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A REARRANGEMENT OF AN ASPIDOSPERMA TYPE ALKALOID INTO A TETRAHYDROQUINOLINE DERIVATIVE; UNAMBIGUOUS CONFIRMATION OF THE RESULTING SKELETON STRUCTURE

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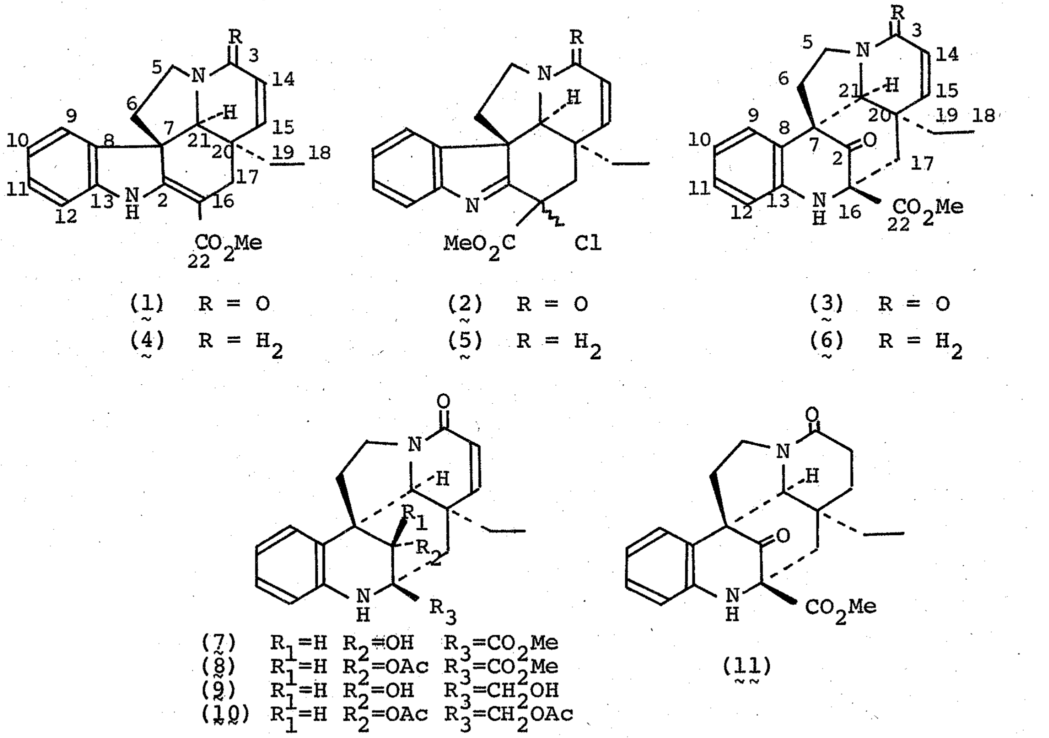
A smooth skeletal rearrangement took place when a chloroindolenine (2) derived from 3-oxotabersonine (1) was treated under solvolytic conditions. The structure of the rearrangement product (3) was clarified unambiguously by X-ray crystal analysis.

KEYWORDS—— indole alkaloid; Aspidosperma type; chemical conversion; skeletal rearrangement; X-ray structure analysis

As an attempt to convert an Aspidosperma type alkaloid to a form of the meloscine-scandine group of alkaloids[1] we attempted a rearrangement of chloroindolenine (2). We chose this starting material (2) because the amide nature of $N_{(b)}$ was likely to preclude the undesired $N_{(b)}$-assisted rearrangement to an indolo[2,3 *b*]quinolizine type compound as described by Bernauer[2] and Le Men.[3] 3-Oxotabersonine (1)[4] was chlorinated to give chloroindolenine (2), which was then treated under solvolytic conditions, and a rearrangement product was obtained in an excellent yield. This product (3) was found not to be a scandine type compound nor the above indolo[2,3 *b*]quinolizine derivative. Instead, (3) was found to be structurally related to the rearrangement product (6) obtained by Lévy *et al.*[5] on treatment of tabersonine chloroindolenine (5) with aqueous sulfuric acid. Their result, however, has been reported only in the form of a patent and full details are not accessible. In this communication we present the independent and fully unambiguous proof of the novel cyclic ring system of (3).[6]

3-Oxotabersonine (1) was chlorinated with *tert*-butyl hypochlorite to give the chloroindolenine (2) [$C_{21}H_{21}N_2O_3Cl$, mp 178-182°C; λ_{max}^{EtOH} nm: 228, 234(sh) and 285; ν_{max}^{KBr} cm^{-1}: 1735, 1660 and 1605; m/z 386(M^++2,10%), 384(M^+,24%) and 227(100%)]. A rearrangement product (3) was obtained when the chloroindolenine (2) was treated with silver perchlorate in acetone-water (1:1) at room temperature (84% yield) or heated in tetrahydrofuran-water (1:1) for 10 h (23% yield). The physical and spectral properties of (3) are : [$C_{21}H_{22}N_2O_4$, mp 192°C; λ_{max}^{EtOH}nm(log ε): 250(4.03), 292(3.50), 300(3.51) and 335(3.07); $\nu_{max}^{KBr}cm^{-1}$: 3400(NH), 1755(C=O) and 1725(CO_2Me); *m/z*: 366(M^+,100%); δ_{CDCl_3}: 0.80(3H, t, $C_{(18)}H_3$), 1.75(2H, m, $C_{(19)}H_2$), 2.28 and 2.64 (ABq, J=16Hz, $C_{(17)}H_AH_B$), 3.84(3H, s, CO_2Me), 3.97(1H, d, J=2Hz, $C_{(21)}H$), 5.76 and 6.20 (ABq, J=10Hz, $C_{(14)}H$ and $C_{(15)}H$), 6.52-7.20 (4H, m, arom. H x 4)]. The spectral data shown above allowed us to formulate the structure of (3) as shown in Chart 1. It is interesting to note that in the ^1H-NMR spectrum the signal due to methylene protons at $C_{(19)}$ appeared at δ 1.75, a position quite low compaired with the corresponding signal at δ 1.00 of the starting material (2). This observation is fully consistent with the deduced structure in which the $C_{(19)}$ methylene is located in the area of the deshielding effect of the newly formed $C_{(2)}$-ketone group. Reduction of (3) with $NaBH_4$ in isopropanol at room temperature gave alcohol (7) (77%), [*m/z*: 368 (M^+, 100%)], as a single isomer, the ^1H-NMR spectrum of which showed a signal due to $C_{(2)}H$ at δ 4.12 as a singlet. A usual acetylation of (7) with acetic anhydride in pyridine afforded the acetyl derivative (8), [$C_{23}H_{26}N_2O_5$, mp 259-261°C; *m/z* 410 (M^+, 100%)]; δ_{CDCl_3}: 2.06 (3H, s, OAc), 5.36 (1H, s, $C_{(2)}H$) and 4.90 (1H, s, NH)]. The chemical shift of the ^1H-NMR signal due to the OAc group showed the absence of shielding effect of the aromatic ring and allowed the stereochemical assignment at $C_{(2)}$ as shown in Chart 1. This configuration of the OH group was also expected on the basis of a possible attack of the reducing agent from the less hindered side of the carbonyl group of (3). When methanol was used as the solvent in place of isopropanol for the $NaBH_4$ reduction of (3), diol (9) was obtained; [$C_{20}H_{24}N_2O_3$, mp 276°C; *m/z*: 340 (M^+, 37%); $\delta_{pyridine\text{-}d_5}$: 4.03 (2H, s, $C_{(22)}H_2$), 4.20 (1H, s, $C_{(2)}H$]. Acetylation



(1) R = O
(4) R = H_2

(2) R = O
(5) R = H_2

(3) R = O
(6) R = H_2

(7) R_1=H R_2=OH R_3=CO_2Me
(8) R_1=H R_2=OAc R_3=CO_2Me
(9) R_1=H R_2=OH R_3=CH_2OH
(10) R_1=H R_2=OAc R_3=CH_2OAc

(11)

Chart 1

of (9) gave diacetate (10); [$C_{24}H_{28}N_2O_5$, mp 242-244°C, *m/z*: 424 (M^+, 93%); δ_{CDCl_3} 2.08 (3H, s, OAc) and 2.12 (3H, s, OAc)]. As was evident from the above results, the NH group in compounds (7) and (9) remained unaffected in the conventional acetylation, probably because of the large steric hindrance. Basicity of the NH group of compound (3) was unexpectedly low, since no difference of the UV absorption curves was observed between those obtained in ethanol and in 6N-H_2SO_4. On the contrary normal protonation occurred in compound (9), in which the methoxycarbonyl group at the α-position of the NH group was reduced to a carbinol group; the UV spectrum of (9) measured in EtOH showed the absorption maxima at 254 nm (log ε 4.19) and 307 nm (log ε 3.60), while that in 6N-H_2SO_4 showed the absorption band at 258 nm (log ε 3.40) as expected for the protonated aniline chromophore. Catalytic reduction of (3) with Adams' catalyst gave dihydro derivative (11) (66% yield); [$C_{21}H_{24}N_2O_4$, mp 180-181°C; *m/z*: 368 (M^+, 100%); δ_{CDCl_3}: 0.80 (3H, t, J=7 Hz, $C_{(18)}H_3$), 1.70 (2H, m, $C_{(14)}H_2$), 1.4 (2H, m, $C_{(15)}H_2$), 3.70 (1H, s, $C_{(21)}H$), 3.86 (3H, s, CO_2Me), 5.30 (1H, s, NH) and 6.70-7.14 (4H, m, arom H x 4)].

The above results suggest that the basic skeleton of (3) is the same as that of the rearrangement product (6) obtained by Lévy *et al*. starting from tabersonine (4).[6] The ultimate confirmation of the structure of this unique ring system was determinated by X-ray analysis.

The crystals of compound (3) showed the following crystal data: orthorhombic; $P2_12_12_1$; a= 12.753(4) Å, b= 17.408(6) Å, c= 8.018(9) Å, and Z=4. Intensity data of 2166 unique reflections with Fo > 2σ(Fo) were measured on a Rigaku diffractometer, AFC-5, by using graphite-monochromated Mo Kα radiation. Scanning was made by the ω-2θ scanning method with the speed of 2°/min in 2θ in the range up to 2θ= 70°. The structure was solved by the direct method using the installed structure determination package based on MULTAN.[7] All the carbon, oxygen, nitrogen and hydrogen atoms were allocated and the final R value was 0.087. The elucidated

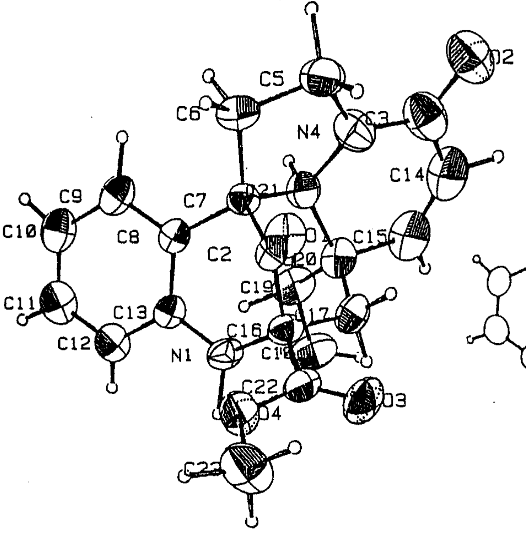


Fig.1. An ORTEP drawing of the structure of (3).

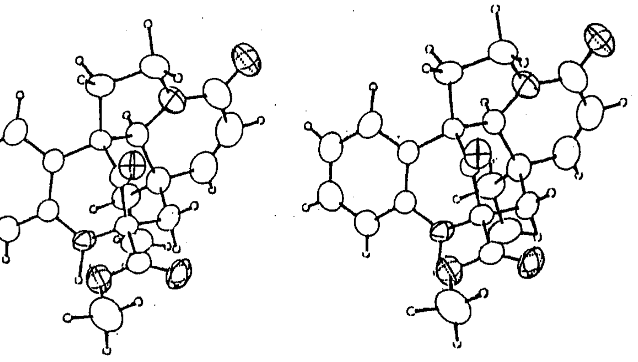


Fig.2. Stereoscopic view of the structure of (3).

structure shown in Fig. 1. and 2.[8] fully confirmed the above structure of (3) and also verified the structures which were proposed by Lévy *et al.* as their rearrangement products, though no direct chemical correlation of their compounds with ours has been made.

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