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THE CONVERSION OF PSEUDOKOBUSINE TO KOBUSINE

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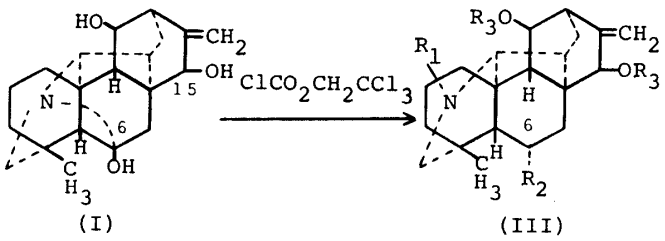
A six step conversion of pseudokobusine (I) to kobusine (Vb) proceeding *via* the ring opening compound (IIIa,b,c) is presented. The C-15 secondary alcohol group of pseudokobusine (I) was found to have the *R* configuration.

KEYWORDS —— diterpene alkaloid; *Aconitum*; chemical conversion; stereochemistry; ring opening reaction; ring closing reaction

Pseudokobusine (I) was transformed *via* rearrangement, oxidation and deoxydation steps to ketodihydrokobusinone (II) which had been derived from kobusine (Vb).[1] Though the stereochemistry of kobusine (Vb) was elucidated by X-ray analysis of (Vb)-CH_3I[2] and CD spectral studies,[3] the configuration of C_{15}-OH of (I) has not been determined.

We now report a direct chemical transformation of (I) to kobusine (Vb) and confirmation of the configuration of C-15-β-hydroxy group.



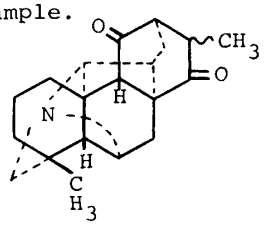
(I) (III)

a: R_1=$CO_2CH_2CCl_3$, R_2= =O, R_3=H
b: R_1=$CO_2CH_2CCl_3$, R_2= =O, R_3=$COCH_3$
c: R_1=$CO_2CH_2CCl_3$, R_2=OH, R_3=$COCH_3$
d: R_1=H, R_2=OH, R_3=$COCH_3$

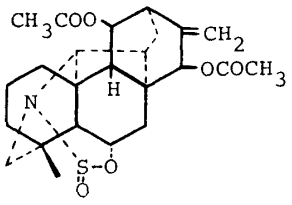
The Schotten-Baumann reaction of (I) with trichloroethyl chloroformate (1.5eq mol) in CH_2Cl_2 and aq.n-NaOH gave rise to ketocarbamate (IIIa) [mp 200 - 201.5°C, $C_{23}H_{28}NO_5Cl_3$, m/z(%): 505 (M^+ + 2, 100), 503 (M^+, 85), CD $\lambda_{ext.}^{MeOH}$ nm(Δε): 309 (-1.3), IR ν_{max}^{KBr} cm^{-1}: 1710, 1680 (C=O), NMR $\delta_{ppm}^{CDCl_3}$: 5.28, 5.08 (each 1H, s, $=CH_2$), 4.86, 4.70 (each 1H, d, J= 11Hz, Cl_3CCH_2OCO-), 3.96 (2H, br s, C_{11}-H and C_{15}-H), 1.09 (3H, s, C_{18}-H_3)] in 78% yield. The presence of a carbonyl group on carbon 6 of (IIIa) was proved by the IR spectrum and was also deduced from the presence of a negative CD maximum which agreed with the prediction from the Octant Rule using a molecular model. A standard acetylation of (IIIa) with acetic anhydride in pyridine afforded an amorphous diacetyl derivative (IIIb), [$C_{27}H_{32}NO_7Cl_3$, m/z(%): 589 (M^+ + 2, 11), 587 (M^+, 7), 527 (M^+ - CH_3CO_2H, 100)]. On reduction

with excess $NaBH_4$ in EtOH for 8 h , (IIIb) gave rise to the alcohol (IIIc) [amorphous, $C_{27}H_{34}NO_7Cl_3$, m/z(%): 591 (M^+ + 2, 50), 589 (M^+, 42), 571 ($M^+ - H_2O$, 19), 237 (100), $\nu_{OH}(CHCl_3)$ 3500 cm^{-1}, δ: 4.23 (1H, m, C_6-βH)] in 87% yield. The urethane group of (IIIc) was then removed by the action of Zn/HOAc at room temp. and diacetyl-seco-dihydropseudokobusine (IIId) [mp 263 - 265°C, $C_{24}H_{33}NO_5$, m/z(%): 415 (M^+, 23), 397 ($M^+ - H_2O$, 100), IR (in KBr) cm^{-1}: 3520, 3420 (OH and NH), 1730, 1710 (C=O), δ: 5.50 (1H, s, like, C_{15}-H), 5.05 (1H, d, J= 4Hz, C_{11}-H), 4.79 (2H, s, like, $=CH_2$), 3.84 (1H, t, J= 7Hz, C_6-βH), 2.13, 2.02 (each 3H, s, $COCH_3$), 1.26 (3H, s, C_{18}-H_3)] was obtained as the sole product in 85% yield.

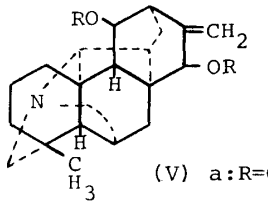
In order to get diacetylkobusine (Va) by the dehydration of (IIIc), vacuum sublimation and acid catalyzed dehydration under azeotropic condition in xylene were attempted but the results were not promising. Thionyl chloride dehydration ($SOCl_2$ 4eq mol / pyridine 6eq mol in CH_2Cl_2) of (IIIb) proceeded gradually to give cyclic sulfinyl derivative (IV) and diacetylkobusine (Va). In the course of this reaction, the cyclic sulfinyl derivative (IV) was produced first and subsequent loss of sulfur dioxide gave 37% of (Va) and 14% of (IV) after 45 h at room temp. The cyclic sulfinyl derivative (IV) [mp 213 - 215°C, $C_{24}H_{31}NO_6S$, m/z(%): 461 (M^+, 15), 397 ($M^+ - SO_2$, 100), ν_{max}^{KBr} cm^{-1}: 1730 (C=O), 1160 (S=O), δ: 4.39 (1H, t, J= 8Hz, C_6-βH)] was converted to (Va), mp 131 - 132°C, by sublimation at 180 - 190°C/ 2mmHg in 80% yield. Diacetylkobusine (Va) derived from pseudokobusine (I), was hydrolysed to give kobusine (Vb) whose mixed melting point, optical rotation, IR, NMR and Mass spectra were shown to be identical with those of an authentic sample.



(II)



(IV)



(V) a:R=$COCH_3$
b:R=H

In conclusion we have established beyond doubt that pseudokobusine (I) has the same 15*R* stereochemistry as the other aconite alkaloids, and presented a chemical conversion method of (I) to (Vb) using a new ring closing reaction.

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2) S.W. Pelletier, L.H. Wright, M.Gary Newton, and H. Wright, *Chem. Commun.*, 1970, 98.

3) See the preceding paper.

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