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# STRUCTURE OF HASUBANONINE

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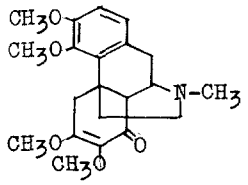
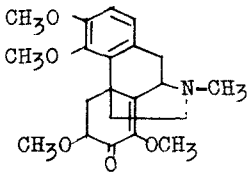
Hasubanonine was first isolated from Stephania japonica Miers (Menispermaceae) by Kondo et al. in 1951 and the structure (Ia) was given by the same authors.[1] Thereafter, Bentley, from the viewpoint of biogenetic considerations of alkaloids, suggested the alternative structure (Ib).[2]

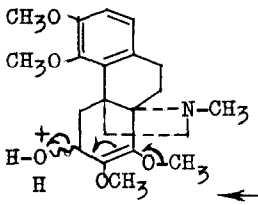
We now propose the structure (Ic) for hasubanonine on the basis of the following evidences.



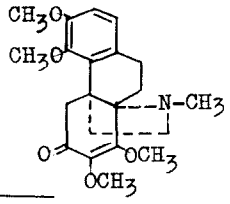
(Ia)



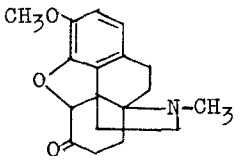
(Ib)



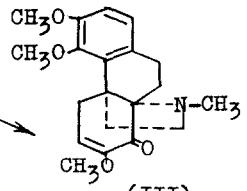
(IIa), (IIb)



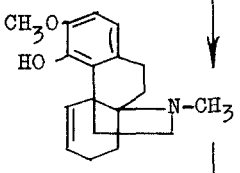
(Ic)



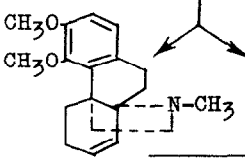
(VI)



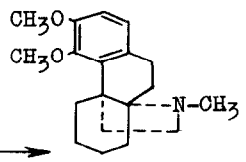
(III)



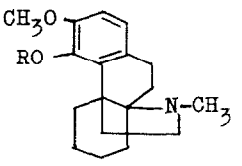
(VII)



(IV)



(Va)



(VIII) R = H

(Vb) R = $CH_3$

Hasubanonine, $C_{21}H_{27}O_2N$,*1 m.p. 116°, contains one $N\text{-}CH_3$ group (N.M.R.*2 $\tau$ 7.48(3H)), four $OCH_3$ groups (N.M.R. $\tau$ 5.92(3H), 6.09(3H), 6.20(3H) and 6.36(3H)), one active methylene group $>C(-CH_2-)C(=O)<$ (N.M.R. $\tau$ doublet (J=16cps) 6.62(1H) and doublet (J=16cps) 7.27(1H)), two aromatic hydrogens (N.M.R. $\tau$ 3.28(2H)) and one conjugated carbonyl group (IR $\nu_{max}^{CHCl_3}$ 1664cm$^{-1}$). The absence of olefinic hydrogen or $>C(-OCH_3)(-H)$ hydrogen in the N.M.R. spectrum indicates that the $>C-CH_2-C(=O)-C(-OCH_3)=C(-OCH_3)-$ system is present in the molecule. Therefore, the structure (Ib) proposed by Bentley was ruled out.

Reduction of hasubanonine with sodium borohydride yielded two epimeric compounds, dihydrohasubanonine-A (IIa) and dihydrohasubanonine-B (IIb). They were separated by careful chromatography on alumina column. Dihydrohasubanonine-A (IIa) showed the following spectroscopic properties: IR $\nu_{max}^{CHCl_3}$ 3525(OH), 1670cm$^{-1}$ ( C=C ), N.M.R. $\tau$ triplet centered at 5.76($>C(-OH)(-H)$), aromatic hydrogens 3.27(2H), $OCH_3$ 6.10 (3H), 6.22(3H), 6.23(3H) and 6.44(3H), $N\text{-}CH_3$ 7.53(3H). PPC Rf 0.68.

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*1 All compounds given by formulae in this communication gave correct elementary analysis.

*2 All N.M.R. spectra were taken on Varian A-60 machine in $CDCl_3$ with $SiMe_4$ as internal standard.

Dihydrohasubanonine-B (IIb) is a hydroxyl epimer of (IIa); IR $\nu_{max}^{CHCl_3}$ 3550(OH), 3300—3400 (hydrogen bonding OH) and 1670cm$^{-1}$( C=C ); N.M.R.$\tau$ triplet centered at 6.12 ($>C<^{OH}_{H}$), aromatic hydrogens 3.29(2H), $OCH_3$ 6.13(3H), 6.19(6H) and 6.52(3H), N-$CH_3$ 7.53(3H). PPC Rf 0.67.*3

(IIb) was more strongly adsorbed on a chromatographic alumina column than its epimer (IIa).(3) In the N.M.R. spectrum $>C<^{OH}_{H}$ proton of (IIb) absorbed at higher field than its epimer (IIa)(4) and in the paper chromatography (IIb) has the lower Rf value than that of (IIa).(5) All these facts indicate that the hydroxyl group of (IIa) is quasi-axial and (IIb) is quasi-equatorial conformations.

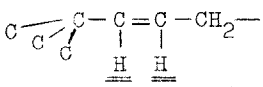
Treatment of (IIa) or (IIb) with dil. hydrobromic acid under mild condition caused demethanolization producing the conjugated carbonyl compound (III) in good yield. Confirmation of the structure of (III) was provided from the N.M.R. spectrum which exhibited three $OCH_3$ groups (N.M.R.$\tau$ 6.10(3H), 6.18(3H) and 6.43(3H)), and the system  was shown by IR spectrum; IR $\nu_{max}^{CHCl_3}$ 1671 (conjugated carbonyl), 1646cm$^{-1}$( C=C ) and N.M.R. spectrum $H_C$ triplet ($J_{H_CH_A}$=6cps, $J_{H_CH_B}$=4cps) centered at 4.33(1H), $H_A$ quartet ($J_{H_AH_B}$=6cps,

*3 PPC (Paper Partition Chromatography); Toyo Filter Paper No. 50, solvent AcOH: BtOH: $H_2O$ = 10: 65: 25.

$J_{H_AH_B}$=18cps) centered at 6.70(1H) and $H_B$ quartet ($J_{H_BH_C}$=4cps, $J_{H_BH_A}$=18cps) centered at 7.30(1H). The compound (III) is characterized as its hydrobromide, $C_{20}H_{25}O_4N.HBr$, m.p. 232° (decomp.), IR $\gamma_{max}^{Nujol}$ 2200-2700 ($\overset{+}{N}H$), 1680 (conjugated carbonyl) and 1629cm$^{-1}$ ( C=C ).

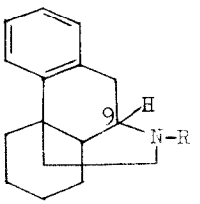
Reduction of (III) with zinc-amalgam in conc. hydrochloric acid gave both the olefinic (IV) and saturated compound(Va). The olefinic compound (IV), $C_{19}H_{25}O_2N$, m.p. 103°, $[\alpha]_D$:-140° ($CHCl_3$), showed in its N.M.R. spectrum the presence of two methoxyl groups at 6.15(3H), 6.21(3H) and two olefinic hydrogens sextet centered at 4.10(1H), sextet centered at 4.50(1H), respectively. The saturated compound (Va) revealed no signal of olefinic hydrogen in the N.M.R. spectrum. (Va) was also prepared from (IV) by catalytic hydrogenation over $PtO_2$. (Va) was characterized as its hydrobromide, $C_{19}H_{27}O_2N.HBr$, m.p. 270-271° (decomp.), $[\alpha]_D$:+33°(MeOH).

Direct proof of the structure (Va) was achieved by comparison of (Va) with an authentic sample of the compound(Vb) which was synthesized from dihydroindolinecodeinone (VI).[6] Thus, Wolff-Kishner reduction[7] of (VI) afforded desoxodihydroindolinecodeinone (VII), N.M.R.$\tau$ aromatic hydrogens, doublet (J=8cps) 3.39(1H), doublet (J=8cps) 3.41(1H); $OCH_3$ 6.20(3H); N-$CH_3$ 7.73(3H) and two olefinic hydrogens

 , sextet centered at 4.50(1H) and sextet centered at 3.54(1H): IR$\nu_{max}^{CHCl_3}$ 3500cm$^{-1}$(OH); (VII) oxalate, $C_{18}H_{23}O_2N.(CO_2H)_2$, m.p. 251°(decomp.). (VII) showed strong blue coloration on 2,6-dichloroquinone-4-chloroimide owing to $C_4$-OH group. Catalytic hydrogenation of (VII) over $PtO_2$ afforded desoxotetrahydroindolinecodeinone (VIII), IR$\nu_{max}^{CHCl_3}$ 3500cm$^{-1}$(OH); (VIII) hydrochloride hemihydrate, m.p.263-264° (decomp.), $C_{18}H_{25}O_2N.HCl.{}^1/_2{\cdot}H_2O$. Methylation of (VIII) with Rodinov reagent[8] gave (Vb); (Vb) hydrobromide, $C_{19}H_{27}O_2N.HBr$, m.p. 270-271°(decomp.), $[\alpha]_D$ -42°(MeOH).

As shown in TABLE 1, properties of the compound (Vb) derived from dihydroindolinecodeinone (VI) was quite identical with those of (Va) derived from hasubanonine (Ic) except signs of specific rotation and the ORD curve of (Va) was antipodal to that of (Vb).

Tsuda et al.[9] have reported that the signal attributable to the $C_9$-H of the compounds possesing the skeleton of type




(IX)

(IX) appeared at 6.35~6.95 $\tau$ without exception in their N.M.R. spectra.

In the N.M.R. spectra of all derivatives of hasubanonine no signal attributable to this proton was observed in this region. This finding was suggestive of the

ethanamine bridge binded at $C_{13}$~$C_{14}$ in the hasubanonine molecule.

On the basis of above experimental results, the structure of hasubanonine is unambiguously assigned to the formula (Ic) including the absolute stereo-structure.

Hasubanonine is not morphine or sinomenine type alkaloids, but a new skeletal alkaloid, hitherto not known in the natural sources.

TABLE 1

| | | (Va) | (Vb) |
|---|---|---|---|
| Free base | IR($CHCl_3$) | identical | |
| | N.M.R. | | |
| | T.L.C.*4 | | |
| Hydrobromide | formulae | $C_{19}H_{27}O_2N.HBr$ | $C_{19}H_{27}O_2N.HBr$ |
| | appearance | colorless prisms | colorless prisms |
| | m.p. | 270-271° (decomp.) | 270-271° (decomp.) |
| | $[\alpha]_D$ (MeOH) | + 33° | - 42° |
| | ORD (MeOH) | antipodal | |
| | IR(Nujol) | identical | |

*4 Thin Layer Chromatography: a) Kieselgel G nach Stahl, solvent, methanol. b) Aluminiumoxyd G nach Stahl, solvent, chloroform.

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