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ALKALOIDS OF THE AMARYLLIDACEAE: BRUNSVIGINE

NMR, ORD/CD AND MASS SPECTROMETRY, DEGRADATION AND INTERCONVERSION STUDIES

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Abstract—The 5,11b-methanomorphanthridine structure of brunsvigine is unambiguously identified through NMR, CD and mass spectrometry. The structure of brunsvigine is related to the other 5,11b-methanomorphanthridine alkaloids by methylation as well as through a series of Hofmann degradations.

Although the literature would appear to indicate that the South African[1] and American[2] researchers studied brunsvigine from dissimilar species of Brunsvigia, it is possible that there is no taxonomic difference between the plant materials.[3,4]

Early work on brunsvigine[1] established the existence of a methylenedioxyphenyl residue, a non-conjugated trisubstituted double bond and two vicinal hydroxyls, then considered to be *trans*; a structure isomeric with lycorine. Inubushi *et al.*[2] subsequently proposed **1**; R_2, R_3 = OH; R_1, R_4 = H for brunsvigine, but this structure was later re-assigned to another alkaloid, pancracine.[5] The correct structure and absolute configuration of brunsvigine was subsequently determined[6] by X-ray crystallography of the 0,0'-di(*p*-bromobenzoyl)derivative **1** (R_2, R_4 = CO·C_6H_4Br; R_1, R_3 = H). We report now on the structural chemistry and properties of brunsvigine.

The mass spectrum of brunsvigine (Table 1) shows close similarities with pancracine.[5] Strong brunsvigine spectra (Table 1) are generated at low probe temperatures (*ca* 135°) from slowly sublimed material. Brunsvigine crystals from acetone behave anomalously in requiring high probe temperatures (>250°) to generate adequate mass spectra, differing only in that peak *m/e* 269 exceeds peak *m/e* 270 in abundance. Speculations on the basis of proposed fragmentation mechanisms[5,7] as to the configuration of the C-3 OH in brunsvigine cannot therefore be made. The mass spectrum of dihydrobrunsvigine (Table 2) shows the predominant peak at *m/e* 175, exceeding the abundance of the mass ion, common to the dihydro derivatives of other 5,11b-methanomorphanthridine alkaloids.[5]

Low solubility precluded a detailed NMR study of brunsvigine. O,O'-diacetylbrunsvigine in deuterochloroform, however, gave an NMR spectrum (Fig. 1) closely similar to that of O,O'-diacetylpancracine[5] differing only in the regions δ = 1·5 to 2·5 and 4·5 to 5·7 where configurational differences would be expected to exert their effect. The NMR data are summarised in Table 3. The axial H-4 signal at δ = 1·72 appears as a quartet with 3 large couplings (≈ 11 Hz) in contrast to pancracine which shows two large and one small splitting. The signal of H-3, centred at δ = 4·93, showed splittings of 3·3, 4·3 and

Table 1. Mass spectrum of brunsvigine ten highest peaks, *m/e* 50–400

Ion, *m/e*	Relative intensity % base peak
287 (M^+)	100·0
199	24·3
185	23·3
288	20·3
214	20·0
270	19·5
243	18·7
226	12·3
242	11·0
175	10·2

Table 2. Mass spectrum of dihydrobrunsvigine sixteen highest peaks, *m/e* 100–400

Ion, *m/e*	Relative intensity % base peak
175	100·0
289 (M^+)	66·6
174	30·9
176	19·5
290	12·6
173	12·4
148	10·7
256	8·8
288	8·3
149	7·6
129	7·6
188	7·1
115	6·7
230	6·6
160	4·5
272	4·2

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12·2 Hz. Decoupling the axial H-4 removed the large coupling, confirming the assignment and establishing the *trans* diaxial H-3 H-4 relationship. The smaller couplings in H-3 are vicinal interactions with H-2 and the equatorial H-4. The signal arising from H-2 is shifted downfield (compared with pancracine) due to the proximity of the neighbouring 3-acetoxy substituent to merge with the signal from H-1. The H-1 resonance shows an unexpected 2 Hz splitting in addition to the vicinal coupling with H-2 of 3·8 Hz. Decoupling experiments proved the 2 Hz splitting to be an allylic coupling to H-4a which has a favourable steric arrangement for this type of coupling ($\theta \approx 90°$).[8]

Further confirmation of these assignments and analyses was provided by the NMR spectrum of O,O′-diacetylbrunsvigine in benzene. Preferential solvent shifts separated H-1 and H-2 as well as H-12 and H-12′ and permitted an unambiguous analysis of the H-4eq signal, which is partially obscured by the acetoxy-signals in deuterochloroform. Decoupling H-2 reduced H-1 to a narrow doublet (2 Hz) and the H-3 resonance to the expected doublet of doublets (spacings 12·2 and 4·3 Hz), thus confirming the relationship between H-1, H-2 and H-3. Approximate values for the 11,12-, 11,12′- and 12,12′-couplings could also be obtained. However, the NMR signals from H-4a, H-6, H-6′, H-11, H-12 and H-12′ remained broad. Heteronuclear {^{14}N}-^{1}H experiments did not affect the line widths, while an increase in temperature sharpened the signals. This suggests that the line broadening is caused by a certain degree of conformational flexibility in the B-ring.

The NMR spectra of O,O′-di(*p*-bromobenzoyl) brunsvigine and O,O′-diacetylbrunsvigine show only small differences. The H-3 signal pattern remains identical, though shifted slightly downfield (δ 5·26), verifying no change in conformation of ring C due to the attachment of the bulkier *p*-bromobenzoyl substituent. The published X-ray structure analysis[6] may therefore be regarded as valid for both derivatives. Corroborative evidence of no conformational changes on derivatisation of brunsvigine is provided by the ORD and CD spectra (Table 4). Comparison with coccinine and montanine[9] also demonstrates how 5,11b-methanomorphanthridine alkaloids may be reliably recognised from CD spectra.

Oxidation of methanomorphanthridine alkaloids offers an important route to identification of structure.[2] Oppenhauer oxidation of brunsvigine with a variety of ketone reagents, or treatment with manganese dioxide does not yield tractable material, however. Unsuccessful partial acetylation and partial saponification experiments with a view to isolating the 3-monoacetoxy base for oxidative studies led to the conclusion that the two OH groups in brunsvigine are of comparable reactivity.

While Hofmann degradation of brunsvigine (2) fails, preparation of dihydrobrunsvigine methine (4) from dihydrobrunsvigine (3) proceeds with ease.[1] The presence

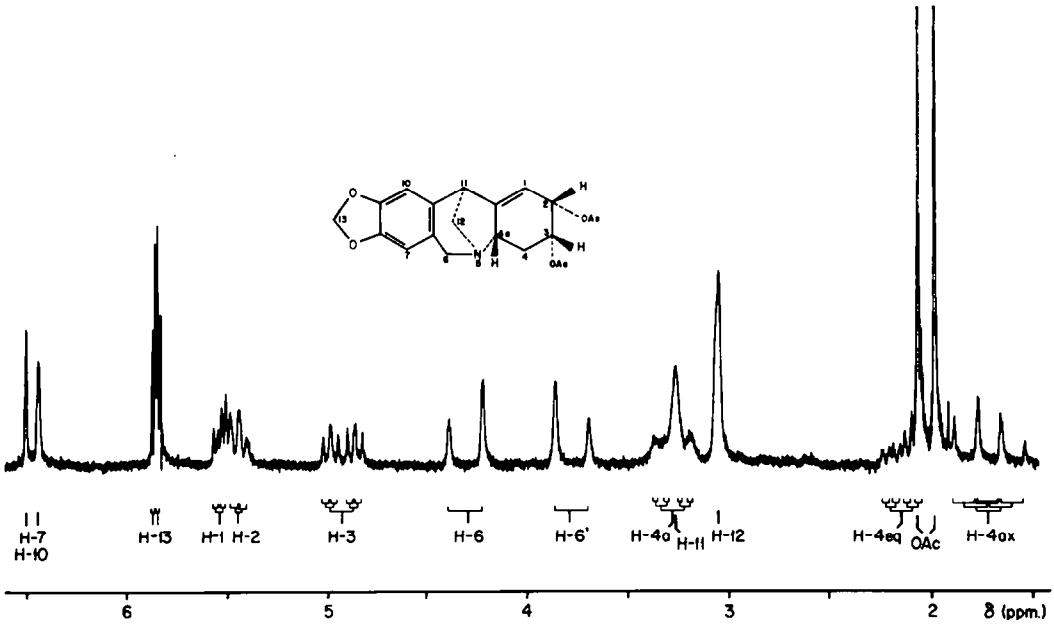


Fig. 1. 100 MHz NMR spectrum of diacetylbrunsvigine in $CDCl_3$.

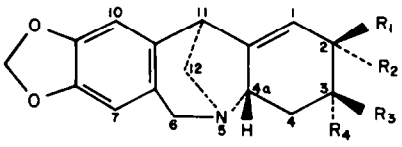
Table 3. NMR parameters of O,O′-diacetylbrunsvigine

Assignment		$H\text{-}4_{ax}$	OAc	OAc	$H\text{-}4_{eq}$	H-12	H-12′	H-11	H-4a	H-6	H-6′	H-3	H-2	H-1	H-13	H-13′	H-10	H-7
Chemical shifts*		1·72	2·00	2·08	2·15	3·07		3·27	3·29	3·80	4·30	4·93	5·45	5·54	5·84	5·86	6·44†	6·50†
Protons	1, 2	1, 4a	2, 3	3, 4_{eq}	3, 4_{ax}	4_{ax}, 4_{eq}		4a, 4_{eq}	4a, 4_{ax}	6, 6′		11, 12		11, 12′	12, 12′			
Couplings	3·8	2·0	4·3	3·3	12·2	(−) 10·8		5·3	11·8	(−) 16·6		≤3‡		≤2‡	~(−) 11·5‡			

*$CDCl_3$ solution, p.p.m. from internal TMS.
†Interchangeable.
‡From C_6D_6 solution.

Table 4. Brunsvigine, O,O'-diacetylbrunsvigine and O,O'-di(*p*-bromobenzoyl)brunsvigine ORD and CD spectroscopic data

Brunsvigine				O,O'-Diacetylbrunsvigine				O,O'-Di(*p*-bromobenzoyl)brunsvigine			
ORD		CD		ORD		CD		ORD		CD	
λ_{nm}	$[\phi]\times10^{-3}$	λ_{nm}	$[\theta]\times10^{-3}$	λ_{nm}	$[\phi]\times10^{-3}$	λ_{nm}	$[\theta]\times10^{-3}$	λ_{nm}	$[\phi]\times10^{-3}$	λ_{nm}	$[\theta]\times10^{-3}$
400	−1	320	0	400	−1	400	0	400	+1	400	0
340	−3	294	−5	340	−3	320	0	340	+3	320	0
306	−7	270	−2	305	−6	293	−5	306	0	290	−11
286	−3	245	−35	287	−3	275	−3	262	+62	273	0
256	−22	233	−25	265	−20	247	−43	255	0	254	+90
245	0	219	−66	248	0	233	−28	246	−133	244	0
237	+14	213	0	235	+26	223	−47	229	0	238	−68
228	+6	204	+140	230	+24	215	0	208	+183	228	−56
212	+110	193	0	210	+139	205	+153	202	0	220	−59
205	0					196	0			213	0
										201	+311
										190	0



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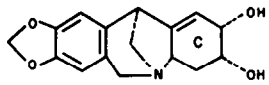

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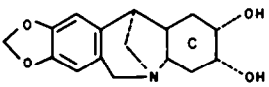

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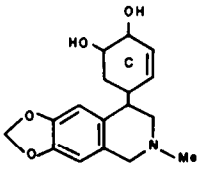

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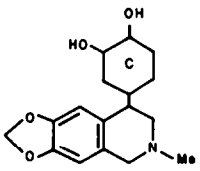

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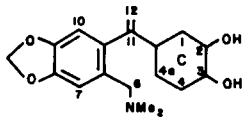

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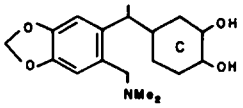

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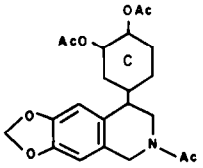

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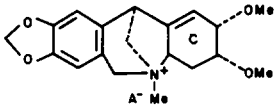

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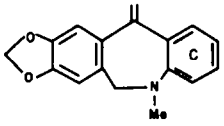

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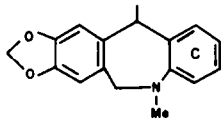

(11)

of a non-conjugated double bond in the methine is supported by no change of the methylenedioxyphenyl UV chromophore. The double bond is endocyclic, supported by the lack of formaldehyde on decomposition of the ozonide. Contrary to expectations, dihydrobrunsvigine dihydromethine methine (**6**) could be prepared from hydrogenated dihydrobrunsvigine methine (**5**) without significant change in the methylenedioxyphenyl chromophore (λ_{max} *ca.* 292 nm) which was stable to pH change in the case of dihydrobrunsvigine dihydromethine methine. Evidence from NMR is in support of structure **6**, however, and dihydrobrunsvigine dihydromethine methine ozonide yielded significant amounts of formaldehyde on hydrolysis. Kuhn–Roth analysis indicated the presence of the C–Me residue in dihydrobrunsvigine dihydromethine dihydromethine (**7**) though the result was somewhat low.

Attempted allylic acetoxy hydrogenolysis of O,O'-diacetylbrunsvigine with Adams catalyst resulted only in the reduction of the double bond. Palladised carbon catalysed hydrogenation of brunsvigine gave a mixture of products from which O,O',N-triacetyltetrahydrobrunsvigine (**8**) could be prepared, verifying the existence of an allylic N–C bond.

A convenient means of interrelating the various 5,11b-methanomorphanthridine alkaloids by O-methylation was used by Inubushi *et al.*[2] but yields intractable material when applied to brunsvigine. Dimethyl sulphate is effective, but the product is a quaternary base. When isolated as O,O',N-

trimethylbrunsvigine picrate, it was found to be identical to O-methyl-β-isocrinamine methopicrate (**9**; $A^- = (NO_2)_3{\cdot}C_6H_2{\cdot}O^-$), prepared by the same method from β-isocrinamine (**1**; R_1, R_3 = H; R_2 = OH; R_4 = OMe). Hofmann degradation of O,O',N-trimethylbrunsvigine hydroxide (**9**; $A^- = OH^-$) resulted in loss of OMe residues and aromatisation of the C-ring to give a methine with a 1,1-diarylethylene skeleton (**10**), confirmed unambiguously by the NMR spectrum. Palladised carbon hydrogenation of the methine (**10**) afforded a product (**11**) having the methylene-dioxyphenyl chromophore present in the parent alkaloid.

EXPERIMENTAL

M.ps were determined with a Kofler hot-stage microscope and are uncorrected. UV spectra were measured on a Beckman DU spectrophotometer. IR spectra were recorded with a Perkin–Elmer Uvicord spectrograph. NMR spectra were recorded at 100 MHz on Varian HA-100 or XL-100 spectrometers in the cases of O,O'-diacetyl- and O,O'-di(*p*-bromobenzoyl) brunsvigine, and at 60 MHz on a Varian A-60 spectrometer in the case of all other brunsvigine derivatives. Solns were in $CDCl_3$ with TMS as internal standard. Mass spectra were recorded on an AEI MS9 spectrometer at 70 electron volts. ORD and CD spectra were measured in MeOH at $c = 0{\cdot}02 - 0{\cdot}04$ g dl^{-1} on a Jasco J-20 spectropolarimeter/dichrograph and units of optical rotation and elipticity quoted in degrees-cm^2-decimole^{-1}.

O,O'-*Diacetylbrunsvigine*. Prepared by the method of Dry *et al.*,[1] m.p. 184°; NMR data have already been listed in the discussion.

O,O'-*Di*(p-*bromobenzoyl*) *brunsvigine*. Brunsvigine (80 mg) in pyridine (10 ml) was heated at 80° with *p*-bromobenzoyl chloride (500 mg) for 2 hr. MeOH (10 ml) was cautiously added and the reaction controlled by cooling. The product was evaporated and benzene (25 ml) added. Evaporation and benzene readdition was repeated twice more before final evaporation to give a product which was left *in vacuo* over sulphuric acid until pyridine-free. Methyl bromobenzoate contamination was mostly removed by sublimation at 80°/0·05 mm. Chloroform extract (20 ml) was loaded on alumina (15 × 1 cm) and washed through with chloroform. The gummy solid left after evaporation of the eluate was freed of methyl bromobenzoate residues by sublimation as before, and dissolved in benzene (10 ml) which was loaded on alumina (3·5 × 1 cm). Elution with EtOAc (50 ml) and solvent evaporation gave a gum which was redissolved in benzene (10 ml) and loaded again on alumina (15 × 1 cm). Benzene eluted a small amount of opaque yellow solid, followed by clear viscous gum. Trituration of the gum with cyclohexane and allowing to stand several days yielded hard white nodules of crystals, m.p. 133–42°. Recrystallisation from cyclohexane gave O,O'-*di*(p-*bromobenzoyl*) *brunsvigine* as nodules 143–145·5°. NMR 100 MHz ($CDCl_3$) δ 7·35–7·95 (8H, 2 × (AA'BB'), 2 × Br, $C_6H_4{\cdot}CO$–), 6·56 (1H, s, H-7), 6·49 (1H, s, H-10), 5·89 (2H, AB, J ≈ 1 Hz, O·CH_2·O), 5·7–5·9 (2H, c, H-1 and H-2), 5·26 (1H, dt, s = 12, 3·5, 3·5 Hz, H-3), 4·10, and 3·85 (2H, AB, J = 17 Hz, H-6), 3·44 (1H, dd, s = 11, 4 Hz, H-4a), 3·34 (1H, s, b, H-11), 3·13 (2H, s, b, H-12), 1·95–2·40 (2H, c, H-4). (Found, dried 0·05 mm: C, 55·1; H, 3·6; N, 2·16; Br, 24·6. $C_{30}H_{23}O_6NBr_2$ requires: C, 55·1; H, 3·5; N, 2·15; Br, 24·5%).

Dihydrobrunsvigine methine (**4**). Prepared according to Dry *et al.*[1] gave needles m.p. 156°. $[\alpha]_D$ +26° (*c* 1·20, $CHCl_3$). λ_{max} (EtOH) 235 nm (log ε 3·65) and 290 (3·72). Ozonolysis by the procedure described elsewhere in this text afforded traces of formaldehyde, isolated as the dimedone derivative (0·06 mole w/w recovery).

Dihydrobrunsvigine dihydromethine (**5**). The methine **4** (175 mg) and 10% Pd–C (40 mg) in MeOH (20 ml) absorbed 13 ml (1·1 mole) H_2 in 4 hr. Evaporation of the filtrate gave a solid, m.p. 195° which recrystallised from acetone as needles. Sublimation at 168°/0·2 mm gave *dihydrobrunsvigine dihydromethine* as small blocks m.p. 196–7°, $[\alpha]_D$ +2° (*c* 0·59, $CHCl_3$). (Found: C, 67·0; H, 7·7; CMe, 0. $C_{17}H_{23}O_4N$ requires: C, 66·9; H, 7·6; CMe, 0%).

Dihydrobrunsvigine dihydromethine methine (**6**). The dihydromethine **5** (150 mg) in MeOH (20 ml) was refluxed with MeI (0·3 ml) for 20 min. Evaporation gave a golden oil which was crystallised as the picrate from water to give *dihydrobrunsvigine dihydromethine methopicrate semihydrate* as large thin plates m.p. 100–3°. (Found, dried 80°/0·5 mm: C, 51·7; H, 5·4. $C_{24}H_{28}O_{11}N_4{\cdot}\frac{1}{2}H_2O$ requires: C, 51·7; H, 5·2%). An aqueous soln (20 ml) of the methiodide oil (200 mg) was stirred with silver oxide (300 mg) until the soln was I_2-free. Evaporation of the filtrate gave a gum which after three slow sublimations at 175°/0·1 mm yielded the *dihydromethine methine* as a colourless hygroscopic glass. $[\alpha]_D$ −19·6° (*c* 1·2, $CHCl_3$); λ_{max} (EtOH) 215 nm (log ε 4·23), 241 (3·81) and 292 (3·65) NMR 60 MHz ($CDCl_3$) δ 7·11 (1H, s, H-7), 6·61 (1H, s, H-10), 3·99 (2H, s, b, O·CH_2·O), 5·26 and 4·89 (2H, AB, J = 2·5 Hz, H-12), 3·6–4·2 (2H, c, H-2 and H-3), 3·34 (2H, s, removed by D_2O exchange, 2 × OH), 6·37 (2H, s, H-6), 2·24 (6H, s, NMe_2), 1·2–2·2 (7H, c, ring C). (Found: C, 67·5; H, 7·8; NMe, 8·7. $C_{18}H_{25}O_4N$ requires: C, 67·7; H, 7·9; NMe, 9·4%). The amorphous *reineckate dihydrate*, m.p. 139° dec, was prepared in acidic acetone–water soln. (Found, dried 0·2 mm: C, 39·4; H, 5·7; residue, 12·4. $C_{22}H_{32}O_4N_7CrS_4{\cdot}2H_2O$ requires: C, 39·2; H, 5·4; Cr_2O_3, 11·3%). Dihydrobrunsvigine dihydromethine methine (185 mg) in a 1:1 pyridine-Ac_2O mixture (6 ml) was heated at 98° for 3 hr. MeOH (5 ml) was added while cooling and evaporation gave a gum which was dissolved in benzene and filtered through alumina (1 g). Evaporation of the benzene gave O,O'-diacetyldihydrobrunsvigine dihydromethine methine as a gum. NMR 60 MHz ($CDCl_3$) δ 7·10 (1H, s, H-7), 6·62 (1H, s, H-10), 6·00 (2H, AB, O·CH_2·O), 4·6–5·5 (4H, c, H-2, H-3 and H-12), 3·32 (2H, s, b, H-6), 2·23 (6H, s, NMe_2), 2·14 and 2·02 (6H, s, 2 × $CH_3{\cdot}CO$), 1·4–2·6 (7H, c, ring C). (Found: Ac, 21·9. $C_{22}H_{29}O_6N$ requires: 2 Ac, 21·4%).

Ozonolysis of dihydrobrunsvigine dihydromethine methine. The base (40 mg) in chloroform (6 ml) at 0° was ozonolysed for 2 hr. The chloroform was then removed by dry N_2 and the gum dried *in vacuo*. This was then dissolved in water (12 ml) and flushed with N_2 while heating at 95°. Formaldehyde was trapped from the N_2 by a bubbler filled with saturated aqueous dimedone to give formaldehyde dimedone (13 mg, 0·36 mole recovery) which recrystallised from methanolic water to give needles (10 mg) m.p. 189–90°, undepressed by admixture with authentic formaldehyde dimedone. The aqueous hydrolysate of the ozonide yielded no tractable product.

Dihydrobrunsvigine dihydromethine dihydromethine (**7**). The base (**6**) (114 mg), 20% Pd–C (40 mg) in MeOH (10 ml) absorbed 8 ml (1 mole) H_2 in 10 hr to give a glass on evaporation of the filtrate. No crystals could be prepared and the material decomposed on attempted sublimation. (Found: CMe, 2·6. $C_{18}H_{27}O_4N$ requires: CMe, 4·7%).

O,O'-*Dimethylbrunsvigine methine* (**10**). Brunsvigine (1 g) and Me_2SO_4 (10 ml) were stirred vigorously while 10% KOH aq was added dropwise over 12 hr. The mixture stood a further 36 hr. Acidification with dil H_2SO_4, followed by addition of reinecke salt soln, gave a ppt of the reineckate which was filtered and washed with water before drying *in vacuo*. An acetone soln of the reineckate was percolated through Amberlite IRA 400 resin (30 g) in the hydroxide form. Evaporation of the eluate gave the methohydroxide (**9**, $A^- = OH^-$) as a gum, which was distilled slowly at 140–155°/0·1 mm to give a crude methine. Elution from alumina (25 × 1·5 cm) with benzene gave a mixture of crystals (80 mg), m.p. 130–200°. Needles were dissolved from platelets with cyclohexane, which was passed through EtOAc neutralised alumina (10 × 0·5 cm) to give needles, m.p. 156–7°. λ_{max} (EtOH) 230 nm (log ε 4·13), 234 (4·14) and 280 (3·97). NMR 60 MHz ($CDCl_3$) δ 6·88 (1H, s, H-7), 6·73 (1H, s, H-10), 7·0–7·6 (2H, c, ring C), 6·7–6·9 (2H, c, ring C), 5·89 (2H, s, O·CH_2·O), 5·61 and 5·14 (2H, AB, J = 3 Hz, olefinic H), 4·29 (2H, s, H-6), 3·02 (3H, s, NMe). (Found, dried 0·1 mm; C, 77·2; H, 6·0; OMe, 0; NMe, 6·1. $C_{17}H_{15}O_2N$ requires: C, 77·0; H, 5·7; OMe, 0; NMe, 5·7%).

Catalytic reduction with Pd–C as described elsewhere in this text afforded the *dihydromethine* (**11**) as un uncrystallisable gum. λ_{max} (EtOH) 234 (log ε 3·89) and 292 (3·70) nm.

O,O',N-*Triacetyltetrahydrobrunsvigine* (**8**). Brunsvigine (1 g) in MeOH (30 ml) with 20% PdC (120 mg) absorbed 80 ml (1·1 mole) H_2 in 18 hr. Evaporation of the filtrate afforded a gum. Elution

from alumina (2·5 × 1·5 cm) with 10% MeOH in chloroform gave a gum, followed by gummy crystals, m.p. 170–190°. Washing and recrystallisation from acetone gave crystals, m.p. 189–201° (110 mg), which on admixture with 3, m.p. 203° gave a depressed m.p. 170–200°. Acetylation by the method already described and elution of the gummy product from alumina with 1:1 ether–benzene gave a clear gum, subliming readily at 190°/0·2 mm to give O,O',N-triacetyl-tetrahydrobrunsvigine. ν_{max} (surface film) 1735 cm^{-1} (O-acetyl) and 1650 (N-acetyl). (Found: C, 63·2; H, 6·3; Ac, 30·7. $C_{22}H_{27}O_7N$ requires: C, 63·3; H, 6·5; 3Ac, 30·9%).

O-Methyl-β-isocrinamine methopicrate and O,O'-dimethylbrunsvigine methopicrate (9). β-isocrinamine (27 mg) and Me_2SO_4 (0·5 g) were stirred rapidly whilst 10% KOH aq (5·6 ml) was added dropwise over 6 hr, and then set aside for 12 hr. The soln was acidified and aqueous picric acid added. The crystals, which formed slowly, were crystallised from water and then from MeOH to give O-methyl-β-isocrinamine methopicrate dihydrate, m.p. 94·5–95°. (Found, dried 50°/0·2 mm: C, 50·9; H, 4·8; N, 9·2. $C_{25}H_{26}O_{11}N_4 \cdot 2H_2O$ requires: C, 50·5; H, 5·1; N, 9·4%). O,O'-Dimethylbrunsvigine methopicrate sesquihydrate, prepared similarly, m.p. 94·5–95° was undepressed on admixture with O-methyl-β-isocrinamine methopicrate dihydrate. (Found: C, 51·0; H, 4·9; N, 9·4. $C_{25}H_{26}O_{11}N_4 \cdot 1\frac{1}{2}H_2O$ requires: C, 51·3; H, 5·0; N, 9·6%).

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