947. *The Alkaloids of the Amaryllidaceae. Part IV.* The Alkaloids of* Brunsvigia cooperi *Baker.*

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Two new alkaloids, brunsvigine and brunsvinine, are isolated from *Brunsvigia cooperi* Baker bulbs collected in summer, lycorine replacing brunsvinine in bulbs collected in late autumn. Crinamine is also isolated throughout. Brunsvigine is shown to be isomeric with lycorine, possessing the same groups as the latter, but differing from lycorine in ease of dehydration and in the behaviour of the dihydro-derivative.

No member of the *Brunsvigia* genus of the family Amaryllidaceae has so far been examined chemically. *Brunsvigia rosea* (Lam.), investigated by Wildman and his co-workers,[1] has been referred back to *Amaryllis rosea* (*A. belladonna* Linn.[2]). The bulbs of *B. cooperi* Baker are now found to contain two new alkaloids: brunsvigine, $C_{16}H_{17}O_4N$, as the main alkaloid, and brunsvinine, $C_{17}H_{19}O_4N$, in very small quantities in bulbs collected during early summer, becoming replaced, seemingly completely so, by lycorine towards autumn. A fourth alkaloid, identified as crinamine,[1,3] was found in more or less constant yield throughout.

Brunsvigine, its hydrochloride, and its picrate all form various solvates. Ready formation of a methiodide showed the nitrogen to be tertiary. The presence of two hydroxy-groups was shown by formation of diacetylbrunsvigine, and a broad band at 3475 cm.$^{-1}$ in the infrared spectrum of the alkaloid indicated that the hydroxy-groups were associated. That the hydroxy-groups are neighbours was indicated by reaction with one mol. of periodic acid in acid solution although no reaction was observed in neutral medium; according to Price and Knell's findings [4] this could mean that the hydroxy-groups are *trans*-oriented. The resulting oxidation product reduced Fehling's solution but failed to crystallise or to yield a tractable picrate or methiodide. Dihydrobrunsvigine similarly reacted with one mol. of periodic acid but also failed to yield a tractable dialdehyde. It is of interest that lycorine consumes ~1 mol. of periodic acid in acid medium in 6 days, and dihydrolycorine reacts more slowly.

Berzoa's test [5] showed the presence of a methylenedioxy-group. Permanganate oxidation of brunsvigine gave a small amount of hydrastic acid.[6]

Catalytic reduction of brunsvigine gave a dihydro-derivative, whose ultraviolet spectrum [$\lambda_{max.}$ 235 and 294 mμ (log ε 3·49 and 3·68 respectively)] closely resembled that of brunsvigine [$\lambda_{max.}$ 242 and 292 mμ (log ε 3·61 and 3·69 respectively)], which suggested that the ethylenic bond was not conjugated with the aromatic ring.[7] At the lower wavelength hydrogenation causes a small decrease in $\lambda_{max.}$ and in ε, which in comparison with the shifts observed by Leonard and Locke [8] does not indicate conclusively an $\alpha\beta$-unsaturated amine. A weak band at 1689 cm.$^{-1}$ in the infrared spectrum of brunsvigine confirmed the ethylenic bond. Conversion into the hydrochloride resulted in the appearance of a strong band at 1623 cm.$^{-1}$ in place of the band at 1689 cm.$^{-1}$, a shift in the opposite direction to that observed by Leonard and Gash [9] on conversion of an $\alpha\beta$-unsaturated amine into its

* Part III, preceding paper.

[1] Mason, Puschett, and Wildman, *J. Amer. Chem. Soc.*, 1955, **77**, 1253.
[2] Index Kewensis, Clarendon Press, London, Suppl. II, 1941—1950, p. 36.
[3] Tanaka, *J. Pharm. Soc. Japan*, 1937, **57**, 139.
[4] Price and Knell, *J. Amer. Chem. Soc.*, 1942, **64**, 552.
[5] Berzoa, *Analyt. Chem.*, 1954, **26**, 1971.
[6] Späth and Kabovec, *Ber.*, 1934, **67**, 1504.
[7] Kondo and Katsura, *Ber.*, 1940, **73**, 1424.
[8] Leonard and Locke, *J. Amer. Chem. Soc.*, 1955, **77**, 437.
[9] Leonard and Gash, *ibid.*, 1954, **76**, 2781.

salt. These authors found, however, that with a mixture of two isomeric α-substituted αβ-unsaturated *N*-methylpyrrolines a shift in the same direction occurred as was observed in brunsvigine. Brunsvigine further showed a medium band at 798 cm.$^{-1}$ and a weaker band at 820 cm.$^{-1}$, both of which may be assigned [10] to out-of-plane ethylenic C–H deformation vibrations for compounds of the type RR′C=CHR″. Both bands disappeared upon hydrogenation (although the 820 cm.$^{-1}$ band may have been obscured in the spectrum of dihydrobrunsvigine by a strong band at 828 cm.$^{-1}$). Brunsvigine further exhibited medium bands at 830, 868, and 730 cm.$^{-1}$, the last two being absent from the spectrum of dihydrobrunsvigine. These findings parallel those of Govindachari and Thyagarajan [11] who assigned a trisubstituted ethylenic bond in a βγ-position to the nitrogen atom to lycorine. Upon conversion into the hydrochloride, however, the lycorine bands at 1716 and 1620 cm.$^{-1}$ shifted to 1682 and 1646 cm.$^{-1}$ respectively, a behaviour not characteristic of βγ-unsaturated amines.[9] The ethylenic bonds in brunsvigine and lycorine appear therefore to be closely similar.

Brunsvigine resisted dehydration by alumina under conditions described by Cook, Loudon, and McCloskey,[12] and attempted dehydration by boric acid (O'Connor and Nace [13]) gave no recognisable products. Whereas according to Kondo and Katsura,[14] dihydrolycorine methohydroxide resisted both Hofmann and Emde degradation, dihydrobrunsvigine methohydroxide readily underwent Hofmann degradation to a methine without loss of the alcoholic groups.

An interesting feature of the bases of *Brunsvigia cooperi* isolated is the possession of one methoxy-group by both brunsvinine and crinamine, each $C_{17}H_{19}O_4N$, whereas neither brunsvigine nor lycorine, each $C_{16}H_{17}O_4N$, has a methoxy-group. Since brunsvigine possesses the same groups as lycorine, a simple relation between the four alkaloids of *B. cooperi* is probable.

EXPERIMENTAL

Microanalyses are by Yvonne Merchant, and spectroscopic data by Dr. E. C. Leisegang and M. von Klemperer.

Extraction.—Bulbs of *Brunsvigia cooperi* Baker collected in May at Dargle, Natal, were sliced and extracted several times with boiling ethanol for 3—5 hr. (wt. of material after extraction and drying, 3·1 kg.). The solvent was removed by flash-evaporation *in vacuo*, residual alcohol removed by steam, and the residue filtered from a small quantity of gum. The acidified filtrate was extracted with ether (which removed a further quantity of non-basic gum), made alkaline with potassium carbonate, and extracted repeatedly with pentyl alcohol. The extracts were dried (Na_2SO_4), concentrated to 200 ml., diluted with ether (600 ml.), and filtered from a large quantity of gummy alkaloid. The filtrate, after removal of the ether and further concentration *in vacuo*, deposited nearly pure brunsvigine (7 g.).

The alkaloidal mixture, precipitated by ether from the pentyl alcohol concentrate, was extracted with boiling chloroform and filtered from some resin. This extract, combined with the residue obtained from the mother-liquor of the brunsvigine crop, was chromatographed on alumina. Elution with chloroform gave, after an initial small gum, nearly pure *crinamine* (1·0 g.) which crystallised in flat needles from chloroform–ether or fine needles from acetone, and had m. p. 196°, $[\alpha]_D^{20}$ +100° (*c* 1 in ethanol) (Found: C, 67·55, 67·7; H, 6·6, 6·5; N, 4·5, 4·3. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4; N, 4·65%). The *picrate* crystallised immediately from alcohol or water in small needles, m. p. 272° (decomp.) not raised on recrystallisation from methanol (Found: C, 52·2; H, 4·5; N, 10·1. $C_{23}H_{22}O_{11}N_4$ requires C, 52·1; H, 4·2; N, 10·6%). The *methiodide* crystallised in long, fine needles (from methanol), m. p. 265° (Found: C, 46·45; H, 5·4. $C_{18}H_{22}O_4NI,H_2O$ requires C, 46·9; H, 5·2%).

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[10] Sheppard and Simpson, *Quart. Rev.*, 1952, **6**, 27.

[11] Govindachari and Thyagarajan, *Chem. and Ind.*, 1954, 374.

[12] Cook, Loudon, and McCloskey, *J.*, 1954, 4176.

[13] O'Connor and Nace, *J. Amer. Chem. Soc.*, 1955, **77**, 1578.

[14] Kondo and Katsura, *Ber.*, 1939, **72**, 2083.

Further elution with chloroform gave lycorine in short, stout needles (0·34 g.), m. p. and mixed m. p. 275° (decomp.) (from water). It gave a hydrochloride, m. p. and mixed m. p. 218°, and a picrate, m. p. 196°. Continued elution with chloroform gave small amounts of brunsvigine, m. p. 240° (from water), but this alkaloid was better removed from the column by extrusion and extraction with boiling ethanol. The lower, colourless portion of the column gave nearly pure brunsvigine (4·2 g.), m. p. 240° after one recrystallisation from water, while the upper portion gave a less pure product (2 g.) from which some brunsvigine (0·5 g.) was obtained by repeated crystallisation from water and acetone.

Bulbs collected in November gave, instead of lycorine after elution of crinamine, a small amount (*ca.* 150 mg.) of *brunsvinine*, m. p. 140—142° after recrystallisation from acetone, 202° after heating at 100°/1 mm. (Found: C, 67·3; H, 6·6; N, 4·6; OMe, 8·8. $C_{17}H_{19}O_4N$ requires C, 67·8; H, 6·4; N, 4·65; OMe, 10·3%). The picrate, m. p. 67—69°, crystallised in nodules of small plates from ethanol.

Brunsvigine crystallised from acetone as *semihydrate* in needles, m. p. 243—245° (Found: C, 65·2; H, 6·4; N, 5·0. $C_{16}H_{17}O_4N,0{\cdot}5H_2O$ requires C, 64·9; H, 6·1; N, 4·7. Found, after drying at 100°/0·5 mm.: C, 66·85; H, 5·7. $C_{16}H_{17}O_4N$ requires C, 66·9; H, 6·0%). Brunsvigine sublimed at 180°/0·1 mm., giving needles of the anhydrous *form*, m. p. 243°, $[\alpha]_D^{20}$ $-76{\cdot}6°$ (*c* 1 in ethanol) (Found: C, 66·8; H, 6·1%). Triangular prisms of a *sesquihydrate*, melting and depositing needles at 140—150°, were obtained from water (Found: C, 60·7; H, 6·5. $C_{16}H_{17}O_4N,1{\cdot}5H_2O$ requires C, 61·1; H, 6·4%). The molecular weight was determined from the ultraviolet extinction coefficient of the picrate (Found: *M*, 294. $C_{16}H_{17}O_4N$ requires *M*, 287).

Brunsvigine Derivatives.—The *picrate* crystallised from water or ethanol as yellow needles, m. p. 190° (Found: C, 50·9, 51·0; H, 4·3, 4·3; N, 11·2. $C_{22}H_{20}O_{11}N_4$ requires C, 51·2; H, 3·9; N, 10·9%). On other occasions yellow needles of a *form*, m. p. 219°, were obtained (Found: C, 51·4; H, 4·4%). The *methiodide* crystallised from ethanol in colourless, fine needles, m. p. 252°, $[\alpha]_D^{20}$ $+29{\cdot}8°$ (*c* 1 in ethanol) (Found: C, 46·4; H, 4·3. $C_{17}H_{20}O_4NI,0{\cdot}5H_2O$ requires C, 46·6; H, 4·8%). The *hydrochloride* was obtained in a hydrated form, m. p. 218—220°, by the evaporation of an aqueous solution (Found: C, 55·1; H, 6·1; Cl, 10·3. $C_{16}H_{18}O_4NCl,1{\cdot}5H_2O$ requires C, 54·8; H, 6·0; Cl, 10·1%). When prepared in ethanol by the addition of either concentrated hydrochloric acid or gaseous hydrogen chloride and by recrystallisation from ether–ethanol, a second *hydrate*, m. p. 245°, was obtained (Found after drying at 130°/1 mm.: C, 57·6; H, 6·05; Cl, 10·65. $C_{16}H_{18}O_4NCl,0{\cdot}5H_2O$ requires C, 57·8; H, 5·7; Cl, 10·7%).

Brunsvigine (110 mg.) in pyridine (3 ml.) was refluxed with acetic anhydride (3 ml.) for 3 hr. Methanol was added, and the mixture boiled for 5 min. and evaporated under reduced pressure to a brown oil which was filtered in benzene through alumina and on evaporation gave a solid *diacetate*. This crystallised from ether–light petroleum in needles, m. p. 184° (Found: C, 64·7; H, 6·0; Ac, 28·6. $C_{20}H_{21}O_6N$ requires C, 64·7; H, 5·7; Ac, 29·6%).

Dihydrobrunsvigine.—Brunsvigine (1 g.) in warm water (60 ml.) and N-hydrochloric acid (4 ml.) was hydrogenated in the presence of Adams's catalyst, 175 ml. hydrogen being absorbed in 6 hr. The solution was filtered, made alkaline with sodium hydrogen carbonate, and extracted with pentyl alcohol (3 × 40 ml.), which gave a gum, solidifying on addition of a little acetone. The solid recrystallised from acetone to give *dihydrobrunsvigine* as colourless needles, m. p. 203°, $[\alpha]_D^{20}$ $+10{\cdot}6°$ (*c* 1 in ethanol) (Found: C, 66·3; H, 6·6. $C_{16}H_{19}O_4N$ requires C, 66·4; H, 6·6%). On evaporation of the basic solution after extraction with pentyl alcohol, more dihydrobrunsvigine was recovered. The picrate crystallised from water as yellow needles, m. p. 218° (Found: C, 50·3; H, 4·75. $C_{22}H_{22}O_{11}N_4$ requires C, 51·0; H, 4·3%). The methiodide crystallised from acetone in nodules or stout needles, m. p. 186°, during 24 hr.

Periodic Acid Oxidation.—The oxidation of brunsvigine was typical of the procedure: brunsvigine (sesquihydrate; 100 mg., 1 mol.) in aqueous 0·14% periodic acid (60 ml., 1·2 mol.) and 2N-sulphuric acid (1 ml.) was set aside for 1 hr. at room temperature after which no further consumption of periodic acid occurred (Found: 0·97 mole of periodic acid consumed).

Dihydrobrunsviginemethine.—Dihydrobrunsvigine methiodide (0·3 g.) in water (50 ml.) was stirred with silver oxide (0·3 g.) until the solution was free from iodide. The filtrate was evaporated to dryness at 50°/30 mm., and the glassy residue heated at 97° *in vacuo* for 30 min. and extracted with boiling dry ether (100 ml.) which gave, on concentration, needles of *dihydrobrunsviginemethine*, m. p. 156°, not raised on recrystallisation from ether (Found: C, 67·35; H, 7·2; N, 4·6; NMe, 9·3. $C_{17}H_{21}O_4N$ requires C, 67·3; H, 7·0; N, 4·6; NMe, 9·6%). The bulk of the ether-insoluble methohydroxide was converted into the methine by further heating. Dihydrobrunsviginemethine methiodide crystallised slowly from acetone in nodules of prisms, m. p. 130° (fast heating) or 179° (slow heating) [mixed m. p. with dihydrobrunsvigine methiodide 160—170° (slow heating)].

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