Summary

The steric effect of matridine (I) on von Braun degradation was investigated. It was concluded that the structure of the degradation product, monobromomatridine monocyanamide (IV), was represented by formula (IVa) and its dehydrogenated product with mercuric acetate, enamine (VI) by formula (VIa).

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18. Yoji Arata[*1] and Shigehiko Sugasawa[*2] : A New Cyclization Reaction of Cyclic Ketoxime.

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As the hitherto unknown prototype of benzoquinolizine derivatives, synthesis of 2,6-methano-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (I) was attempted. For this purpose, end cyclization of lactam (II) appears attractive, because the cyclization product (III) should give (I) on hydrogenation.

At first sight, however, the formation of (III) appears quite problematic, because this compound has an N-C double bond at a bridge head of the bicyclic ring system violating the Bredt's rule. In order to examine the possibility of the formation of such a ring system, cyclization of a simpler lactam (IV) was preliminarily investigated, which may be advantageously prepared by the Beckmann rearrangement of readily accesible 2-veratryl-cyclopentanone oxime (V).

It is known in the literature that oximes of suitably substituted carbonyl compounds give rise to isoquinoline derivatives in one step in Beckmann rearrangement conditions, sometimes in an excellent yield. Thus, Sugasawa and Yoshikawa[1] prepared 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (VIII) in 85% yield by treating Bis-(3,4-dimethoxyphenethyl) ketone oxime (VII) with phosphoryl chloride in boiling toluene. Several other similar examples are also recorded.[2]

2-Veratrylidenecyclopentanone was prepared after Walton's method.[3] This was reduced catalytically to afford 2-veratrylcyclopentanone whose oxime (V) was treated with phosphoryl chloride in boiling toluene, when intermediary formation of 6-veratryl-2-piperidone (IV) was to be expected as one of the rearrangement products. By the agency of boiling phosphoryl chloride, the latter may suffer further change, in which case formation of isoquinolinium derivative (VI) might not be excluded.

From the reaction mixture there was obtained a crystalline base of m.p. 120~121°, the ethanol solution of which exhibited ultraviolet maxima at 335(4.15) and 325 mμ (log ε

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1) S. Sugasawa, H. Yoshikawa : J. Chem. Soc., **1933**, 1583.

2) S. Ishiwata, K. Suzuki : Yakugaku Zasshi, **70**, 197 (1950); A. Kaufmann, R. Radosevič : Ber., **49**, 675 (1916).

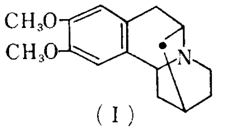
3) H.M. Walton : J. Org. Chem., **22**, 1161 (1957).

4.03). In hydrochloric acid, a distinct bathochromic shift was observed, the maximum appearing at 355 mμ (log ε 4.26). In ethanolic solution, this base absorbed hydrogen activated over Adams platinum catalyst to yield a crystalline base of m.p. 123~124°, in which a presence of NH-group was proved from its infrared chart. Its ultraviolet maximum in ethanol appeared at 304 mμ (log ε 3.55) and in hydrochloric acid, the maximum shifted hypsochromically to 280 mμ (log ε 3.57).

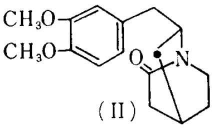
The above-mentioned spectral features, especially the hypsochromic shift of ultraviolet maximum of the reduction base in hydrochloric acid, suggest the presence of a partial structure (A) rather than (B) in this base. Thus 6,7-dimethoxy-2,3-dihydro-1*H*-cyclopenta-[*b*]quinoline (X) was assigned to the original base. The formation of this compound is to be understood that the oxime (V) suffered an intramolecular dehydration between OH and ring hydrogen to give (IX) prior to the Beckmann rearrangement, followed by spontaneous dehydrogenation. In the authors' knowledge such dehydration reaction in which oxime-OH takes part has seldom been found in the literature, though several unsuccessful attempts have been recorded to cyclize 4-phenyl-3-buten-2-one oxime through dehydration to form quinaldine.[4]

The base (X) had already been synthesized by Borsche and Barthenheier.[5] An authentic sample was prepared according to their method by condensation of cyclopentanone with 6-aminoveratral-*p*-toluidine. The base thus prepared formed colorless prisms of m.p. 119~120° (reported[5] m.p. 112~113°), which was proved to be identical with the one obtained as above by mixed melting point test, infrared spectra, and also through identical Rf values in paper chromatograms.

By substituting cyclohexanone for cyclopentanone in the above reaction 6,7-dimethoxy-1,2,3,4-tetrahydroacridine was obtained in a like manner. A minute amount of a compound of unspecified nature was also isolated as colorless pillars, m.p. 139~143°.



(I)



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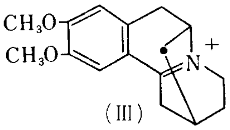

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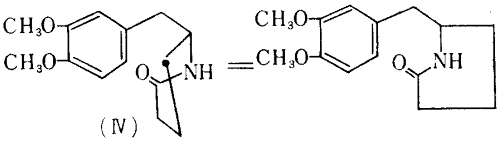
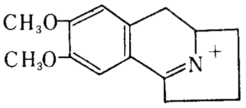
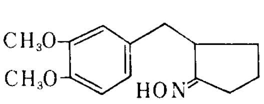


(IV)



(VI)



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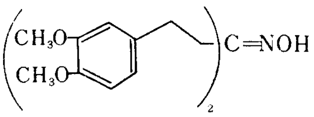
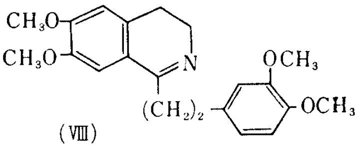
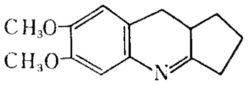


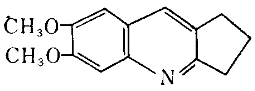
(VII)



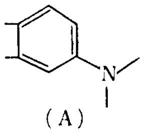
(VIII)



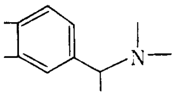
(IX)



(X)



(A)



(B)

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[4] N. Zelinsky: Ber., **20**, 922 (1887); E. Bamberger, C. Goldschmidt: *Ibid.*, **27**, 1954 (1894); C. Goldschmidt: *Ibid.*, **28**, 818 (1895); H. Burstin: Monatsh., **34**, 1443 (1913).

[5] W. Borsche, J. Barthenheier: Ann., **548**, 50 (1941).

In contrast to the facile isoquinoline formation in the above-mentioned examples, the present experiment shows the difficulty of the formation of (VI) having a double bond at a bridge-head position, and lactams resulting from the Beckmann rearrangement of the oxime (V) must have suffered some further complicated change through boiling phosphoryl chloride to yield a resinous unspecified substance.

The isolation of the lactam (IV) and its behavior towards various cyclization agents will be the subject of future study.

Experimental

2-Veratrylidenecyclopentanone—To a solution of veratraldehyde (16.6 g., 0.1 mole) and cyclopentanone (9.3 g., 0.11 mole) in Et_2O (50 cc.), 1*N* NaOH solution (250 cc.) was added and the mixture was shaken vigorously. After ca. 15 min., the solution became yellow and yellow solid began to separate in ca. 45 min. After being shaken for 2 hr., the separated solid was collected and dissolved in benzene, this solution was washed with H_2O, dried, and the solvent was evaporated to leave a yellow crystalline solid (21.8 g.), which formed faint yellow plates (from EtOH), m.p. 113~114°; yield, 18 g. *Anal.* Calcd. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9. Found : C, 72.2; H, 6.7.

Some 2,6-diveratrylidene derivative (ca. 2 g.) was also formed, which is sparingly soluble in EtOH and was purified from toluene to yellow pillars, m.p. 166.5~167.5°. *Anal.* Calcd. for $C_{23}H_{24}O_5$: C, 72.7; H, 6.4. Found : C, 72.6; H, 6.2.

2-Veratrylcyclopentanone—The foregoing cyclopentanone (14 g.) in EtOH (200 cc.) was reduced over Raney Ni (ca. 3 g.) at atmospheric pressure and room temp., absorbing 1445 cc. of H_2 rapidly in 30 min. The resultant faint yellow solution was worked up as usual and the residue was distilled *in vacuo* to furnish a colorless viscous oil, b.p.$_{1\sim2}$ 153~155°; yield, 11.6 g.
Semicarbazone : Colorless plates (from EtOH), m.p. 199.5~200.5°. *Anal.* Calcd. for $C_{15}H_{21}O_3N_3$: C, 61.8; H, 7.3; N, 14.4. Found : C, 62.0; H, 7.7; N, 14.9.

The oxime (V) was prepared by the usual method, which separated first as an oil. This was dissolved in Et_2O-hexane, from which solution most of Et_2O was removed and the residual portion was kept in an ice-chest to deposit a crystalline solid. The latter was recrystallized readily from Et_2O-hexane to colorless plates, m.p. 103.5~104.5°. *Anal.* Calcd. for $C_{14}H_{19}O_3N$: C, 67.4; H, 7.7; N, 5.6. Found : C, 67.6; H, 7.5; N, 5.65.

6,7-Dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline (X)—A solution of the foregoing oxime (5 g.) in toluene (30 cc.) was mixed with $POCl_3$ (25 g.) with cooling. The mixture was gently refluxed in an oil bath for ca. 1 hr., when the evolution of HCl gas almost subsided giving an orange-red solution. After standing overnight, crystalline solid deposited on the wall was collected (1.5 g.), a portion of which was purified from EtOH to form colorless pillars, m.p. 218~218.5° (decomp.).

This solid was suspended in H_2O, and basified with 10% NaOH solution. The base that liberated was collected in benzene, washed, dried, and the solvent was evaporated to leave a dark orange oil, which solidified on standing. The benzene solution of this solid was purified through an alumina column. Evaporation of the filtrate left 1.0 g. of a yellow crystalline solid, which was dissolved in a minimum amount of benzene, adsorbed on an alumina layer, and eluted with benzene-hexane (1:1). The residue of the eluate formed colorless prisms, m.p. 120~121°. Rf 0.9 (BuOH-AcOH-H_2O = 5:1:4). *Anal.* Calcd. for $C_{14}H_{15}O_2N$: C, 73.3; H, 6.6; N, 6.1. Found : C, 73.1; H, 6.5; N, 5.8.
Picrate : Yellow plates (from Me_2CO), m.p. 228~230° (decomp.). *Anal.* Calcd. for $C_{20}H_{18}O_9N_4$: C, 52.4; H, 4.0; N, 12.2. Found : C, 52.45; H, 3.7; N, 11.9.

On removing the solvent and excess of $POCl_3$ from the original supernatant layer, there remained a dark orange-red, syrupy residue, from which a small amount of the same substance (m.p. 120~121°) was recovered on being worked.

Reduction of (X)—A solution of (X) (100 mg.) in EtOH (15 cc.) acidified with 10% HCl (1 cc.) absorbed 13 cc. of H_2 over Adams-Pt in 3 hr. From the reduction solution a colorless solid was recovered, which formed colorless pillars from hexane, m.p. 123~124°. IR : ν_{N-H} 3355 cm^{-1} (Nujol).

2-Veratrylidenecyclohexanone—A mixture of veratraldehyde (16.6 g., 0.1 mole), cyclohexanone (14.7 g., 0.15 mole), and 1*N* NaOH solution (100 cc.) was refluxed for 5 hr. with stirring. After being allowed to stand overnight the resultant yellow solution was extracted with benzene, which was washed, dried, and evaporated to leave a yellowish orange oil. This was distilled *in vacuo* to furnish a faint yellow distillate, b.p.$_7$ 196~198°, which solidified on standing; yield, 11.3 g. Purified from EtOH this formed very faint yellow pillars, m.p. 88~89°. *Anal.* Calcd. for $C_{15}H_{18}O_3$: C, 73.1; H, 7.4. Found : C, 73.2; H, 7.2.

2-Veratrylcyclohexanone—The foregoing compound in EtOH was reduced over Raney Ni catalyst to give a faint yellow oil, b.p.$_2$ 196~200°.

Semicarbazone : Colorless plates (from EtOH), m.p. 191.5~192.5°. *Anal.* Calcd. for $C_{16}H_{23}O_3N_3$: C, 62.4; H, 7.6; N, 13.8. Found : C, 62.7; H, 7.2; N, 13.9.
Oxime : Colorless prisms (from EtOH), m.p. 121~121.5°. *Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.4; H, 8.0; N, 5.3. Found : C, 68.6; H, 7.8; N, 5.3,

6,7-Dimethoxy-1,2,3,4-tetrahydroacridine—The foregoing oxime (1.5 g.) was dissolved in warm toluene (8 cc.) and the resultant solution was mixed with $POCl_3$ (6.0 g.) with ice cooling. The whole was refluxed in an oil bath for 5.5 hr. and the orange-red solution obtained was allowed to stand overnight. The solvent and excess of $POCl_3$ were removed *in vacuo* and the brownish orange residue was repeatedly extracted with dil. HCl. The combined acid solution was shaken with benzene, basified with K_2CO_3, and the base liberated was collected in benzene. Benzene extract was washed, dried, and the solvent was evaporated to leave an orange syrup (0.5 g.). Benzene solution of the latter was repeatedly purified over alumina to furnish colorless prisms (hexane), m.p. 122~123°; yield, 50 mg. This was identified with an authentic specimen, m.p. 122~123° (reported[5]) m.p. 124°) prepared according to the known method.[5])

Microanalyses were carried out by the members of the Central Analysis room of this Faculty, Women's Department, Tokyo College of Pharmacy, and the Tokyo Laboratory of Tanabe Seiyaku Co., Ltd., to all of whom the authors' thanks are due.

Summary

When treated with phosphoryl chloride in boiling toluene 2-veratrylcyclopentanone oxime suffered an intramolecular dehydration, in which oxime-OH took part, to form 6,7-dimethoxy-2,3,9,9a-tetrahydro-1*H*-cyclopenta[*b*]quinoline. Spontaneous dehydrogenation of the latter resulted in the formation of 6,7-dimethoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinoline as the ultimate product. 2-Veratrylcyclohexanone oxime behaved similarly, but gave an inferior yield of 6,7-dimethoxy-1,2,3,4-tetrahydroacridine. Both products were identified with the authentic specimens. This is a novel dehydration reaction of an oxime.

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