Tetrahedron Letters No. 22 + 23, pp I79I - I794, I975. Pergamon Press. Printed in Great Britain.

REVISION OF THE CONFIGURATION OF THE C-4 HYDROXYMETHYLENE GROUP IN BUXUS ALKALOIDS BY ^{13}C NMR SPECTROSCOPY [1]

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(Received in UK 24 March I975; accepted for publication I6 April I975)

The two substituents at C-4 of a great number of steroidal Buxux alkaloids are a hydroxymethylene and a methyl group [2].On the basis of ^{1}H nmr studies [3] the axial β-configuration has been assigned to the hydroxymethylene group of all these compounds, most of which have been chemically correlated [2].This paper presents evidence for the necessity of structural revision since ^{13}C nmr spectroscopy shows unambiguously the axial configuration at C-4 of the methyl group of the compounds examined.

Application of chemical shift rules [4], single frequency decoupled (SFORD) and noise off-resonance decoupled (NORD) ^{13}C nmr spectra, the resonance positions of the carbons of cycloartanol 1 [1] as well as spectral comparison of the structurally related compounds of Figure 1 led to the assignments shown in Table 1.

Based on the ^{13}C nmr spectrum of cycloartanol 1 the chemical shifts of cycloprotobuxine-F 2 can be easily assigned.The aminomethine resonances due to C-3 and C-20 appear at 61.3 and 60.0 ppm respectively.Their differentiation is based on a comparison with the spectrum of 3a in which both of these signals are expected to be shielded as a result of the presence of a hydroxyl group at γ position with respect to each of these carbon atoms.In agreement with the effect of the replacement of an equatorial hydroxyl group by an amino function [5], C-3 of 2 resonates about 18 ppm higher field compared to C-3 of 1 [1].The C-21 signal of 2 is strongly shielded as a consequence of the γ-effects due to the N_B-methyl carbons and C-2 of 2 resonates a little lower field than the same carbon of 1 as a result of the greater β-effect of an equatorial amino group with respect to that of a hydroxyl function [4a].

The ^{13}C nmr spectrum of cyclobuxidine-F 3a appears to be in contrast with the previously proposed structure of this compound.As compared to the spectrum of 2 the major modifications due to the introduction of the two hydroxyl functions are the presence of the low field oxymethine and oxymethylene signals.Further expected influences are observed: deshielding β-effects for C-4, C-15 and C-17 and shielding γ-effects for the hydrogen bearing sites C-3, C-5 and C-20.Inspection of the C-methyl resonances of 3a as compared to those of 2 indicates small chemical shift changes for three signals corresponding to C-18, C-21 and C-28.One C-methyl resonance of 2,either C-29 or C-30 , is replaced by the low field oxymethylene signal at 73.7 ppm while the remaining C-methyl signal of 3a which represents the carbon attached to C-4 appears at 9.6 ppm.Since the 14.0 ppm signal of 2 represents the axially oriented C-30 [1],

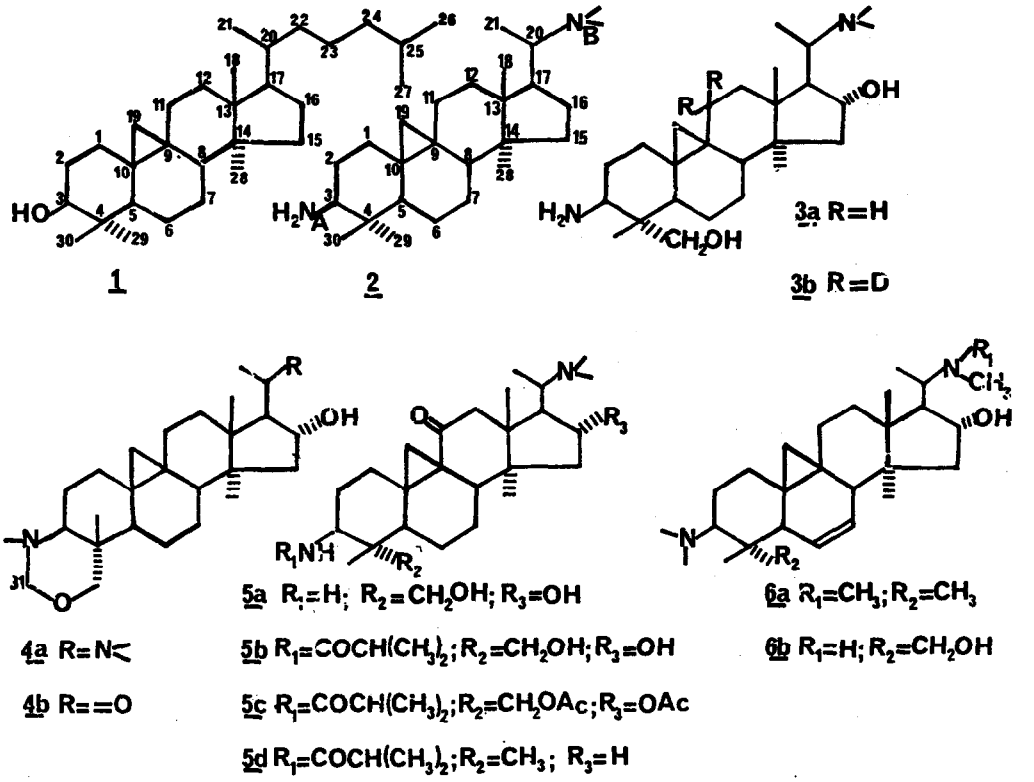


Fig:1

the methyl signal of 3a at 9.6 ppm must be assigned to C-30 of axial configuration. A 4.4 ppm γ-effect due to the alcoholic oxygen atom is in consonance with previous findings [4]. As a consequence, the hydroxymethylene group of 3a is α-equatorial and not β axial [+]. Signal assignments for all the alkaloids studied support these conclusions. The trans stereochemistry at the junction of the A and the heterocyclic rings of 4a and 4b is illustrated by the high field shift of C-30 in these compounds.

The ^{13}C nmr spectrum of several alkyl-substituted cyclohexanones [6] and steroidal ketones [7] has indicated that large upfield shifts appear on the γ-carbon when this atom is eclipsed or nearly eclipsed with the keto-group. For instance, C-9 of androstane and 1-androstanone indicate resonance positions at 55.1 and 47.2 ppm respectively [7].

[+] This conclusion has been recently confirmed by X-ray crystallography. J. Guilhem unpublished results.

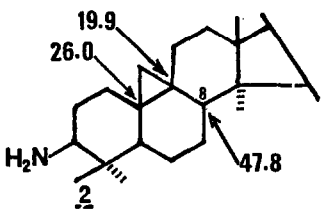
TABLE 1.

	1[a]	2	3a	4a	4b	5a	5b[b]	5c[b,c]	5d[b]	6a	6b
C-1	31.9	31.0	31.4	31.5	31.4	30.4	30.6	30.3[d]	29.3	31.0[d]	30.9[d]
C-2	30.3	32.5	32.7	23.9	23.9	33.4	27.8	28.1[d]	28.5	18.3	18.5[e]
C-3	78.5	61.3	59.0	71.9	71.6	57.9	50.7	49.6	55.1	71.2	73.4[e]
C-4	40.3	39.7	42.0	38.8	38.7	42.3	41.3	42.6[e]	39.5	41.5	42.2
C-5	47.0	47.8	44.8	44.5	44.5	44.8	44.5	43.0[e]	48.2	48.6[e]	45.2[f]
C-6	21.0	21.3	20.9	20.1	20.0[d]	18.3	18.3	18.7[d]	19.8	128.2[e]	129.3[f]
C-7	28.0	26.9	25.9	25.6	25.8[d]	27.8	27.8	27.6[d]	27.7	127.4[e]	125.6[f]
C-8	47.8	47.8	47.9	47.2	46.5	41.4[d]	41.3[d]	41.3[f]	41.1[d]	43.2	43.2
C-9	20.0	19.7	19.0	19.0	18.8	34.2[d]	34.4[d]	33.9[f]	33.9[d]	20.8	20.7
C-10	26.0	26.0	25.9	25.6	25.8[d]	37.6	37.8	37.4	37.6	28.8	27.9
C-11	26.0	26.0	25.9*	25.6	25.3[d]	210.2	211.4	210.7	208.9	24.8[d]	24.8[d]
C-12	35.5	35.1	34.6	32.6	32.5[e]	51.4	51.5	51.9	51.9	31.8	31.9
C-13	45.1	44.1	44.8	44.8	48.4[e]	44.4	44.5	44.5	44.0	45.1	45.2
C-14	48.7	48.9	47.2	47.2	47.6[e]	47.0	47.1	47.4[e]	48.2	49.7	49.6
C-15	32.8	32.5	44.8	44.8	45.7[f]	42.7	42.8	42.6[e]	33.6	41.5	41.6
C-16	26.5	26.3	79.0	79.0	71.6[f]	78.3	78.3	78.0	26.7	79.1	78.4
C-17	52.2[d]	50.6[d]	62.5[d]	62.4[d]	70.4[f]	61.8	62.0[e]	59.5[g]	49.2[e]	62.5	61.5
C-18	17.9[d]	18.2[d]	19.0	18.7[d]	20.4	17.7[e]	17.9[e]	17.8[g]	16.9[e]	18.3	18.5
C-19	29.8	29.5	30.4	30.7	30.2	24.5	24.3	24.4	24.3	19.9	18.5
C-20	36.0[d]	59.6	57.0	57.1	209.5	55.8	55.8	55.1	60.6	56.7	58.9
C-21	18.3[d]	9.3[d]	9.6[d]	9.6[d]	31.4	9.8[e]	9.9[e]	9.8[g]	9.6[e]	10.0	18.5
C-28	19.3[d]	19.2[d]	20.9[d]	20.9[d]	20.4	20.7[e]	20.8[e]	20.0[g]	19.4[e]	15.3	15.5[e]
C-29	25.4	25.8	73.7	78.1	78.0	71.7	64.1	65.4	25.7	26.0	73.7
C-30	14.0	14.0	9.6	13.8	13.7	9.8	11.2	11.3	15.0	16.5	12.1
N_A-CH_3	-	-	-	36.5	36.5	-	-	-	-	2x44.1	2x43.2
N_B-CH_3	-	2x39.7	2x40.6 C-31	2x40.6 88.8	- 88.7	2x40.5	2x40.6	2x40.2	2x39.5	2x40.0	33.8

^{13}C nmr chemical shifts for cycloartanol 1 and for related alkaloids. Spectra were recorded in $CDCl_3$ solution on a Bruker HX 90E spectrometer at 22.63 MHz. Chemical shifts are given in ppm with respect to TMS used as an internal standard. [a] the cycloartanol carbons above C-21 are as follows: C-22 36.4; C-23 24.0; C-24 39.4; C-25 28.0; C-26 22.5 and C-27 22.7 ppm. [b] isobutyryl carbons: 5b 19.4; 20.3; 35.4 and 178.7; 5c 19.4; 19.4; 35.7 and 176.4; 5d 18.9; 18.9; 35.5 and 174.3; [c] acetate carbons: 21.0; 21.0; 170.4 and 171.1. [d,e,f,g] assignments may be reversed although those given here are preferred. * assignment confirmed by recording the spectrum of 3b.

While a similar phenomenon has not been observed for C-8 in 11-androstanone, the 11-keto alkaloids studied clearly show this conformational effect, C-8 being strongly shielded in the spectrum of 5a, 5b, 5c and 5d.(Fig 2).

In view of the unusual β-effect of a carbonyl group adjacent to cyclopropanes (8) the differentiation of C-9 and C-10 in the 11-keto alkaloids should be considered at present time as being only tentative.In the ^{13}C nmr spectrum of cycloviro-buxeine-A 6a and cyclomycrophylline-B 6b an anomalous downfield homoallylic endocyclic effect (9) is noticed on the cyclopropane quaternary carbons.This effect may be due to the great strain imposed on the molecule by the presence of its Δ^6 double bond.Another unexpected effect is observed in the spectra of the 16α-hydroxy alkaloids 3a, 3b, 4a, 5a, 5b, 6a but not in the ^{13}C nmr spectrum of 6b.While C-20 appears as a sharp signal, the N_B-methyl carbons show important line broadening as a result of the strongly hydrogen bonded nitrogen atom.At higher temperature (+ 60°) the N_B-methyl signals become sharp as they are at room temperature in the spectrum of 5c.



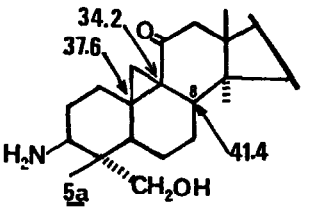


Fig:2

Acknowledgment - The authors wish to thank Dr. Kazuo Tori, Shionogi Research Laboratory, for stimulating discussions.

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