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STUDIES ON SECURININE AND ALLOSECURININE

I. Satoda, M. Murayama, J. Tsuji and E. Yoshii
Research Laboratory, Nippon Shinyaku Co.
Kyoto, Japan

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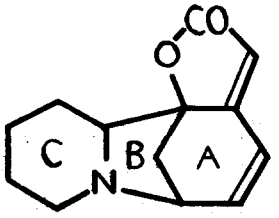
THE isolation of securinine, $C_{13}H_{15}O_2N$, m.p. 141-142°, α_D^{25} -108.9° (EtOH), pk_a' 7.17, from Securinega suffruticosa was first reported by Russian workers[1], but its structure has hitherto never been investigated. The present preliminary communication deals with our structural studies on the alkaloid isolated from the domestic plant, and the structure(I) is proposed on the basis of the following evidences.



I

Two oxygens in securinine(I) were assigned as unsaturated γ-lactone from its infrared absorption bands at 1792 and 1764 cm^{-1}

[1] V. I. Murav'eva and A.I. Ban'kovskii, Trudy Vsesoyuz. Nauch. Issledovatel. Inst. Lekarstv. i Aromat. No. 11, 16(1959). and the references cited therein.

in CCl_4. Splitting of the band of $\alpha\beta$-unsaturated γ-lactone possessing α-hydrogen is known.[2] Ultraviolet absorption spectrum showed a broad band at 256 mμ(ε=18200)[3], indicating the presence of an $\alpha\beta,\gamma\delta$-unsaturated γ-lactone group in I.

The lactone is quite stable and recovered on acidification after its alkaline hydrolysis. By catalytic hydrogenation over Pd on $SrCO_3$ in bensene, or by $NaBH_4$ reduction in EtOH, I readily gave a dihydroderivative(II), $C_{13}H_{17}O_2N$, m.p. 53.5°, α_D^{27}+5.9°, I.R. (CCl_4) 1810, 1767 cm^{-1}, U.V. 215 mμ(ε=17700), pk_a' 8.35. The infrared and ultraviolet data show the presence of an $\alpha\beta$-unsaturated γ-lactone in II. When reduced catalytically over Pd on carbon or PtO_2 in EtOH, I gave rise to a tetrahydroderivative (III), $C_{13}H_{19}O_2N$, m.p. 67-69°, pk_a' 9.03, which shows a normal infrared absorption band for a γ-lactone at 1789 cm^{-1} in CCl_4. Although III shows an end absorption(210 mμ, ε =1760), addition of HCl decreases the extinction to 140 at the same wave length, showing that III is saturated, and hence securinine should be a tetracyclic.

Dihydrosecurinine(II) was reduced with $LiAlH_4$ to an oily diol(IV), $C_{13}H_{21}O_2N$, hydrochloride, m.p. 165°, I.R.(KBr) 3226 cm^{-1}(OH). Ozonolysis of IV-hydrochloride in acetic acid afforded glycoaldehyde and an oily α-ketol(V), $C_{11}H_{17}O_2N$, characterized as hydrochloride, m.p. 213°, I.R.(mujol) 3300(OH), 1728 cm^{-1}(C=O). The absorption band indicates that the α-ketol ring might be a six membered. V reduced the Tollens reagent, but did not react

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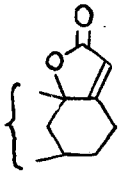
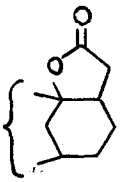
[2] R. N. Jones, C. L. Angell, T. Ito and R. J. Smith, Can. J. Chem. 37, 2007(1959).

[3] Ultraviolet spectra were measured in EtOH unless specified.

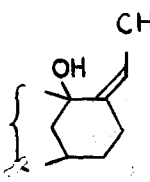
with cupric acetate in hot acetic acid[4] or CrO_3 in acetic acid at a room temperature. HIO_4 yielded an oxoamino acid which contained iodine and could not be identified. In addition, V formed only a monoxime, m.p. 207-208°, under forced condition. II was recovered after hydrolysis with potassium t-butoxide, showing that the migration of the exocyclic double bond to an enol lactone is not possible.[5] These evidences indicate a tertiary nature of the hydroxyl in the α-ketol.



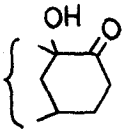
II



III



IV



V

Since securinine shows no N-H absorption band in infrared spectrum and readily gives a methiodide, the nitrogen must be tertiary. Also no $N-CH_3$ was detected. The ultraviolet absorption maximum of I at 256 mμ does not change by its conversion to hydrochloride and methiodide, indicating that the nitrogen in I is isolated, but not far, from the conjugated double bonds. N. M. R. spectra of I, II and III provide an aditional support to this conjugated double bond system. Here, H_b, H_c and H_d consist an ABX system, and the signals of AB part of the system are observed as 8 peaks as is expected(Figure 1). The signal of H_a is observed as a sharp singlet. 8 peaks due to H_b and H_c disappeared in the spectrum of II and the singlet due to H_a disappeared in the spectrum of III.

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[4] A. T. Blomquist and L. H. Liu, J. Am. Chem. Soc. 75, 2153(1953).

[5] C. Djerassi and W. Rittel, J. Am. Chem. Soc. 79, 3528(1957).

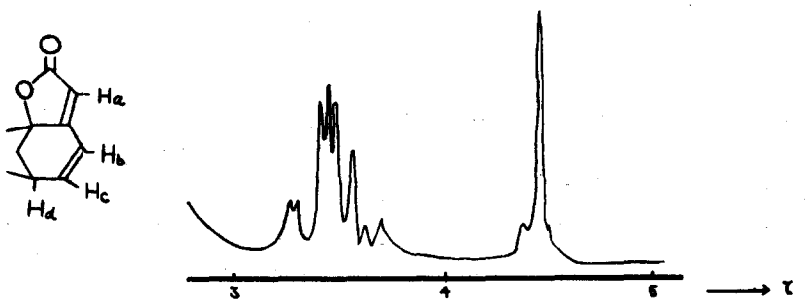

Figure 1. N.M.R. spectrum of securinine.(60 m.c. in $CHCl_3$ with tetramethylsilane as an internal reference.)

Treatment of I with Zn in alcoholic sulfuric acid at a room temperature caused a profound change of the molecule and a lactam (VI), $C_{13}H_{15}ON$, m.p. 74-75°, α_D^{25} +13.9°(EtOH), I.R.(KBr) 1634 cm^{-1}, U.V. 265,272 mμ(ε =450,420), was obtained. On exhaustive oxidation with $KMnO_4$, VI afforded phthalic acid, the formation of which clearly indicates that VI is an o-disubstituted benzene derivative. Neither Zn nor H_2SO_4 could induce this interesting aromatization reaction, and the both reagents are essential. This smooth aromatization reaction of I is rationally explained by the following two step mechanism; 1) concerted electron displacement from Zn to the positively charged nitrogen through the unsaturated γ-lactone system, causing hydrogenolysis of allylic C-N bond, 2) an acid catalyzed lactam formation and subsequent dehydration to the aromatic ring. The same type of aromatization reaction of monascamine was reported.[6]

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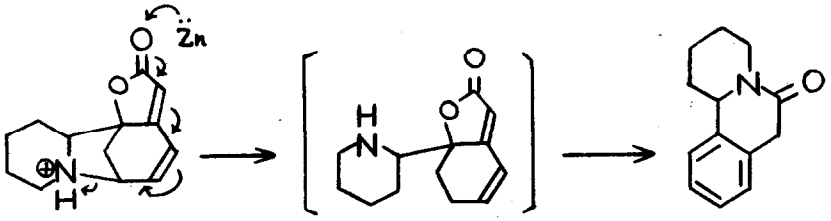
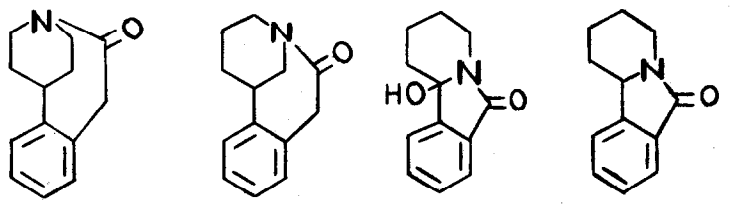
[6] M. Ohashi, S. Kumasaki, S. Yamamura and K. Nakanishi, J. Am. Chem. Soc. 81, 6339 (1959).



I VI

The oxidation of the lactam (VI) with a limited amount of $KMnO_4$ gave a hydroxylactam (VII), $C_{12}H_{13}O_2N$, m.p. 182-183°, I.R. 3300 (OH), 1661 cm^{-1}, U.V. ($CHCl_3$) 253 mμ(ε =4460), in high yield. The absorption band at 1661 cm^{-1} shows that VII still holds a lactam group, but its U.V. absorption band indicates that the carboxyl is directly attached to the aromatic ring. The hydroxyl group of VII was easily hydrogenolyzed over Pd on carbon to give a dehydroxylactam(VIII), $C_{12}H_{13}ON$, m.p. 78-80°, I.R. (nujol) 1675 cm^{-1}(lactam), showing that the hydroxyl is benzylic. In addition to the structure VI shown in the above, the structures VIa and VIb should be considered for the lactam.



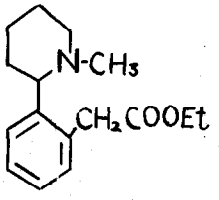
VIa VIb VII VIII

Among these possibilities, VIa is excluded because the lactam is optically active. Furthermore, the lactam VIb is unlikely because it contains a bridge head lactam, which should show a ketone band, rather than amide band in I.R.[7] Also the bridge

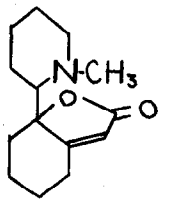
[7] S.W. Pelletier, Tetrahedron 14, 76(1961).

head lactam is in general difficult to form and easy to hydrolyze; actually the lactam(VI) was formed in acidic condition and hydroxylactam(VII) was formed in basic medium, showing that both lactams are stable. Thus, the hydroxylactam and dehydroxylactam are expressed by the structures VII and VIII shown in the above.

Securinine methiodide was also easily aromatized by the action of Zn in sulfuric acid, forming an oily ester. $C_{16}H_{23}O_2N$, to which structure (IX) was assigned from I.R. and U.V. spectra of its perchlorate, m.p. 171-172°, I.R.(KBr) 1724(ester) 759 cm^{-1} (o-disubstituted benzene), U.V. 266, 272 mμ(ε=840,739). On the other hand, the action of Zn in acetic acid did not induce the aromatization, but gave a α,β-unsaturated γ-lactone(X), perchlorate, m.p. 197-199°, U.V. 215 mμ(ε=13600), I.R.(KBr) 1742, 1678 cm^{-1}(α,β-unsaturated γ-lactone).



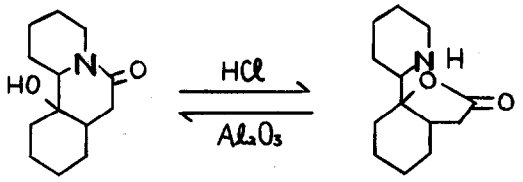
IX



X

Concerning the easy formation of the lactam(VI), the formation of a hexahydroderivative by hydrogenation of I should be mentioned. When crude product obtained by catalytic hydrogenation of I over Pd on carbon or PtO_2 was chromatographed through alumina, tetrahydrosecurinine(III) was first eluted with iso-propyl ether; further elution with benzene containing 2% MeOH gave a crystalline hexahydroderivative, $C_{13}H_{21}O_2N$, m.p. 223-225°, I.R.(KBr) 3279 (OH), 1603 cm^{-1}(lactam), $\alpha^{24.5}_{546}$ +47.6°. On treatment with methanolic HCl, the hexahydroderivative(hydroxylactam) was partly converted into a

γ-lactone(confirmed by I.R. spectrum), which was reconverted into the original hydroxylactam by passing through alumina. For the hydroxylactam, the structure(XI) is given. XI is the product of hydrogenolysis of C-N bond,[8,9] and subsequent saturation of the two double bonds.



XI

From the evidences mentioned in the above, we would like to propose the structure (I) for securinine. for the final and conclusive proof of the structure, especially of the size of the nitrogen containing ring, further degradation of securinine and synthesis of one of the degradation products are under progress.

Although the Russian workers reported the isolation of securinine alone, the authors succeeded in isolating another minor alkaloid from the same plant and named it allosecurinine. The new alkaloid, $C_{13}H_{15}O_2N$, m.p. 136-138°, $[\alpha]_D^{26}$ -1082°(EtOH), I.R. (nujol) 1818, 1754($\alpha\beta$, $\gamma\delta$ unsaturated γ-lactone), 1631 cm^{-1}(conjugated double bonds), U.V. 257 mμ(ε =15400), pk_a' 6.91 forms a crystalline oxalate, m.p. 174-176°, which made its separation from an oily oxalate of securinine possible. It has the same molecular formula

[8] H. Conroy, R. Bernasconi, P. R. Brook, R. Ikan, R. Kurtz and K. W. Robinson, Tetrahedron Letters No. 6, 1(1960).

[9] D. Chakravarti, R. N. Chakravarti and R. Ghose, Tetrahedron Letters No. 11, 25(1960).

and almost the same optical rotation as securinine. A little difference was observed in the finger print region of the infrared spectra of both the alkaloids. $NaBH_4$ reduction of allosecurinine gave a dihydroallosecurinine, $C_{13}H_{17}O_2N$, m.p. 85-86°, $[\alpha]_D^{26}$ +25.2° ($CHCl_3$), I.R.(KBr) 1818, 1739 cm^{-1} ($\alpha\beta$-unsaturated δ-lactone), U.V. 215 mμ(ε =19500), which is different from dihydrosecurinine(II). When reduced catalytically over PtO_2 in EtOH, followed by chromatography through alumina, allosecurinine afforded, in addition to the above mentioned dihydroallosecurinine, a hexahydroderivative, $C_{13}H_{21}O_2N$, m.p. 263°, $[\alpha]_D^{27}$ +44.7°($CHCl_3$), I.R.(KBr) 3311, 1613 cm^{-1}, possessing hydroxy and lactam groups. Interestingly enough, no tetrahydroderivative was obtained under any hydrogenation conditions. Aromatization of allosecurinine with Zn in alcoholic H_2SO_4 gave a lactam, m.p. 69°, $[\alpha]_D^{24.5}$ -32.7°(EtOH), which showed an infrared spectrum identical with VI, but had different melting point and optical rotation. Oxidation of the lactam with $KMnO_4$ afforded a hydroxylactam, identical with VII, obtained from securinine. Therefore, it can be concluded that allosecurinine is a stereoisomer of securinine, possibly arising from the difference in B/C ring juncture.