3-*epi*-*Dihydrocorynantheol* (XXXIII)

A mixture of XXX (200 mg), well-powdered K_2CO_3 (180 mg) and 1-phenyl-5-chlorotetrazole (138 mg) in DMF (5 ml) was stirred at 50° overnight under N_2. The reaction mixture was diluted with water (approx 20 ml) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 5% NaOH and then with water, dried over K_2CO_3 and the solvent removed. The residue was dissolved in benzene and extracted with 10% HCl. The acidic layer was made basic with conc NH_4OH under ice-cooling and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent removed to give XXXII as an amorphous powder (264 mg). A sample was purified by preparative TLC on silica gel KGF (Merck), developing with $CHCl_3$-MeOH (4:1), as a white amorphous powder (68%), $[\alpha]_D^{24}$ + 10·1° (*c*, 0·513, EtOH); UV λ_{max} (log ε): 231·5 (4·62), 288 (3·93), 293 (sh) (3·91), λ_{min} mμ (log ε): 213 (4·40), 264 (3·81). A soln of the crude XXXII (315 mg) in EtOH (14 ml) was hydrogenated over 5% Pd-C (330 mg) at atmospheric pressure and room temp for 10 h. Disappearance of XXXII was checked by TLC. After removal of the catalyst and the solvent, the residue was made alkaline with 5% NaOH 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 recrystallized from EtOAc-Et_2O to give XXXIII as needles (135 mg), m.p. 171–173° (lit[8] 173–175°), $[\alpha]_D^{25}$ + 155·8° (*c*, 0·767, pyridine) (lit[8] + 128° (pyridine)); UV λ_{max} mμ (log ε): 226 (4·55), 275 (sh) (3·85), 283 (3·87), 290 (3·81), λ_{min} mμ (log ε): 249 (3·36), 288 (3·80); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3608 (OH), 3460 (NH): NMR ($CDCl_3$) τ: 2·02 (1H, disappeared on addition of D_2O, N<u>H</u>), 2·4–3·1 (4H, aromatic <u>H</u>), 6·09 (1H, broad, C_3-<u>H</u>), 6·23 (t, J = 6 c/s, —$CH_2C\underline{H}_2OH$), 9·18 (3H, t, J = 6 c/s, —$CH_2C\underline{H}_3$); CD: $[\theta]_{275}$ − 8260, $[\theta]_{227}$ − 2400 (*c*, 0·0328, EtOH). (Found: C, 76·51; H, 8·82; N, 9·32. Calc for $C_{19}H_{26}ON_2$: C, 76·47; H, 8·78; N, 9·39%).

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