Tetrahedron Letters No. 20, pp. 707-715, 1961. Pergamon Press Ltd. Printed in Great Britain

THE STRUCTURE OF TUBEROSTEMONINE

M. Götz, T. Bögri and A.H. Gray

Department of Chemistry, University of New Brunswick, Fredericton, Canada

(Received 21 August 1961; in revised form 25 October 1961)

Tuberostemonine, $C_{22}H_{33}NO_4$, constitutes the major alkaloid of Stemona tuberosa. H.Schild[1] described a number of degradation reactions on an alkaloid, $C_{22}H_{33}NO_4$, isolated from Stemona sessifolia. A group of Japanese workers[2] showed that Schild's alkaloid was identical with tuberostemonine isolated by K.Suzuki from Stemona tuberosa[3]. Subsequent studies led to the clarification of the funcional groups; tuberostemonine is a tertiary base[1], containing two γ-lactone rings[4].

Our own studies can be summarized by the structures Ia or Ib. Tuberostemonine melts at 86-88°, pK = 6.4 (60% ethanol), IR (KBr): ν_{max} 1765 cm^{-1}. The NMR spectrum[5] of the base reveals three C-methyl groups. Two sharp peaks at 8.63 and 8.77 ppm are either two unsplit C-methyls or two superimposed doublets. That the latter is the case will become obvious in

---

[1] H.Schild, Ber. 69, 74 (1936).

[2] H.Kondo, K.Suzuki and M.Satomi, J.Pharm.Soc.Japan 59, 177 (1939).

[3] K.Suzuki, J.Pharm.Soc.Japan 54, 96 (1934).

[4] T.Kaneko, Ann.Rep. ITSUU Lab. 11, 45 (1960).

[5] All NMR spectra are measured in $CDCl_3$ with $(CH_3)_4Si$ as internal reference.

the sequel. Since both C-methyls are deshielded, they may be placed α to the lactone carbonyls. A third C-methyl group, split into a badly resolved triplet, is centered at 9.02 ppm. A multiplet at 5.62 ppm with the integrated area of two protons accounts for the two secondary γ-hydrogens of the lactones. The spectrum proves the absence of N-methyl; the Zeisel determination indicates the absence of N-alkyl. Experiments to demonstrate a CC double bond were negative. We can therefore conclude that tuberostemonine contains two hetero- and one carbocyclic ring, in addition to the γ-lactones.

Permanganate oxidation[1] of the alkaloid yields 1-methyl-succinic acid ($[\alpha]_D^{24^\circ} = -12.6^\circ$) and a neutral compound II, m.p. 135-138°. Found: C, 69.92; H, 8.95; O, 16.30; N, 4.77; C-CH_3, 9.4 . IR (KBr): ν_{max} 1765 cm^{-1} (γ-lactone), 1685 cm^{-1} (γ-lactam). The NMR spectrum exhibits a doublet for one C-methyl at 8.70 and a triplet at 9.03 ppm. The oxidative cleavage of I into 1-methyl-succinic acid and II leaves no doubt that the two C-methyls deshielded in tuberostemonine have to be placed at different carbons. The formation of optically active methylsuccinic acid proves, furthermore, that both deshielded C-methyls in I are doublets.

Tuberostemonine reacts with three moles of phenyl magnesium bromide to afford III, m.p. 178-187°. Found: C, 78.52; H, 8.27; O, 10.89; N, 2.48; C-CH_3, 6.26. IR (KBr): ν_{max} 1605(w) cm^{-1}.

On treatment of III with acetic acid/acetic anhydride at room temperature, a double bond is introduced by loss of

the elements of water and the secondary hydroxyl is acetylated to give IV, m.p. 85-93°. Found: C, 79.56; H, 8.45; O, 10.05; N, 2.05; C-CH_3, 8.8; O-Ac, 5.9. IR (KBr): ν_{max} 1735, 1600(w) cm^{-1}. UV (ethanol): λ_{max} 280 mμ, ε =9900. The NMR spectrum shows a multiplet for one proton at 4.81 ppm (α hydrogen of secondary acetate), and singlets at 7.85 ppm (acetate) and 8.1 ppm (methyl on a CC double bond). A multiplet at 8.81 - 9.13 ppm proves the presence of the two remaining C-methyls.

On oxidation of IV with CrO_3 in acetic acid a methyl ketone (V) is obtained. IR ($CHCl_3$): ν_{max} 3400, 1723 (sh., acetate), 1715 (ketone, benzoate), 1605(w) cm^{-1}. The NMR spectrum clarifies the functionality of V: two protons at 2.08 ppm represent the ortho hydrogens of the benzoate, 13 protons at 2.54 - 2.89 ppm are the rest of the aromatic hydrogens. The secondary hydrogen α to the benzoate, expected at 4.88, is deshielded by the methyl ketone in ß-position to 4.54 ppm. A one proton multiplet at 4.91 ppm is in agreement with a secondary acetate, and singlets at 7.89 and 7.92 ppm account for the acetyl group and the methyl ketone, respectively. V cannot be recrystallized since it loses benzoic acid with extreme ease.

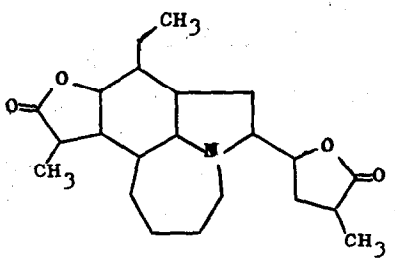
Passing of V through basic alumina yields on elution with benzene-ether an α,ß-unsaturated methyl ketone (VIa or b), m.p. 105-120°. Found: C, 79.06; H, 8.71; O, 10.10; N, 2.19; C-CH_3, 6.99. IR ($CHCl_3$): ν_{max} 3600, 3400, 1670, 1620(w), 1610(w) cm^{-1}. UV (ethanol): λ_{max} 225 mμ, ε =12000. The NMR spectrum shows a doublet at 3.37 ppm for the ß-hydrogen of

the unsaturated ketone, the methyl ketone peak appears at 7.69 ppm and the remaining two C-methyls are at 8.82 - 9.15 ppm (m).

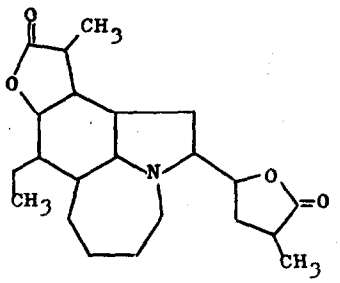
Refluxing of VI in ethanol/KOH in the presence of air gives basic and acidic material. In addition to starting material, the chromatography of the basic fraction through basic alumina yields pale yellow crystals (VII), m.p. 185 - 189°. Found: C, 79.72; H, 7.70; O, 9.40; N, 2.38. IR ($CHCl_3$): ν_{max} 3600, 3400, 1680, 1605(m), 1570(m) cm^{-1}. UV (ethanol): λ_{max} 252 mμ, ε = 17800; λ_{max} (sh) 275 mμ, ε = 8700; λ_{max} 354 mμ, ε = 1900. UV (ethanol/HCl): λ_{max} 252 mμ, ε=12900; λ_{max} 282 mμ, ε = 3200. The UV spectrum in ethanol is typical for an ortho- or meta-amino acetophenone. The UV spectrum in acidic solution is characteristic for an alkyl-substituted acetophenone [6]. The NMR spectrum of VII exhibits eleven hydrogens in the aromatic region (2.49 - 2.77 ppm); the methyl ketone at 7.47 ppm is in excellent agreement with an acetophenone. A C-methyl triplet (J_{AB} = 6.6 cps) is centered at 8.82 ppm, the expected position for an ethyl benzene. The remaining C-methyl doublet appears again at 9.1 ppm. The UV spectrum does not differentiate between an ortho- or meta-amino acetophenone. However, the NMR spectrum clearly shows the presence of one hydrogen on the newly formed aromatic ring, and the substitution pattern could be decided by a study of the shifts of this hydrogen in approp-

---

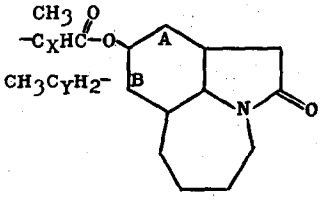
[6] E.A.Braude and F.Sondheimer, J.Chem.Soc. 1955 3754



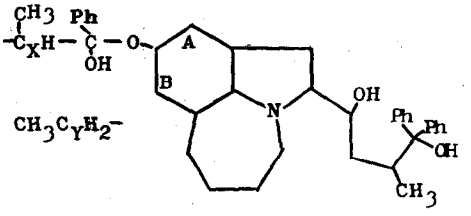
Ia



Ib

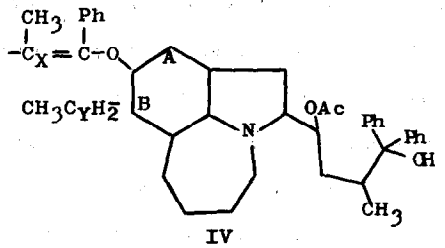


II

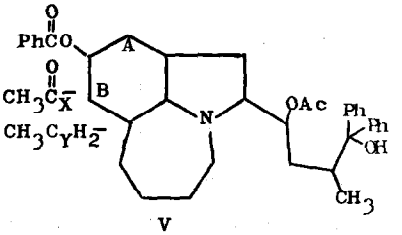


III

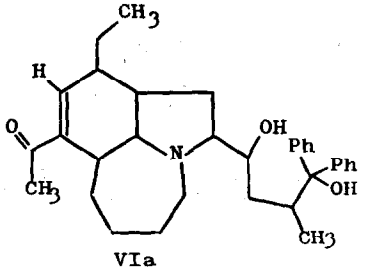
(C_X joined to C_A, C_Y to C_B, or vice versa)



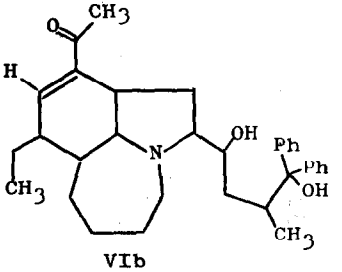
IV



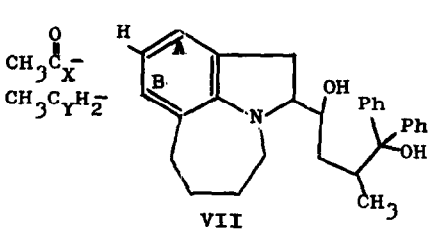
V



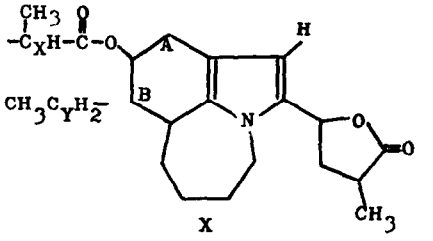
VIa



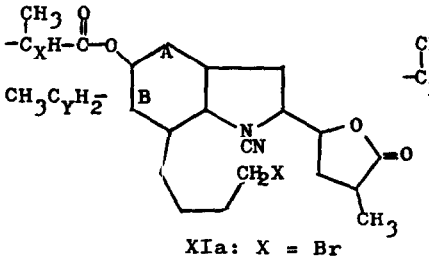
VIb



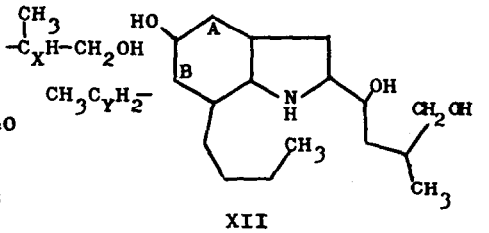
VII



X



XIa: X = Br
XIb: X = OAc



XII

riate derivatives [7]. Only a hydrogen ortho to the acetogroup would be expected to be significantly deshielded in the NMR spectrum of VII in $CDCl_3$/HCl. The smaller deshielding effect on a meta or para hydrogen would be compensated by the shielding influence of the alkyl-substituents. The spectrum exhibits, besides ten protons at 2.78 ppm, a one proton singlet at 2.33 ppm corresponding to the expected position of a proton ortho to the aceto group.

Reduction of the ketone of VII with $NaBH_4$ in methanol affords VIII, m.p. 173-176°. IR ($CHCl_3$): ν_{max} 3600, 3400 cm^{-1}.

---

[7] K.M.Jackman, Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry, Pergamon Press, New York, 1959.

UV (ethanol): λ_{max} 254 mμ, ε =3900; λ_{max} 269 mμ, ε =1850. UV (ethanol/HCl): λ_{max} 253 mμ, ε = 1300; λ_{max} 269 mμ, ε =1580; λ_{max} 277 mμ, ε =1580. The NMR spectrum of VIII has a ten proton peak at 2.78 ppm and a one proton singlet at 3.36 ppm. Such a marked shift toward higher field can only arise if the hydrogen is either ortho or para to the amino group. It follows that the relative position of the aceto- and amino-group has to be meta.

From the acidic fraction γ,γ -diphenyl-ß-methylbutyrolactone (IX) was isolated, m.p. 140-141°. Found: C, 80.25; H, 7.10; O, 12.79; C-CH_3, 5.92; sap. equiv., 255. IR (KBr): ν_{max} 1780, 1605(w) cm^{-1}.

To gain more information about the neighbourhood of the nitrogen, we prepared the pyrrol (X), m.p. 174-177°, already described by Schild[1] and H.Kondo et al.[8] X is formed from tuberostemonine under very mild oxidative conditions. Found: C, 71.02; H, 7.82; O, 17.40; N, 3.87; C-CH_3, 8.63. IR (KBr): ν_{max} 1760 cm^{-1}. UV (ethanol): λ_{max} 234 mμ, ε =10900; λ_{max} = 278 mμ, ε =1500. The NMR spectrum exhibits a pyrrol ß-hydrogen at 4.08 ppm, split into a narrow doublet (J = 2.2 cps, 1:3 split). One of the secondary γ-lactone hydrogens is further deshielded by the pyrrol nucleus to 4.61 ppm. The γ-hydrogen of the other lactone group appears at 5.39 ppm. A quartet for two C-methyls is placed at 8.54, 8.6, 8.67 and 8.7 ppm. A C-methyl triplet is centered at 8.96 ppm. This NMR spectrum proves that tuberostemonine contains a

[8] H.Kondo, M.Satomi and T.Kaneko, Ann.Rep.ITSUU Lab. 9, 99 (1958).

2,3,5-trisubstituted pyrrolidine ring. However, so far we were unable to provide any data about the nature of the third carbon connected with the nitrogen. The NMR spectrum of the von Braun degradation product of tuberostemonine offers this information and confirms the substitutional pattern ascertained for the two other carbons α to the nitrogen.

Action of BrCN on tuberostemonine gave in our hands compound XIa, m.p. 80-85°. A Japanese group reports the isolation of a substance melting at 200-202° [9]. Found: C, 57.22; H, 7.08; N, 6.23; Br, 18.90; C-CH_3, 6.31. IR (KBr): ν_{max} 2200, 1775 cm^{-1}. We ascribe a multiplet for two protons at 5.52 ppm in the NMR spectrum to the two γ-hydrogens of the lactones. A one hydrogen peak at 6.16 ppm accounts for a proton α to the cyanamide, which is further deshielded by the ß influence of one of the lactones. A three proton peak centered at 6.66 ppm represents the second hydrogen α to the cyanamide and the two hydrogens α to the bromine. That this assignment is in fact correct is proven by converting the primary bromide into the primary acetate (XIb) with silver acetate in pyridine. Two of the hydrogens of the 6.66 peak of the bromide spectrum should be shifted down field to approximately 6 ppm. The NMR spectrum of XIb shows indeed two protons at 5.52 ppm, three at 6.03 ppm, and one at 6.67 ppm.

The acetate (XIb) melts at 145-146°. Found: C, 65.13; H, 7.92; O, 21.06; N, 6.11; C-CH_3, 9.28. IR (KBr): ν_{max}

[9] H.Kondo, K.Suzuki and M.Satomi, J.Pharm.Soc.Japan 61, 111 (1941).

2200, 1775, 1725 cm^{-1}.

Finally we performed a modified Kuhn-Roth oxidation [10] on tuberostemonine and on XII, the lithium aluminum hydride reduction product of XIa. Tuberostemonine yields acetic- and propionic acid. XII yields acetic-, propionic-, butyric- and valeric acid, in agreement with the assigned structures I and XII, respectively. The acids were identified in the form of their methyl esters by vapor phase chromatography.

Acknowledgements: M.G. is greatly indebted to Professors K.Wiesner and Z.Valenta for the opportunity to work in their laboratories and for constant encouragement.
A.H.G. wants to acknowledge a NRC studentship.

---

[10] H.Bickel, H.Schmid and P.Karrer, Helv. 38, 649 (1955).