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ALKALOIDS FROM BUXUS SEMPERVIRENS L. V.[x]

CONFIGURATION OF BUXTAUINE AND BUXPIINE

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In our previous communication[1] we have reported the structure elucidation and mass spectrometric fragmentation of buxtauine (Ia) a novel, one nitrogen containing type of alkaloid isolated from Buxus sempervirens L. Buxtauine was shown to be a representative of a new class of cyclopropane steroidal alkaloid possesing a C-20 oxygen function for which the convention on use of letter suffixes to designate substitution pattern of Buxus alkaloids[2] does not fit.

We wish to present herewith the structure of an additiona alkaloid of this series, buxpiine which is very closely related to buxtauine and the configuration of both these alkaloids.

Buxpiine, $C_{25}H_{39}NO_2$ (Ic), m.p. 173°; $[\alpha]_D^{21}$ +158 ±3° (c 0.173, chloroform) was isolated from fraction C by column chromatography on alumina[3]. Its infra-red spectrum[4] exhibited absorption bands attributed to a cyclopropane ring (1458 cm^{-1}),

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x For part IV, see Z. Votický, J. Tomko, L. Dolejš, V. Hanuš, Collection Czechoslov. Chem. Commun. 30, in press.

a carbonyl group (1709 cm^{-1}) a hydroxyl group (1037 and 3583 cm^{-1}), and an exocyclic double bond (903, 1653 and 3093 cm^{-1}) There was no peak indicating the presence of a hydrogen free amino group. The n.m.r. spectrum[5] of buxpiine showed signals at 0.08 and 0.29[6] (cyclopropyl methylene), 4.66 and 4.95 (terminal methylene), 2.35 (6H, dimethylamino group), 2.23 (hydrogen adjacent to oxygen), 0.92 and 1.15 (6H, two quarternary methyl groups). In the mass spectrum[7] the base peaks were formed besides the molecular peaks - of m/e 58 ions (dimethylamino group) and m/e 43 ions (acetyl group). All these observations suggested that buxpiine is the N-methylderivative of buxtauine. Reduction of buxpiine by $NaBH_4$ led to the diol $C_{25}H_{41}NO_2$ (IIc) m.p. 198-200°; $[\alpha]_D^{28}$ +102 ±3° which mass and infra-red spectra were superimposable with those obtained from buxtauine after succesive $NaBH_4$ reduction and methylation according to the Eschweiler-Clarke method. In attemping to carry out direct methylation of buxpiine by this way a molecule of water was split off, yielding anhydrobuxpiine $C_{25}H_{37}NO$ (IIIb) λ_{max}^{EtOH} 241 nm (log ε 4.02). This product was found to be identical with N-methylanhydrobuxtauine.

As the Eschweiler-Clarke methylation of buxtauine affored the N-methyl anhydroderivative only, the conversion of buxtauine to buxpiine was carried out by methylation of buxtauine oxime. Recovery of the original carbonyl group took place as a result of formic acid action. Full agreement was found when all characteristic data of the respective products were compared and therefore buxpiine was systematically denominated as 3-dimethylamino-4-methylene-14-methyl-9,19-cyclo-16-hydroxypregnan-20-one.

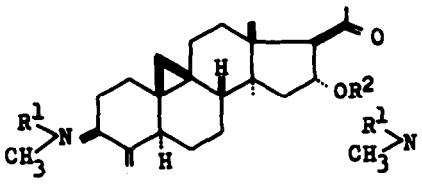
Thus the interrelation between buxtauine and its N-methyl derivative buxpiine was demonstrated. In order to establish the configuration of both these alkaloids, buxtauine was hydrogenated on Adams catalyst in acetic acid, yielding 4,4^{a}-dihydro-derivative (IV) which, in turn was degradated according the Rushig method[9] to the proper 16-ene-3,20-dione (V), this being characterized by spectroscopic data. In the infra-red spectrum peaks were observed at 1709 cm^{-1} (carbonyl group), 1676 cm^{-1} (conjugated carbonyl group), 907 and 1600 cm^{-1} (double bond) and 1460 cm^{-1} (cyclopropyl methylene), while the ultra-violet spectrum exhibited a maximum at 241 nm ($\log\varepsilon$ 4.83). Selective hydrogenation of the endione (V) over palladium on charcoal in ethanol-acetic acid furnished, after purification on alumina, the dione $C_{23}H_{34}O_2$ (VI) having its characteristic data in accord with those reported[8] for 4α, 14α-dimethyl-9β,19-cyclo--5α-pregnane-3,20-dione. This experiment not only afforded evidence for configuration at six assymetric centers but also confirmed the C-17 position of the acetyl group. This C-17 acetyl group was assigned to have β-configuration, since the o.r.d. curve exhibited a similar positive Cotton effect as 17β-pregnan-20-ones[10].

The easy dehydratation of buxtauine (Ia) to anhydro-buxtauine (IIIa) under various mild reaction conditions suggested that the hydroxyl group had to be in the adjacent C-16 position. The average increment of change in molecular rotation at the C-16 position of steroids, namely 16α-hydroxy to 16α-acetoxy is reported as being -240°, while the average increment for the β-counterparts is +65° [11] and therefore the acetylation of buxpiine was attempted. The resulting acetyl-

derivative $C_{27}H_{41}NO_3$ (Ib) m.p. 205-207°; $[\alpha]_D^{27}$ +99 ±2°, showed Δ M -208° [12], thereby determining the[α]position of the C-16 hydroxyl group.

Biogenetic precedence favored the 3β-position for both the methyl- and dimethylamino group of the alkaloids in question. The evidence of this assignement could be established by the weak negative Cotton effect of the 4-ketoderivative[8]. The 20-keto group in buxtauine (Ia), having been transformed to the appropriate hydroxyl group, the amino diol (IIa) was acetylated to the triacetylderivative (IIb) and the 4-exomethylene group was converted by ozonolysis to the 4-ketoderivative $C_{30}H_{45}NO_6$ (VII). Its o.r.d. curve actually exhibited a weak Cotton effect comparable with that of cholestane-4-one which is to be accepted as a proof for the 3β-(equatorial) position of the nitrogen function[8].

Thus buxtauine (Ia) is formulated as 3β-methylamino-14α--methyl-4-methylene-9β,19-cyclo-5α-pregnane-16α-ol-20-one and buxpiine (Ic) as its N-methylderivative.



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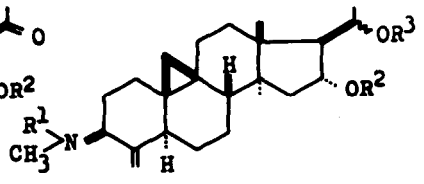
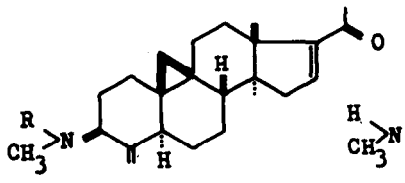
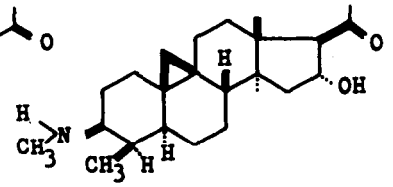
b $R^1=CH_3$, $R^2=COCH_3$
c $R^1=CH_3$, $R^2=H$



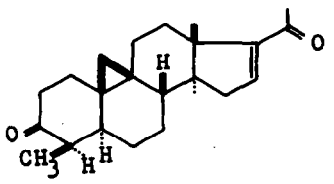
II a $R^1=R^2=R^3=H$
b $R^1=R^2=R^3=COCH_3$
c $R^1=CH_3$, $R^2=R^3=H$



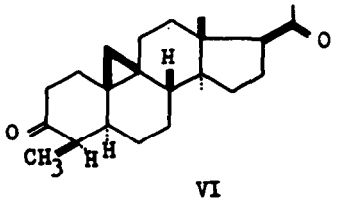
III a R=H
b $R=CH_3$



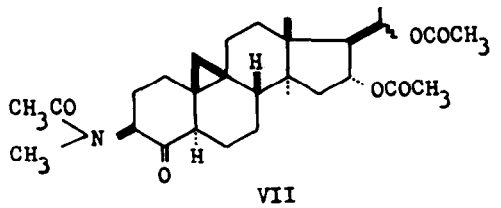
IV



V



VI



VII

References

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(4) Infra-red spectra were taken with a UR-10 Zeiss spectrophotometer either in KBr pellets or in carbon tetrachloride.

(5) We are greatly indebted to Mme Allais, Institut de Chimie des Substances Naturelles, Gif-sur-Yvette for operating the Varian A-60 spectrometer. The spectrum was measured in deuterochloroform solution using tetramethylsilane as internal standard.

(6) Given as [δ] values.

(7) cf. reference 1.

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(12) Molecular rotation of acetoxy derivative minus hydroxy derivative.