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TRANSFORMATION OF QUININE INTO THE INDOLE ALKALOIDS—I

THE ABSOLUTE CONFIGURATION OF HUNTERBURNINE α- AND β-METHOCHLORIDE

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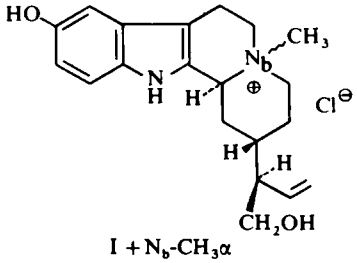
Abstract—The absolute configuration of hunterburnine α- and β-methochlorides (I and II) has been confirmed by the synthesis of dihydrohunterburnine α-methochloride (XXX) from quinine (III).

AMONG the quaternary bases so far isolated from *Hunteria eburnea* Pichon, hunterburnine α- and β-methochlorides were not only the first recognized examples of the occurrence in nature of N_b diastereoisomers, but also the first examples of the isolation of this new yohimbinoid variant.[1] The structures of the alkaloids were elucidated by



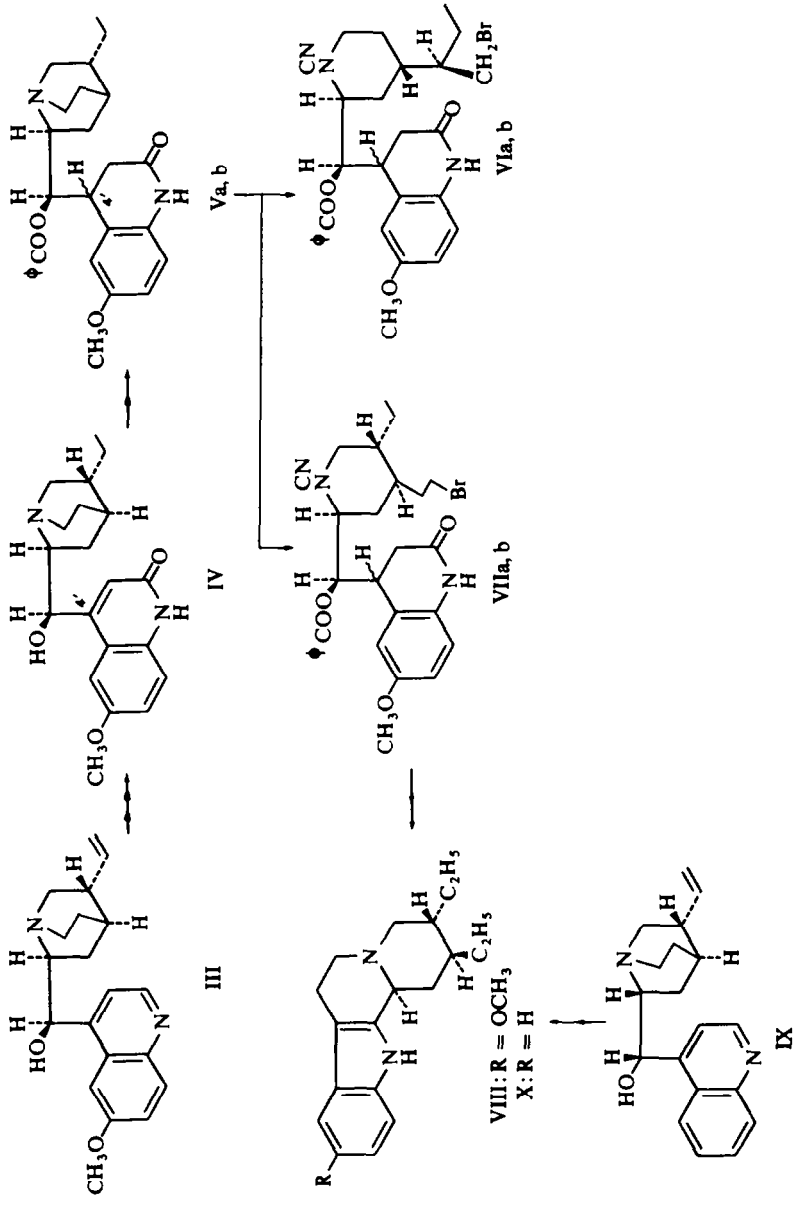
I + N_b-CH_3α
II + N_b-CH_3β

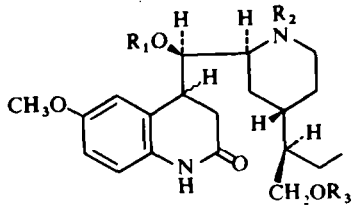
X-ray crystallographic techniques, but the absolute configuration depicted for these alkaloids was based upon biogenetic considerations.[2–4]

In order to confirm this, we synthesized dihydrohunterburnine α-methochloride (XXX) from quinine (III) in accordance with Ochiai's methods which were established by the synthesis of 10-methoxydihydrocorynantheane (VIII)[6] from quinine (III) and dihydrocorynantheane (X)[5] from cinchonine (IX) as had been suggested by Taylor.

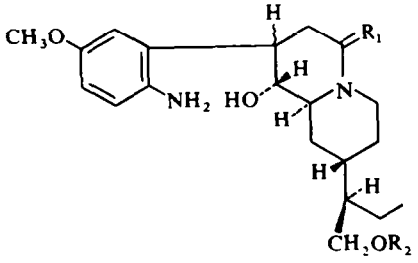
The normal and *allo* N-cyanobromides[6] (VIa and VIb),* prepared by the von Braun reaction from normal and *allo* 9-benzoyl-2′-oxohexahydroquinines (Va and Vb) along with the isomeric N-cyano bromides (VIIa and VIIb), served as starting materials for this synthesis. Treatment of the N-cyanobromides (VIa and VIb) with silver acetate

* The tentative prefixes, i.e. normal and *allo*, have been used to distinguish between the epimers at the asymmetric centre C'_4, which were generated by the reduction of 2′-hydroxydihydroquinine (IV).[6] The compounds of normal and *allo* types are denoted (a) and (b), respectively. The elucidation of this configuration will be reported in the future.

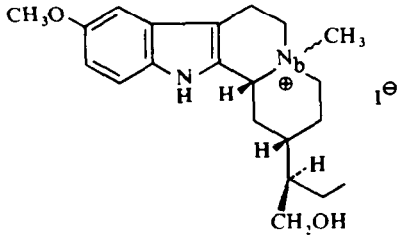




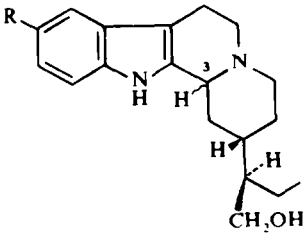
XIa, b: R_1 = $-CO\phi$, R_2 = CN, R_3 = Ac
XIIa, b: R_1 = $-CO\phi$, R_2 = $-CONH_2$, R_3 = H
XIIIa, b: R_1 = $-CO\phi$, R_2 = H, R_3 = H
XIVa: R_1 = H, R_2 = $CO\phi$, R_3 = H
XVa: R_1 = H, R_2 = H, R_3 = H
XVIa, b: R_1 = $CO\phi$, R_2 = H, R_3 = THP
XVIIa, b: R_1 = H, R_2 = H, R_3 = THP



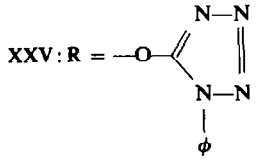
XVIIIa: R_1 = O, R_2 = H
XIXa, b: R_1 = O, R_2 = THP
XXa, b: R_1 = H_2, R_2 = THP
XXIb: R_1 = H_2, R_2 = H



XXVII: $^{\oplus}N_b$-$CH_3\alpha$
XXVIII: $^{\oplus}N_b$-$CH_3\beta$

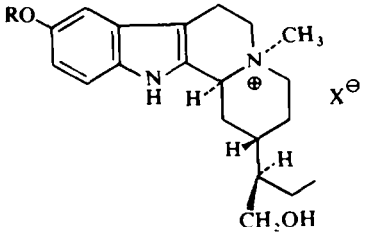


XXII: R = $-OCH_3$, C_3-Hα
XXIII: R = $-OCH_3$, C_3-Hβ
XXIV: R = $-OH$, C_3-Hα



XXV: R = C_3-Hα

XXVI: R = —H, C_3-Hα



XXIX: R = CH_3
XXX: R = H

in pyridine afforded the corresponding N-cyanoacetates, XIa, m.p. 158–159°, and XIb, m.p. 200–201°, in about 75% yields, respectively. Acid hydrolysis of the N-cyanoacetates gave the O-benzoyl amonoalcohols, XIIIa, m.p. 181° (perchlorate), and XIIIb, m.p. 201° through the respective N-amides, XIIa, m.p. 251° and XIIb, m.p. 218°. The IR spectra of XIIa and XIIb showed N-amide bands at about 1580 cm^{-1} which disappeared on further hydrolysis.

The compounds XIIIa and XIIIb, after protection of the primary OH groups with dihydropyran, were converted to the respective quinolizidones, XIXa, m.p. 195–196° and XIXb, m.p. 149–150°, in good yields by removal of the benzoyl groups with boiling aqueous methanol followed by the lactam ring conversion in one of the dipolar aprotic solvents.

This procedure was established by utilizing the following interesting behaviors of the O-benzoyl aminoalcohol XIIIa. Treatment of XIIIa with dilute ethanolic KOH caused the migration of the benzoyl group to give the N-benzoate XIVa which was recommended to the starting compound XIIIa by the action of dilute ethanolic HCl, while the heating with 70% methanol removed the benzoyl group to give the des-benzoyl compound XVa. In the UV spectrum this compound XVa did not show maximum absorption at 235 mμ due to the benzoyl chromophore but had maximum absorption at 259 and 295 mμ due to the dihydrocarbostyril chromophore. Furthermore, the lactam ring of XVa reacted from the intramolecular attack of the secondary amino group in the piperidine moiety to give the quinolizidone derivative XVIIIa, m.p. 191–192°, the UV spectrum of which exhibited maximum absorption due to the *p*-anisidyl chromophore at 236 and 302 mμ. This intramolecular S_N2 type of reaction successfully proceeded in dipolar aprotic solvents such as acetone, acetronitrile and nitromethane, but not in the protic solvents such as methanol and aqueous methanol. The ring conversion proceeded more easily in the normal series (XVIIa–XIXa) than in the allo series (XVIIb–XIXb). The UV spectrum of the normal quinolizidone (XIXa) varied remarkably in 0·01N ethanolic HCl solution and the resulted absorption curve was identical with that of XVa. However, the UV spectrum of the allo quinolizidone (XIXb) in the same solvent did not change, even two days later. This showed that the quinolizidone system is readily convertible to the dihydrocarbostyril system in the normal series. This difference between the normal and allo compounds was assumed to depend upon the configuration at C_4, of the aminoalcohols (XVIIa and XVIIb). Reduction of the quinolizidones (XIXa and XIXb) with LAH afforded the corresponding quinolizidines (XXa and XXb) in good yields. The *trans* and *cis*-ring fusions were assigned to the quinolizidine systems of XXb and XXa, respectively, since the absorption bands due to the trans quinolizidine system[7] were observed at 2813 and 2768 cm^{-1} in the IR spectrum of the former and not in that of the latter.

The modified Oppenauer oxidation of the normal quinolizidine (XXa) followed by removal of the tetrahydropyranyl group with acid gave an indole compound (XXII), m.p. 242–243° (hydrochloride) in 69·5% yield, while the allo quinolizidine (XXb) resisted the oxidation giving the quinolizidine (XXIb), which was obtained by removal of the tetrahydropyranyl group by the action of acid. Treatment of the indole compound (XXII) with acetic acid at 130° for 20 hr afforded an equilibrium mixture of XXII and its C_3-epimer (XXIII), m.p. 180–181·5°. The sterochemical assignment at C_3 of these compounds was made using the empirical Klyne's correlation[8] which shows that the optical rotatory dispersion curves can be used to determine the absolute

configuration at C_3 of indole alkaloids of the yohimbane and corynantheane types. By application of this correlation, the α- and β-configurations were assigned to the C_3-hydrogens of XXII and XXIII, respectively because in the CD curves the former showed a positive Cotton effect at 276 mμ and the latter a negative Cotton effect at 273 mμ. The C/D ring conformation of these indole compounds was proven on the basis of the Bohlmann band[7] in the IR spectra and the C_3 proton signals in the NMR spectra.[9-10] The lack of the C_3 proton signal at below 6·8 τ in the NMR spectrum of the indole compound (XXIII) which has the β-hydrogen at C_3 was evidence for a *trans* quinolizidine system. This was confirmed by the presence of the Bohlmann band at 2780 and 2720 cm^{-1} in the IR spectrum. On the other hand, the indole compound (XXII) which has the α-hydrogen at C_3, showed the signal of the C_3-proton at 5·87 τ with a narrow width (W_H = 8 c/s) and no Bohlmann band, both of which were characteristic of a *cis* quinolizidine system. The conformation, in which the C_3 proton was gauche to the adjacent methylene protons, was also suggested by the narrow signal of the C_3 proton and the examination of the Dreiding models.

Quaternization of the C/D-*trans* indole compound (XXIII), with methyliodide afforded two methiodides, XXVII, m.p. 277–279° and XXVIII, m.p. 254–255°, in 36·5 and 44·5% yields, respectively. The chemical shift attributed to the quaternary N-Me of XXVIII was found at a lower field (6·65 τ) than in the case of XXVII (6·92τ). According to Katritzky's findings,[11-12] the C/D ring fusions of the methiodides, XXVII and XXVIII, were proven to be *trans* and *cis*, respectively. On the other hand, quaternization of the C/D-*cis* indole compound (XXVII) and the corresponding phenolic compound (XXIV), m.p. 226–227°, obtained by demethylation of XXII by the action of boron tribromide gave only one methiodide, XXIX, m.p. 285° and XXX, m.p. 272–273°, respectively. The NMR spectra of these methiodides showed respective quaternary N-Me signals at 6·63 and 6·56 τ, both of which were characteristic of the *cis* N-Me quinolizidinium system. The methochloride, m.p. 317–318° (dec), obtained from the methiodide (XXX) by the use of an anion exchanger, showed the same m.p. as that reported on dihydrohunterburnine α-methochloride[13] and its NMR spectrum exhibited an quaternary N-Me signal at 6·52 τ which was comparable to that of hunterburnine α-methochloride (I) (6·53 τ).[1]

The direct comparison of the IR spectra proved the identity of our methochloride with dihydrohunterburnine α-methochloride which was donated by the courtesy of Scheuer.

Elimination of the phenolic OH grouping from the tertiary phenolic compound (XXIV) by means of Musliner's method,[14] i.e. hydrogenolysis of the corresponding tetrazolyl ether (XXV), m.p. 185–186°, gave dihydroantirhine (XXVI), m.p. 120–125° (130° with foaming), $[\alpha]_D$ +23·6°, the absolute configuration of which was established chemically by Johns.[15]

The identity of the synthesized and the natural dihydroantirhine (the latter was kindly given by Johns) was confirmed by the direct comparison of their IR spectra and the mixed m.p. method.

Consequently, the absolute configuration of hunterburnine α-methochloride (I) as assigned by Taylor *et al.* was proven to be correct and hence the absolute configuration of the β-methochloride (II), the N_b-epimeric quaternary alkaloid of the α-methochloride was also illustrated to be assigned correctly by Taylor *et al.*

EXPERIMENTAL

All m.ps are uncorrected. The UV spectra were measured in 95% EtOH unless otherwise noted. The NMR spectra were determined with a Varian A-60 spectrometer in $CDCl_3$ unless otherwise noted, using TMS as a reference.

Normal and allo-N-*cyanobromides* (VIa, b). These compounds were prepared by the method of Ochiai *et al.*[6] VIa, m.p. 218 (lit.[6] 219–220°), $[\alpha]_D^{24.5}$ +113·7° (*c*, 2·138, $CHCl_3$). (Found: C, 60·60; H, 5·91; N, 7·70; Br, 14·71. Calc. for $C_{28}H_{32}O_4N_3Br$: C, 60·65; H, 5·82; N, 7·58; Br, 14·41%). VIb, m.p. 210° (lit.[6] 206–207°), $[\alpha]_D^{24.0}$ +17·4° (*c*, 2·087, $CHCl_3$). (Found: C, 60·58; H, 5·83; N, 7·74; Br, 14·16. Calc. for $C_{28}H_{32}O_4N_3Br$: C, 60·65; H, 5·82; N, 7·58; Br, 14·41%).

Normal N-*cyanoacetate* (XIa). To a soln of VIa (22·2 g) in pyridine (42 g) was added AcOAg (13·4 g). After heating at 130–135° for 10 min, the mixture was stirred with NaCl aq to decompose the excess AcOAg. 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 *in vacuo*. The residue was taken up in CH_2Cl_2, the CH_2Cl_2 soln was washed with dil HCl and then with water, dried over K_2CO_3 and the solvent was removed under reduced press. The residue was crystallized from MeOH to give XIa (12·32 g) as colourless needles, m.p. 158–159°. The material from the mother liquor was dissolved in CH_2Cl_2 and chromatographed on alumina (70 g). Elution with CH_2Cl_2 gave a solid product which was recrystallized from MeOH to yield XIa (3·79 g) as colourless needles, m.p. 158–159°. The total yield was 16·11 g (75·5%), $[\alpha]_D^{25.5}$ +135·6° (*c*, 2·107, $CHCl_3$); UV λ_{max} mμ (log ε): 235 (4·26), 258 (4·17), 298 (3·50); λ_{min} mμ (log ε): 223 (4·15), 249 (4·16), 291 (3·47); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH), 2206 (CN), 1727 (ester), 1683 (sec. lactam); NMR τ: 6·10 (d, J = 5c/s, 2H, —C<u>H</u>$_2$OAc), 8·09 (s, COC<u>H</u>$_3$). (Found: C, 67·73; H, 6·74; N, 8·00. $C_{30}H_{35}O_6N_3$ requires: C, 67·52; H, 6·61; N, 7·88%).

allo-N-*Cyanoacetate* (XIb). Treatment of VIb (12·0 g) in pyridine (20 g) with AcOAg (7·3 g) as described above gave XIb (8·5 g, 73·3%), m.p. 200–201°. Recrystallization from MeOH gave colourless needles, m.p. 200–201°, $[\alpha]_D^{20.0}$ +20·0° (*c*, 2·039, $CHCl_3$); UV λ_{max} mμ (log ε): 235 (4·22), 259 (4·16), 300 (3·49); λ_{min} mμ (log ε): 222 (4·09), 248 (4·12), 291 (3·45); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3394 (NH), 2227 (CN), 1728 (ester), 1685 (sec. lactam); NMR τ: 8·07 (s, COC<u>H</u>$_3$). (Found: C, 67·71; H, 6·74; N, 7·97. $C_{30}H_{35}O_6N_3$ requires: C, 67·52; H, 6·61; N, 7·88%).

Hydrolysis of normal N-*cyanoacetate* (XIa). To a soln of XIa (30·0 g) in EtOH (300 ml) was added 15% H_2SO_4 (450 ml) and the mixture was refluxed for 60·5 hr. After neutralization with NH_4OH aq and concentration of the soln under reduced press, the separated crystals were collected and recrystallized from $CHCl_3$-MeOH to give XIIa as colourless needles (4·63 g, 15%), m.p. 251° (dec), $[\alpha]_D^{24}$ +133·8° (*c*, 1·082, MeOH); UV λ_{max} mμ (log ε): 235 (4·25), 257·5 (4·16), 300 (3·48); λ_{min} mμ (log ε): 224·5 (4·19), 249·5 (4·15), 292 (3·46); IR ν_{max}^{Nujol} cm^{-1}: 1712 (COϕ), 1668 (sec. lactam), 1573 (NCONH$_2$). (Found: C, 66·16; H, 6·91; N, 8·37. $C_{28}H_{35}O_6N_3$ requires: C, 65·99; H, 6·92; N, 8·25%). The filtrate was made basic with conc 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 was removed. The residue was dissolved in EtOH and acidified with 60% $HClO_4$ to give XIIIa as perchlorate (20·6 g, 63·1%), m.p. 160° (dec), which was recrystallized from $CHCl_3$–EtOH (8:1) to raise its m.p. to 181°; UV λ_{max} mμ (log ε): 236 (4·26), 257·5 (4·16), 300 (3·48); λ_{min} mμ (log ε): 222·5 (4·12), 250 (4·16), 292 (3·45); IR ν_{max}^{Nujol} cm^{-1}: 1715 (COϕ), 1649 (sec. lactam). (Found: C, 57·07; H, 6·33; N, 4·98; Cl, 6·32. $C_{27}H_{34}O_5N_2 \cdot HClO_4$ requires: C, 57·19; H, 6·22; N, 4·94; Cl, 6·25%). The mother liquor was concentrated *in vacuo* and made alkaline with NH_4OH aq. The separated crystals were collected and washed with CH_2Cl_2. Recrystallization from $CHCl_3$–MeOH gave further XIIa as colourless needles (1·6 g, 6·7%), m.p. 251° (dec).

Hydrolysis of normal N-*amide* (XIIa). To a soln of XIIa (1·02 g) in EtOH (20 ml) was added 15% H_2SO_4 (30 ml) and the mixture was refluxed for 30 hr. After removal of the solvent, the mixture was made alkaline with NH_4OH aq and extracted with CH_2Cl_2. The insoluble crystals were filtered and recrystallized from $CHCl_3$–MeOH to recover XIIa (430 mg, 42%), m.p. 251° (dec). The CH_2Cl_2 layer was washed with water, dried over K_2CO_3 and the solvent was removed. The resulting material was converted to a crystalline perchlorate (466 mg, 39·8%), m.p. 160° (dec), which was recrystallized from $CHCl_3$–EtOH to give colourless needles, m.p. 181° (dec) and identified as the perchlorate of XIIIa by means of its IR spectrum and mixed m.p. method.

Hydrolysis of allo-N-*cyanoacetate* (XIb). To a soln of XIb (5·34 g) in EtOH (53 ml) was added 15% H_2SO_4 (80 ml) and the mixture was refluxed for 15 hr. Treatment of the reaction mixture as above gave XIIb (800 mg, 15·7%), m.p. 214–215° (dec) and XIIIb as an amorphous powder (3·9 g). The N-amide XIIb was recrystallized from MeOH–CH_2Cl_2 as colourless needles, m.p. 218° (dec), $[\alpha]_D^{21.5}$ +2·5 (*c*, 1·027, MeOH); UV λ_{max} mμ (log ε): 234 (4·21), 258 (4·15), 298 (3·51); λ_{min} mμ (log ε): 223 (4·12), 248 (4·10), 292 (3·50); IR ν_{max}^{Nujol} cm^{-1}: 3380 (OH, NH), 1721, 1692 (COϕ), 1641 (sec. lactam), 1590 (NCONH$_2$). (Found: C, 65·88; H, 7·15;

N, 8·34. $C_{28}H_{35}O_6N_3$ requires: C, 65·99; H, 6·92; N, 8·25%). The aminoalcohol XIIIb was converted to the oxalate (2·38 g, 46·5%) m.p. 255° (dec), in MeOH. Recrystallization from MeOH gave colourless needles, m.p. 255° (dec). (Found: C, 65·51; H, 6·98; N, 5·51. $C_{28}H_{34}O_5N_2 \cdot \frac{1}{2}(COOH)_2$ requires: C, 65·73; H, 6·90; N, 5·48%). The amino alcohol XIIIb liberated from the oxalate was recrystallized from acetone as colourless needles, m.p. 201°, $[\alpha]_D^{21·5}$ −32·7° (*c*, 2·042, EtOH); UV λ_{max} mμ (log ε): 234 (4·21), 258 (4·14), 298 (3·51); λ_{min} mμ (log ε): 223 (4·10), 247·5 (4·11), 292 (3·49); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3536, 3404 (OH, NH), 1705 (COϕ), 1679 (sc. lactam). (Found: C, 69·65; H, 7·51; N, 6·01. $C_{27}H_{34}O_5N_2$ requires: C, 69·50; H, 7·35; N, 6·00%).

Hydrolysis of allo-N-*amide* (XIIb). A suspension of XIIb (2·7 g) in 15% H_2SO_4 (70 ml) was refluxed for 13 hr. The clear 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 evaporated. The residue was converted to the oxalate and recrystallized from MeOH as colourless needles (1·96 g, 73%), m.p. 255° (dec), which was identical with the oxalate of XIIIb.

Benzoyl group migration. To a soln of normal XIIIa (760 mg) in EtOH (10 ml) was added 5% ethanolic KOH (0·2 ml). The mixture was refluxed for 2 hr and the solvent was removed *in vacuo*. The residue was dissolved in $CHCl_3$, the $CHCl_3$ soln was washed with water and dried over K_2CO_3. After removal of the solvent, the residue (760 mg) was purified by preparative TLC ($CHCl_3$–MeOH 4:1) to give XIVa as an amorphous powder, (513 mg, 64%), which showed one spot on TLC ($CHCl_3$–MeOH 4:1), $[\alpha]_D^{24}$ −12·6° (*c*, 1·591, $CHCl_3$); UV λ_{max} mμ (log ε): 257 (4·18), 300 (3·48); λ_{min} mμ (log ε): 232 (3·98), 287 (3·42); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3393 (NH), 1674 (sec. lactam), 1623 (NCOϕ); NMR τ: 0·95 (broad, 1H, NH), 2·65 (s, 5H, aromatic H), 3·3–4·3 (3H, aromatic H). The N-benzoyl XIVa (50 mg) was refluxed with 5% ethanolic HCl (3 ml) for 32 hr. After removal of the solvent, the residue was made alkaline with NH_4OH aq and extracted with CH_2Cl_2. The CH_2Cl_2 layer was washed with water, dried over K_2CO_3 and the solvent was removed. The resulting material was dissolved in EtOH and acidified with 60% $HClO_4$. The separated crystals were collected and recrystallized from EtOH–$CHCl_3$ to yield XIIIa as perchlorate (14 mg, 26·7%), m.p. 181° (dec).

Normal desbenzoylaminoalcohol (XVa). A soln of XIIIa (700 mg) in 70% MeOH (25 ml) was refluxed for 8 hr and the solvent was removed. The residue was made alkaline with NH_4OH aq to remove the benzoic acid and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with water and dried over K_2CO_3. After removal of the solvent, the residue was chromatographed on alumina (7·0 g). Elution with $CHCl_3$ afforded an amorphous powder (520 mg, 97%); UV λ_{max} mμ (log ε): 259 (4·08), 295 (3·44); λ_{min} mμ (log ε): 229 (3·47), 287 (3·43); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH, NH), 1670 (sec. lactam).

Normal quinolizidine derivative (XVIIIa). A soln of XVa (500 mg) in MeCN (20 ml) was refluxed for 2hr. Concentration of the solution gave XVIIIa as crystals (460 mg, 92%), m.p. 189–190°, which was recrystallized from EtOH as pillars, m.p. 191–192°, $[\alpha]_D^{24}$ +69·8° (*c*, 2·030, EtOH); UV λ_{max} mμ (log ε): 236 (3·93), 302 (3·51); λ_{min} mμ (log ε): 266 (2·66); IR ν_{max}^{Nujol} cm^{-1}: 3400, 3336, 3274 (OH, NH), 1594 (tert. lactam). (Found: C, 66·36; H, 8·40; N, 7·76. $C_{20}H_{30}O_4N_2$ requires: C, 66·27; H, 8·34; N, 7·73%).

Conversion of normal O-*benzoylaminoalcohol* (XIIIa) to quinolizidone (XIXa). To a soln of XIIIa liberated from the perchlorate (41 g) in $CHCl_3$ (250 ml) was added TsOH H_2O (17·3 g). After azeotropical removal of water, dihydropyran (8·82 g) was added to the solution under ice cooling. After standing for 1 hr at room temp, the reaction mixture was washed with NH_4OH aq and then water, dried over K_2CO_3 and the solvent was evaporated *in vacuo* to give XVIa as an oil (44·8 g). Without further purification the oily material was dissolved in 70% MeOH (1·41) and refluxed for 8 hr. The solvent was removed under reduced press. The residue was made alkaline with NH_4OH aq and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent was removed to give XVIIa as an oil (41 g). The crude material was dissolved in CH_3CN (500 ml) and refluxed for 1 hr. After cooling, the separated crystals were collected and recrystallized from EtOH to yield XIXa as colourless pillars, (21·85 g, 70·5%), m.p. 195–196°, $[\alpha]_D^{23}$ +57·4° (*c*, 1·057, EtOH). UV λ_{max} mμ (log ε): 236·5 (3·92), 303 (3·52); λ_{min} mμ (log ε): 225 (3·83), 266 (2·68); $\lambda_{max}^{1/100\,N\,HCl-EtOH}$ mμ (log ε): 258·5 (4·13), 298 (3·49); $\lambda_{min}^{1/100\,N\,HCl-EtOH}$ mμ (log ε): 226 (3·42), 287 (3·44); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH, NH), 1626 (tert. lactam). (Found: C, 67·38; H, 8·65; N, 6·28. $C_{25}H_{38}O_5N_2$ requires: C, 67·23; H, 8·53; N, 6·27%).

allo-*Tetrahydropyranylether* (XVIb). To a soln of XIIIb (2·23 g) in $CHCl_3$ (50 ml) was added TsOH H_2O (1·24 g). After azeotropical removal of the water, dihydropyran (13·8 g) was added to the soln under ice-cooling and the mixture was allowed to stand for 1 hr at room temp. The soln was washed with dil NH_4OH and then with water, dried over K_2CO_3 and the solvent was removed under reduced press. The crystalline residue (2·59 g), m.p. 150–157°, was recrystallized from EtOAc to yield XVIb as colourless needles (1·97 g, 72%), m.p. 164–165°, $[\alpha]_D^{24}$ −34·2° (*c*, 1·001, EtOH); UV λ_{max} mμ (log ε): 233 (4·21), 258 (4·16),

298 (3·49); λ_{min} mμ (log ε): 222·5 (4·14), 247 (4·11), 290 (3·48); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3395 (NH), 1719 (COϕ), 1680 (sec. lactam). (Found: C, 69·86; H, 7·69; N, 4·87. $C_{23}H_{42}O_6N_2$ requires: C, 69·79; H, 7·69; N, 5·09%). The material obtained from the mother liquor was dissolved in MeOH (5 ml) and acidified with HCl aq. After removal of the solvent and washed 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 under reduced press. The residual material (480 mg) was crystallized from acetone to yield starting XIIIb as colourless needles (240 mg, 10·8%), m.p. 201°.

allo-*desbenzoylaminoalcohol* (XVIIb). A soln of XVIb (1·10 g) in 70% MeOH (100 ml) was refluxed for 8 hr. After removal of the MeOH, 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 *in vacuo*. The resulting material was purified by chromatography on alumina (10 g). Elution with $CHCl_3$ gave XVIIb as an amorphous powder (856 mg), 95%), $[\alpha]_D^{24}$ −11·0° (*c*, 1·030, EtOH); UV λ_{max} mμ (log ε)† 259 (4·08), 295 (3·44), λ_{min} mμ (log ε): 228·5 (3·48), 287·5 (3·42); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400, 3220 (OH, NH), 1677 (sec. lactam).

allo-*Quinolizidone* (XIXb). A soln of XVIIb (3·70 g) in CH_3NO_2 (100 ml) was refluxed for 48 hr under an N_2 stream. After removal of the solvent, the residue was recrystallized from EtOAc to yield as colourless pillars (1·22 g), m.p. 146–148°. After removal of the solvent from the mother liquor, the residue was dissolved in benzene and chromatographed on alumina (45 g). Elution with benzene–$CHCl_3$ (4:1 and 1:1) afforded XIXb as a solid (1·36 g), which was recrystallized from EtOAc as colourless pillars (1·02 g), m.p. 146–149°, total yield 2·24 g (60·5%). Further recrystallization from EtOAc raised its m.p. to 149–150°, $[\alpha]_D^{24}$ −45·9° (*c*, 1·053, EtOH); UV λ_{max} mμ (log ε): 235 (3·92), 302 (3·52); λ_{min} mμ (log ε): 226 (3·87), 266 (2·66); $\lambda_{max}^{1/100\,N\,HCl-EtOH}$ mμ (log ε): 276 (3·29), 283, 283 (3·26); $\lambda_{min}^{1/100\,N\,HCl-EtOH}$ mμ (log ε): 245 (2·28), 281 (3·25); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3576, 3396 (OH, NH), 1630 (tert. lactam). (Found: C, 67·43; H, 8·41; N, 6·09. $C_{25}H_{38}O_5N_2$ requires: C, 67·43; H, 8·53; N, 6·27%).

Normal quinolizidine (XXa). A soln of XIXa (880 mg) in dry THF (30 ml) was added dropwise to a well stirred suspension of LAH (500 mg) in dry THF (20 ml) under refluxing. After the addition was completed, the mixture was refluxed for 1 hr and the excess reagent was destroyed by addition of EtOAc under ice-cooling. The mixture was treated with 20% NaOH and the organic layer was evaporated under reduced press. The residue was taken up in $CHCl_3$, washed with water, dried over K_2CO_3 and the solvent was removed. The residual oil (840 mg) was dissolved in benzene and chromatographed on alumina (17 g). Elution with $CHCl_3$ afforded XXa as an oil (545 mg, 76%); UV λ_{max} mμ (log ε): 236·5 (3·88), 302 (3·46), λ_{min} mμ (log ε): 222 (3·70), 266 (2·69); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3620, 3440 (OH, NH).

allo-*Quinolizidine* (XXb). Reduction of XIXb (1·42 g) LAH (1·4 g) by the above mentioned procedure gave an amorphous powder (1·4 g). Chromatography on alumina (28 g) gave, on elution with benzene and $CHCl_3$, a solid product (1·25 g), which was recrystallized from $CHCl_3$-n-hexane to afford XXb as colourless needles (1·19 g, 86%), m.p. 102–103°, $[\alpha]_D^{24}$ −71·1° (*c*, 0·971, EtOH); UV λ_{max} mμ (log ε): 234·5 (3·85), 300 (3·46); λ_{min} mμ (log ε): 264 (2·49); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3593, 3403, 3328 (OH, NH), 2813, 2768 (*trans*-quinolizidine). (Found: C, 62·57; H, 8·08; N, 5·62; Cl, 10·46; $CHCl_3$, 11·27. $C_{25}H_{40}O_4N_2 \cdot \frac{1}{2}CHCl_3$ requires: C, 62·21; H, 8·29; N, 5·69; Cl, 10·80; $CHCl_3$, 12·12%).

O-*Methyldihydrohunterburnine* (XXII). (1) The mixture of XXa (2·0 g), t-BuOLi (2·0 g) and benzophenone (14 g) in dry benzene (40 ml) was heated at 115° for 72 hr in a sealed tube under N_2. The reaction mixture was poured into ice-water and acidified with conc HCl under stirring. The separated crystals (1·31 g, 80·5%), m.p. 240–242° (dec), were filtered and recrystallized from EtOH–acetone to yield XXII as the hydrochloride (1·23 g, 69·5%), m.p. 242–243° (dec). (Found: C, 62·62; H, 8·23; N, 7·48; Cl, 9·52. $C_{20}H_{28}O_2N_2 \cdot HCl \cdot H_2O$ requires: C, 62·72; H, 8·16; N, 7·32; Cl, 9·26%). The free base (XXII) was an amorphous powder, $[\alpha]_D^{24}$ +35·6° (*c*, 2·078, EtOH); λ_{max} mμ (log ε): 225 (4·39), 282 (3·90), 295 (sh) (3·86); λ_{min} mμ (log ε): 251·5 (3·33); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3651 (OH), 3496 (NH), 1627, 1590 (aromatic C-H); NMR τ: 1·72 (broad s, 1H, NH), 2·84–3·27 (ABX, 3H, aromatic H), 5·87 (broad s, W_H = 8 c/s, 1H, C_3—H), 6·18 (s, O$C\underline{H}_3$), 6·35 (broad s, 2H, —$C\underline{H}_2$OH); CD (EtOH): $[\theta]_{308·5}$ −3500, $[\theta]_{276}$ +6200.

(2) An Oppenauer oxidation of XXb (700 mg) with t-BuOLi (850 mg) and benzophenone (5·0 g) in dry benzene (14 ml) was carried out by the above mentioned procedure. The reaction mixture was poured into ice–water and acidified with conc HCl under stirring. After washing with Et_2O, the aqueous layer was made alkaline with NH_4OH aq and extracted with $CHCl_3$. The $CHCl_3$ soln was washed with H_2O, dried over K_2CO_3 and the solvent was removed under reduced press. Preparative TLC ($CHCl_3$–MeOH 4:1) of the residual oil (550 mg) afforded an oily material (297 mg, 53%), which was identified as XXIb by comparison of the TLC and the IR spectra, and no XXII was obtained.

allo-*Quinolizidine* (XXIb). A soln of XXb (30 mg) in 1% methanolic HCl (3 ml) was allowed to stand for a

few min and the MeOH was removed. The residue was treated with water, washed with Et_2O, 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 under reduced press to yield an oily residue (22 mg, 92%), $[\alpha]_D^{21}$ −35·2° (*c*, 1·037, EtOH); UV λ_{max} mμ (log ε): 234·5 (3·86), 300 (3·46); λ_{min} mμ (log ε): 264 (2·68); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3584, 3404 (OH, NH), 2824, 2784 (*trans-quinolizidine*).

Dihydrohunterburnine (XXIV). To a soln of XXII (910 mg) in $CHCl_3$ (25 ml) was added a soln of BBr_3 (2·3 g) in $CHCl_3$ (3 ml) under ice-cooling. After standing for 10 min at room temp, the reaction mixture was poured into well stirred conc NH_4OH under ice-cooling. The separated crystals (720 mg, 88%) were collected and recrystallized from EtOH–H_2O (5:1) to yield XXIV as colourless needles (520 mg, 63·5%), m.p. 226–227° (dec), $[\alpha]_D^{26}$ 34·3° (*c*, 1·101, EtOH); UV λ_{max} mμ (log ε): 222·5 (4·40), 281 (3·94), 295·5 (sh) (3·85), λ_{min} mμ (log ε): 252 (3·43); IR ν_{max}^{Nujol} cm^{-1}: 3413, 3243 (OH, NH); CD (EtOH): $[\theta]_{310}$ −2300, $[\theta]_{275}$ +10,700. (Found: C, 72·49; H, 8·64; N, 8·80. $C_{19}H_{26}O_2N_2$ requires: C, 72·58; H, 8·34; N, 8·91%).

3-*Epi*-O-*methyldihydrohunterburnine* (XXIII). A soln of XXII (1·0 g) in AcOH (50 ml) was heated under N_2 at 125–130° for 20 hr in a sealed tube. After removal of the solvent, the residue was dissolved in 1N-methanolic NaOH (30 ml) and stirred for 30 min. The MeOH was removed and the residue was dissolved in $CHCl_3$. The $CHCl_3$ soln was washed with water, dried over K_2CO_3 and the solvent was removed *in vacuo* to give an amorphous powder (1·0 g) which showed two spots on TLC ($CHCl_3$–MeOH 4:1). These were separated by preparative TLC ($CHCl_3$–MeOH 4:1) and each product was extracted with $CHCl_3$–MeOH (4:1). The minor component (368 mg, 36·8%) gave the crystalline hydrochloride, m.p. 242–243° (dec), which was identified as XXII hydrochloride by mixed m.p. and comparison of its IR spectra. The major component (586 mg, 58·3%) was recrystallized from MeOH–H_2O (5:2) (7 ml) to give XXIII as colourless needles (536 mg), m.p. 180–181·5°, $[\alpha]_D^{24}$ +18·8° (*c*, 0·959, MeOH); UV λ_{max} mμ (log ε): 226 (4·30), 281 (3·83), 294 (sh) (3·77); λ_{min} mμ (log ε): 250 (3·26); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3660 (OH), 3480 (NH), 2780, 2720 (*trans*-quinolizidine); CD (EtOH): $[\theta]_{307}$ +900, $[\theta]_{273}$ −9400, $[\theta]_{232·5}$ −24,00. (Found: C, 69·89; H, 9·00; N, 7·60; MeOH, 8·40. $C_{20}H_{28}O_2N_2 \cdot CH_3OH$ requires: C, 69·97; H, 8·95; N, 7·77; MeOH, 8·89%).

O-*Methyldihydrohunterburnine* α-*methoiodide* (XXIX, X = I). To a soln of XXII liberated from the hydrochloride (100 mg) in MeOH (1 ml) was added excess MeI. The mixture was allowed to stand overnight at room temp and the separated crystals were collected and recrystallized from EtOH to give colourless needles (108 mg, 88%), m.p. 285° (dec); NMR (CF_3COOH): τ 6·05 (s, $OC\underline{H}_3$), 6·63 (s, $+NC\underline{H}_3$); CD (70% MeOH): $[\theta]_{269}$ +13,200. (Found: C, 53·75; H, 6·71; N, 5·71; I, 27·08. $C_{21}H_{31}O_2N_2I$ requires: C, 53·62; H, 6·64; N, 5·96; I, 26·98%).

O-*Methyldihydrohunterburnine* α-*methochloride* (XXIX, X = Cl). A soln of XXIX (X = I; 50 mg) in 50% EtOH (25 ml) was passed through a column of Amberlite IRA-410 (Cl^-) (2·5 ml) and washed with 50% EtOH. After removal of the solvent, the crystalline residue was recrystallized from EtOH to yield colourless needles (25 mg), m.p. >293°. (Found: C, 66·76; H, 8·28; N, 7·44; Cl, 9·46. $C_{21}H_{31}O_2N_2Cl$ requires: C, 66·56; H, 8·25; N, 7·39; Cl, 9·36%).

Dihydrohunterburnine α-*methoiodide* (XXX, X = I). Quaternization of XXIV (250 mg) by the above mentioned procedure gave crystals (345 mg, 96·9%), m.p. 271–272° (dec). Recrystallization from EtOH afforded XXX (X = I) as colourless needles (282 mg, 79%), m.p. 272–273° (dec), $[\alpha]_D^{24}$ +7·6° (*c*, 0·318, 50% MeOH); NMR (CF_3COOH): τ 6·56 (s, $+NC\underline{H}_3$). (Found: C, 52·90; H, 6·49; N, 5·86; I, 27·81. $C_{20}H_{29}O_2N_2I$ requires: C, 52·63; H, 6·41; N, 6·14; I, 27·81%).

Dihydrohunterburnine α-*methochloride* (XXX, X = Cl). Treatment of XXX (X = I; 200 mg) with Amberlite IRA-410 (Cl^-) (80 ml) as above gave a crystalline material (161 mg), m.p. 314° (dec) (in evacuated tube), which was recrystallized from EtOH to yield XXX (X = Cl) as colourless needles (133 mg, 76%), m.p. 317–318° (dec) (in evacuated tube), $[\alpha]_D^{24·5}$ +13·4° (*c*, 0·209, 50% MeOH); UV λ_{max}^{MeOH} mμ (log ε): 274 (3·96), 301 (3·66), 309 (sh) (3·60); λ_{min}^{MeOH} mμ (log ε): 245·5 (3·47), 295 (3·64); NMR (CF_3COOH): τ 6·52 (s, $+NC\underline{H}_3$); CD (50% MeOH): $[\theta]_{302}$ −2000, $[\theta]_{266}$ +9000. (Found: C, 66·13; H, 7·92; N, 7·83; Cl, 9·72. $C_{20}H_{29}O_2N_2Cl$ requires: C, 65·82; H, 8·01; N, 7·68; Cl, 9·72%). This compound was identified as dihydrohunterburnine α-methochloride by comparison of its IR spectra and m.ps with those of an authentic sample given by the courtesy of P. J. Scheuer.

Quaternization of 3-*epi*-O-*methyldihydrohunterburnine* (XXIII) *with methyliodide*. To a soln of XXIII (500 mg) in MeOH (30 ml) was added MeI (2·0 g) and the mixture was allowed to stand overnight at room temp. Removal of the solvent gave the crystalline residue which showed two +NMe signals at 6·65 and 6·92 τ in the NMR spectrum. Careful fractional recrystallization from EtOH gave XXVII (231 mg, 36·5%), m.p. 277–279° (dec) and XXVIII (279 mg, 44·5%), m.p. 254–255° (dec). The compound XXVII was recrystallized from MeOH as colourless needles, m.p. 254–255° (dec), $[\alpha]_D^{23·5}$ −19·1° (*c*, 1·019, DMSO); UV λ_{max}

mμ(log ε): 218(4·63), 275·5(3·90), 296(sh)(3·68), 308(sh)(3·55); λ_{min} mμ(log ε): 247·5(3·32); NMR(CF_3COOH): τ 6·92 (s, $+NC\underline{H}_3$); CD (70% MeOH): $[\theta]_{275}$ −12,400. (Found: C, 53·58; H, 6·74; N, 5·64; I, 27·00. $C_{21}H_{31}O_2N_2I$ requires: C, 53·62; H, 6·64; N, 5·96; I, 26·98%). The compound XXVIII was recrystallized from MeOH as colourless prisms, m.p. 254–255° (dec), $[\alpha]_D^{23}$ −5·3° (c, 0·990, DMSO); UV λ_{max} mμ (log ε): 219(4·67), 272·5(3·94), 296(3·70), 307(sh)(3·61), λ_{min} mμ (log ε): 246·5(3·47), 293·5(3·70); NMR(CF_3COOH): τ 6·65 (s, $+NC\underline{H}_3$); CD (70% MeOH) $[\theta]_{298}$ 2200, $[\theta]_{272}$ −10,500. (Found: C, 53·35; H, 6·62; N, 5·67; I, 27·02. $C_{21}H_{31}O_2N_2I$ requires: C, 53·62, H, 6·64; N, 5·96; I, 26·98%).

Elimination of the phenolic hydroxyl group of dihydrohunterburnine (XXIV)

Tetrazolyl ether (XXV). To a soln of XXIV (250 mg) in DMF (8 ml) was added finely powdered K_2CO_3 (220 mg) and 1-phenyl-5-chlorotetrazole (174 mg). After heating for 3 hr at 50° under an N_2 stream, the reaction mixture was poured into ice-water and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with 5% NaOH and the 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 alkaline with NH_4OH aq under ice-cooling and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried over K_2CO_3 and the solvent was removed. The crystalline material (360 mg) was recrystallized from EtOAc to give XXV as colourless prisms (306 mg, 83·6%), m.p. 185–186°, $[\alpha]_D^{25}$ +47·7° (c, 0·535, EtOH); UV λ_{max} mμ (log ε): 231 (4·63), 288 (3·94), 293 (sh) (3·93); λ_{min} mμ (log ε): 212·5 (4·38), 263 (3·79); IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3610 (OH), 3460, 3300 (NH). (Found: C, 68·10; H, 6·59; N, 18·30. $C_{26}H_{30}O_2N_6$ requires: C, 68·10; H, 6·59, N, 18·33%).

Dihydroantirhine (XXVI). A soln of XXV (260 mg) in EtOH (12 ml) was hydrogenated over 5% Pd–C (280 mg) at room temp for 12 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. The residue was converted to a crystalline picrated and recrystallized from EtOH to give yellow needles (197 mg, 65%), m.p. 191–192° (dec). (Found: C, 56·34; H, 5·64; N, 13·05. $C_{19}H_{26}ON_2$ $C_6H_3O_7N_3 \cdot \frac{1}{3}H_2O$: requires: C, 56·28; H, 5·60; N, 13·13%). The free base (XXVI) was recrystallized from aqueous MeOH as needles, m.p. 120–125° (130° with foaming), $[\alpha]_D^{23}$ +23·6 (c, 0·296, $CHCl_3$); UV λ_{max} mμ (log ε): 226 (4·53), 276 (sh) (3·85), 283·5 (3·87), 290·5 (3·82), λ_{min} mμ (log ε): 249 (3·38), 288·5(3·81); CD (EtOH): $[\theta]_{272}$ 4600, $[\theta]_{232.5}$ 18,300. (Found: C, 71·79; H, 8·91; N, 8·67. $C_{19}H_{26}ON_2 \cdot H_2O$ requires: C, 72·11; H, 8·92; N, 8·85%). The mixed m.p. det and the comparison of its IR spectra and specific rotations showed that this compound was identical with dihydroantirhine donated by the courtesy of S. R. Johns.

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