The Stereochemistry and Absolute Configuration of Stenine and Tuberostemonine

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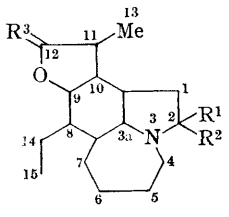
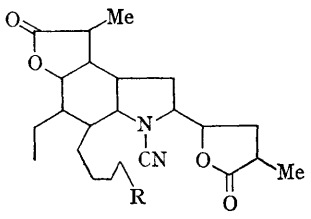
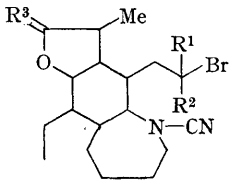
WE have reported previously that the structure of stenine,[1] an alkaloid recently isolated from *Stemona tuberosa* Lour. (*Stemonaceae*), is represented by formula (I). We now report the stereochemistry and absolute configuration of this alkaloid as well as of tuberostermone[2] (II), which is identical in structure and stereochemistry with the former except for the presence of an additional lactone grouping attached to C-2. *cis*-Orientation of the γ-lactone in stenine is revealed by the n.m.r. spectrum ($CDCl_3$; 60 Mc./sec.) of its methiodide in which the C-11 proton showed a quartet at τ 7·18 (1H) (J 7·5 c./sec.), which was supported by a double-resonance experiment, no significant spin–spin coupling being observed between protons at C-11 and C-10. The dihedral angle between these



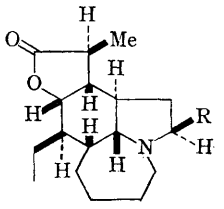
(I) $R^1=R^2=H$, $R^3=O$
(II) $R^1=$(i), $R^2=H$, $R^3=O$
(III) $R^1=R^2=D$, $R^3=D_2$
(IV) R^1, $R^2=O$, $R^3=O$
(VII) $R^1=R^2=H$, $R^3=H_2$



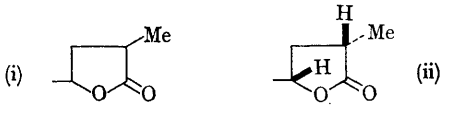
(VIII) R=Br
(IX) R=OAc



(V) $R^1=R^2=D$, $R^3=D_2$
(VI) $R^1=R^2=H$, $R^3=D_2$



(X) R=(ii)
(XI) R=H



protons must, therefore, be approximately 90°. Dreiding models show that this result is consistent only with *cis*-fusion of the lactone ring and a chair-form cyclohexane ring to which an equatorial C-10–C-11 chain is attached in stenine.

Next, attempts were made to determine the configuration of the skeleton of the molecule which consists of a five-, a six-, and a seven-membered ring. 2,2,12,12-Tetradeuterodeoxystenine (III) was prepared by reduction with lithium aluminium deuteride and subsequent dehydration with dilute sulphuric acid of the lactone-lactam[2] (IV) which was obtained by permanganate oxidation of tuberostemonine. von Braun degradation of this deuterated deoxystenine (III) gave compound (V), as shown by its n.m.r. spectrum which exhibited no triplet centred at τ 6·47 (2H) [which is observed, due to CH_2Br protons, in the n.m.r. spectrum of the similar product (VI) obtained from natural deoxystenine (VII)]. Since the signal of the proton at C-3a in this compound (VI) was overlapped by the signal of one of the two protons adjacent to nitrogen, appearing as a multiplet (2H) centred at τ 7·02, we were unable to interpret the peaks adequately. Consequently we turned to the product[2] (VIII) of von Braun cyanogen bromide reaction on tuberostemonine (II). The acetate (IX) derived from the bromide (VIII) showed a quartet due to one C-3a proton at τ 6·65 (J 4·0 and 10·0 c./sec.). These coupling constants imply that the proton at C-3a and one of the two vicinal protons are oriented in an axial–axial conformation and the other one is in an equatorial orientation. Therefore if the six- and the five-membered rings in this compound are *trans*-fused, the six- and the seven-membered rings must be *cis*-fused or *vice versa*. A choice between these two possibilities cannot be made, however, from these data.

Since the n.m.r. data for the compounds did not give sufficient information as to the entire stereochemistry of the alkaloids, we have undertaken an *X*-ray crystallographic study, using Cu-K_α radiation and a single crystal of tuberostemonine methobromide dihydrate, $C_{22}H_{33}NO_4,CH_3Br,2H_2O$. The crystals are orthorhombic, a = 15·91, b = 22·07, c = 7·18 Å; space group $P2_12_12_1$, D_m = 1·339 g. cm.$^{-3}$, D_c = 1·334 g. cm.$^{-3}$ for Z = 4 molecules per cell. 2017 equi-inclination Weissenberg data were estimated visually and used to determine the structure by the heavy-atom

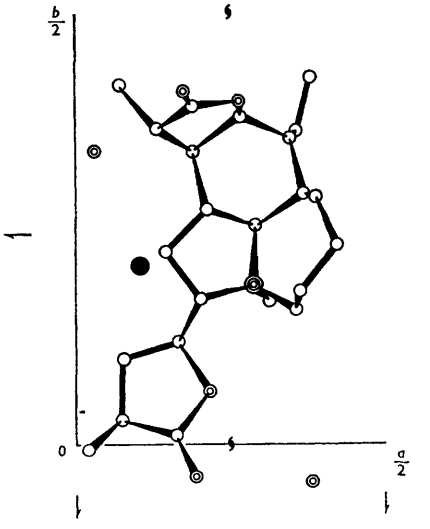


FIGURE. *Perspective drawing of a chemical unit in the tuberostemonine methobromide dihydrate. Black, open, double circles, and triple circle represent bromine, carbon, oxygen, and nitrogen atoms respectively.*

and three-dimensional Fourier methods. The co-ordinates of the bromine atom were determined unambiguously from Patterson syntheses and the remaining atoms, excluding hydrogen atoms, were located in the three-dimensional electron-density distribution. The reliability factor R is 16·7% at present and further refinement of the atomic co-ordinates by the method of least squares is in progress. The absolute configuration was also established using the effect of anomalous dispersion of the bromine atom. The Figure shows the molecular structure as projected along the c-axis.

This absolute configuration of tuberostemonine is represented by (X) which is in agreement with the chemical evidence that oxidation of the base gave (−)-methylsuccinic acid[2] whose absolute configuration has been established.[3] With the elucidation of the stereochemistry of tuberostemonine, that of stenine can also be formulated as (XI). It may be added that stenine (XI) gives a positive Cotton effect (peak $[\phi]$, +1630 at 233 mμ; peak $[\theta]$, +7300 at 217 mμ) in good agreement with the new sector rule proposed by Snatzke and his co-workers.[4]

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