Notes

[Chem. Pharm. Bull. 18(6)1269—1273(1970)]

UDC 547.94.04 : 547.388.4.04

Studies on the Morphine Alkaloids and Its Related Compounds. XIX.[1] The Beckmann Rearrangement of the Oximes of Dihydrothebainones and Its Hofmann Degradation Products

Isao Seki[2]

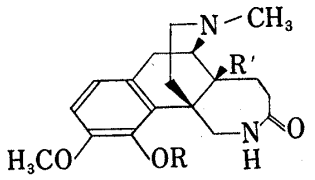
Central Research Laboratories, Sankyo Co., Ltd.[2]

(Received September 3, 1969)

Studies on the geometrical isomerism and the Beckmann rearrangement of oximes of 6-oxo-morphinans have never been reported except the description on the extraordinary Beckmann rearrangement of dihydrocodeinone oxime to iso-oxime with thionyl chloride which wasattempted to distinguish between the Robinson's formula and the Wieland's one on the ethanamine chain.[3] This paper is a report on the Beckmann rearrangement of the oximes of dihydrothebainones and its Hofmann degradation products which was carried out under the expectation of an enlargement of the C-ring in morphinan skeleton with introduction of a basic center into the C-ring in the interest of pharmacological consideration.

Treatment of the oximes (II) prepared from dihydrothebainones (I) with polyphosphoric acid (PPA) under 100—110° for one hour gave the lactams (III) as shown in Table I. In the case, both the oximes (II) and the lactams (III) were obtained as sole product. Sulfuric acid, phosphorus chlorides, and *p*-toluenesulfonyl chloride were unavailable as catalyst because of complicated reaction accompanied with decomposition or recovery of the starting materials. The structure of the lactams was supported by the infrared (IR) spectra which showed absorption bands at 2.90—2.91 μ (NH) and 6.02—6.05 μ (CO). An arrangement of amide group in the lactam-ring was confirmed as shown in formula III, which supposed from the

Table I.



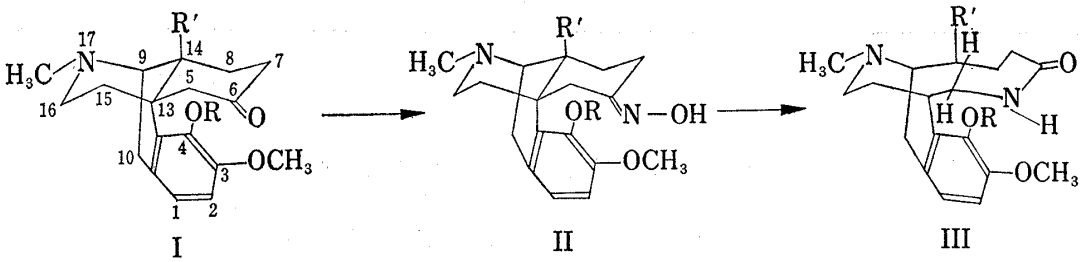
III

III R	III R′	Yield (%)	mp°[a]	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	54.8	241 —243	$C_{18}H_{24}O_3N_2$	68.33	7.65	8.85	67.87	7.72	8.63
CH_3	H	56.5	217.5—220.5	$C_{19}H_{26}O_3N_2$	69.06	7.93	8.48	68.87	7.94	8.53
H	OH	64.6	252 —254	$C_{18}H_{24}O_4N_2$	65.04	7.28	8.43	65.00	7.25	8.44
CH_3	OH	71.8	241 —243[b]	$C_{25}H_{29}O_{11}N_5 \cdot 0.5H_2O$[b]	51.30	5.17	11.96	51.25	5.18	12.10

a) recrystallized from benzene–$CHCl_3$
b) picrate The base is oily substance.

1) Part XVIII: I. Seki and H. Takagi, *Chem. Pharm. Bull.* (Tokyo), **18**, 1104 (1970).
2) Location: *1-Chome Hiromachi, Shinagawa-ku, Tokyo.*
3) C. Schöpf, *Ann.*, **452**, 211 (1927).

NII-Electronic Library Service



I II III

Chart 1

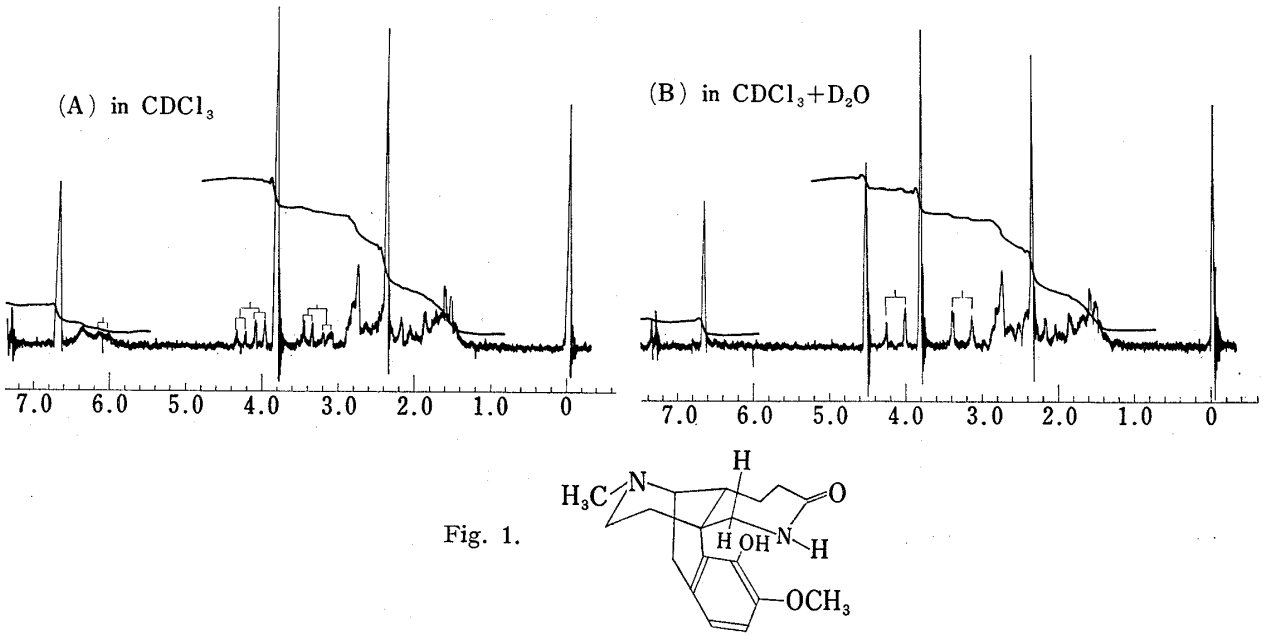


Fig. 1.

TABLE II. NMR Spectra of NH and Geminal Protons of the 5-Position in the Lactams[a]

Lactam	NH	$H_{5\alpha}$ (equatorial)		$H_{5\beta}$ (axial)	
		In $CDCl_3$	With D_2O	In $CDCl_3$	With D_2O
III (R=R′=H)	6.10 (b)[b]	4.27 (d, J=6) 4.05 (d, J=6)	4.14 (d, J=15)	3.40 (d, J=6) 3.13 (d, J=6)	3.27 (d, J=15)
III (R=H,R′=OH)	6.05 (b)	4.22 (d, J=6) 3.97 (d, J=6)	4.10 (d, J=15)	3.72 (d, J=6) 3.47 (d, J=6)	3.61 (d, J=15)
III (R=CH_3,R′=H)	6.00 (b)	4.08 (d, J=7) 3.85 (d, J=7)	3.97 (d, J=15)	3.43 (d, J=7) 3.17 (d, J=7)	3.30 (d, J=15)
VII	6.00 (b)	4.41 (d, J=6) 4.15 (d, J=6)	4.28 (d, J=15)	3.82 (d) 3.57 (d)	3.69 (d, J=15)
VIII	6.40 (b)		3.59 (m)		3.32 (m)
IX	5.67 (b)	4.12 (q)	4.08 (d)	3.57 (q)	3.55 (d)

a) centered value (δ from Me_4Si) measured by a Varian A60
b) b: broad, d: doublet, q: quartet, m: multiplet

consideration of stereochemistry on the morphinan skeleton, by the nuclear magnetic resonance (NMR) spectra. Thus, both of the 5β(axial)-proton at δ 3.3—3.6 and the 5α(equatorial)-one at δ 4.0—4.2 showed as a quartet (J=6—7 cps), and these change to a doublet (J=15 cps) by treatment with D_2O indicating the presence of a coupling with the NH-proton at δ 6.0—6.1 as shown in Table II and Fig. 1 which was illustrated as an example. Consequently, the geometrical isomerism of the oximes (II) can be appointed to the anti-form toward the 5-position in morphinan skeleton.

NII-Electronic Library Service

Table III

Lactam	Yield (%)	mp°[a]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VII	34.4	251—252 (decomp.)	$C_{19}H_{28}O_4N_2$	65.48	8.10	8.04	65.67	8.01	8.02
VIII	53.5	229—236	$C_{17}H_{21}O_3N$	71.05	7.37	4.87	70.52	7.43	4.53
IX	43.7	187—188	$C_{18}H_{23}O_4N$	68.12	7.31	4.41	67.81	7.12	4.37

a) recrystallized from EtOH

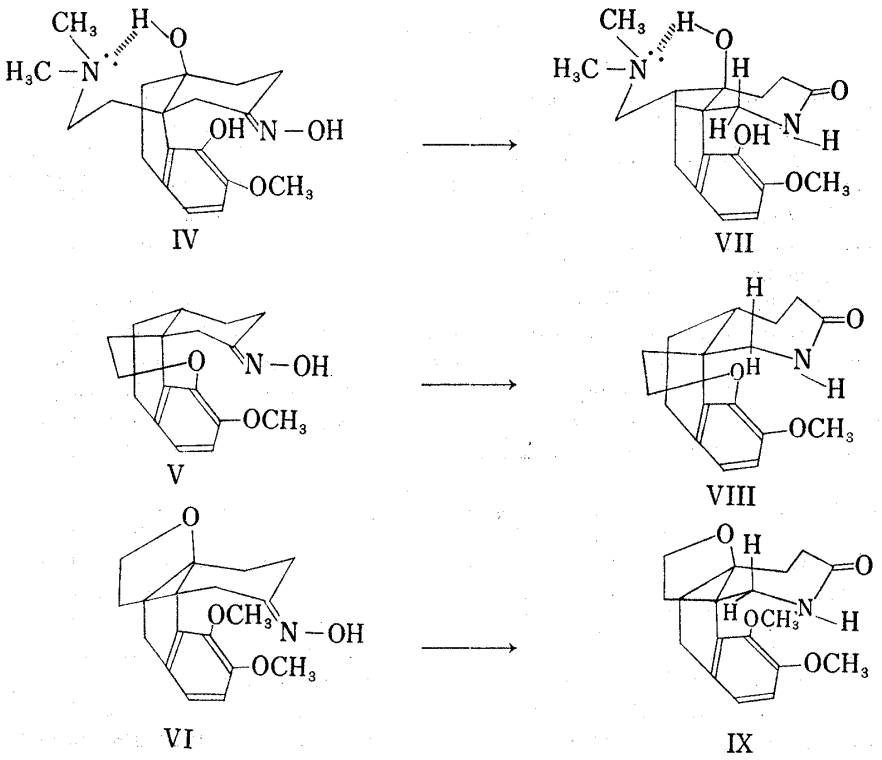
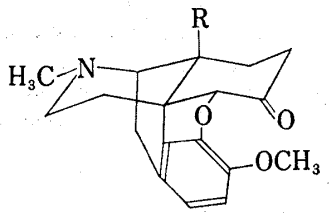


Chart 2

Also, treatment of the oximes (IV—VI) of Hofmann degradation products derived from dihydrothebainones (I) under same conditions mentioned above afforded the basic (VII) and non-basic (VIII, IX) lactams as shown in Table III. Since in the NMR spectra of these products a coupling between the NH-proton and the geminal protons of the 5-position were shown by treatment with D_2O it was considered that the geometrical isomerism of the oximes (IV—VI) and an arrangement of amide group in the lactams (VII—IX) are same that in the case of the dihydrothebainone oximes (II) and the derived lactams (III).



X: R=H
XI: R=OH

Chart 3

Beckmann rearrangement on the oximes of dihydrocodeinone (X) and 14-hydroxydihydrocodeinone (XI) with PPA were attempted comparing with the reaction using thionyl chloride which was reported to afford the iso-oxime.[3] Although the rearrangement occurred by heating at 100—110° for 10 minutes, the reaction was more complex accompanied with marked

NII-Electronic Library Service

decomposition than the case of dihydrothebainone oximes (II) mentioned above. By the observations of IR spectra and $FeCl_3$-color reaction of the products, the orientation of rearrangement was considered as follows: (1) dihydrocodeinone oxime rearranges to afford a normal lactam ($FeCl_3$-reaction: negative; IR: 2.9 μ (NH), 5.98 μ (lactam CO); the product yield by weight: 79.1% when heating at 100—110° for 10 min, 29.1% at 120° for one hour) and in the case the formation of iso-oxime was not observed. (2) in 14-hydroxydihydrocodeinone oxime the cleavage of 4,5-ether ring and the formation of γ-lactone-ring, which probably have a concern in the 14-hydroxyl group, instead of expected lactam-ring were observed in the product ($FeCl_3$-reaction: bluish-green; IR: 2.8 μ (4-OH), 5.6 μ (γ-lactone CO); the product yield by weight: 31.8% when heating at 120° for one hour, 40.9% at 110° for 10 min).

No pharmacological activities of these lactams were observed by Dr. H. Takagi of this laboratories.

Experimental[4]

Beckmann Rearrangement of the Oximes (II)——To polyphosphoric acid (PPA) prepared from 85% H_3PO_4 (95.5 ml) and P_2O_5 (150 g) by heating at 90° for 2 hours was added 0.05 moles of the oxime (II) under room temperature. The mixture was heated at 100—110° for 0.5—1 hours. The mixture was diluted with ice-water (500 ml), neutralized with Na_2CO_3, made alkaline to pH 9.0 with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed, dried over Na_2SO_4, decolorized with a mixture of active charcoal and active alumina, and evaporated to dryness *in vacuo*. The residue was treated with boiling benzene (20 ml) to give the lactams (III) as shown in Table I.

Beckmann Rearrangement of 14-Hydroxydihydrothebainone Dihydromethine Oxime (IV)——A mixture of 14-hydroxydihydrothebainone dihydromethine (7.0 g, 0.02 moles), $NH_2OH \cdot HCl$ (1.6 g), and water (50 ml) was heated at 50—60° for one hour. After ice-cooling, the mixture was made alkaline with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was treated with ether to give 14-hydroxydihydrothebainone dihydromethine oxime (3.8 g). mp 169—170°. IR $\nu_{max}^{CHCl_3}$ μ: 2.84, 3.76, 6.02. *Anal.* Calcd. for $C_{19}H_{28}O_4N_2$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.21; H, 8.08; N, 8.06.

To PPA prepared from 85% H_3PO_4 (19.5 ml) and P_2O_5 (30.6 g) by heating at 90° for 3 hours was added the oxime (3.5 g) under room temperature. The mixture was heated at 70—80° for 10 min. The purplish solution was diluted with ice-water (200 ml), neutralized with Na_2CO_3, made alkaline with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, decolorized with a mixture of active charcoal and active alumina, and evaporated to dryness *in vacuo*. The reddish-brown residue (3.15 g) was treated with boiling benzene to give the lactam (VII; 1.2 g). mp 251—252°. The hydrochloride was prepared in boiling EtOH with HCl-EtOH at pH 3.0. mp 266—267° (decomp.). *Anal.* Calcd. for $C_{19}H_{29}O_4N_2Cl$: C, 59.28; H, 7.58; N, 7.28; Cl, 9.23. Found: C, 58.82; H, 7.33; N, 7.37; Cl, 9.32.

Beckmann Rearrangement of the Oximes (V, VI) of Thebenone[5] and Dihydrothebaone Methyl Ether[6]——The oximes was prepared from the ketones (0.01 mole), $NH_2OH \cdot HCl$ (0.8 g), NaOAc (1.5 g), EtOH (70 ml), and water (3 ml) by refluxing for 3 hours. Thebenone oxime (V) was recrystallized from EtOH. mp 190—196° (lit.[5] mp 201—204°). IR $\nu_{max}^{CHCl_3}$ μ: 2.81, 6.04. Dihydrothebaone methyl ether oxime (VI) was oily substance. IR $\nu_{max}^{CHCl_3}$ μ: 2.81, 6.04.

To PPA prepared from 85% H_3PO_4 (10 ml) and P_2O_5 (16 g) by heating at 90° for 3 hours was added the oxime (0.005 moles) under room temperature. The mixture was heated at 100—110° for 10 min. The reaction mixture was diluted with ice-water (100 ml), neutralized with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The oily residue was crystallized by treatment with ether and recrystallized from EtOH to give the lactams (VIII, IX) as shown in Table III.

Methylation of the 4-Hydroxy-lactams (III; R=H)——To a mixture of KOH (0.19 g, 0.00339 moles), EtOH (10 ml), and the 4-hydroxy-lactam (III; R=H, 0.00324 moles) was added methyl *p*-toluenesulfonate (0.63 g, 0.00339 moles), and refluxed for one hour. After cooling, the mixture was filtered to remove potassium *p*-toluenesulfonate. The filtrate was made acidic with 10% HCl, and evaporated to dryness *in vacuo*. The sirupy residue was diluted with water, made alkaline to over pH 12 with 30% KOH, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The colorless oily residue obtained from III (R=H, R'=OH) (59.1%) was converted to picrate in

4) All mp are uncorrected.
5) H. Wieland and M. Kotake, *Ann.*, **444**, 91 (1925).
6) I. Seki, *Yakugaku Zasshi*, **85**, 359 (1965).

NII-Electronic Library Service

acetone. mp 241—243° [alone and mixed with the sample prepared from III (R=CH_3, R'=OH)]. The crude crystalline residue obtained from III (R=R'=H) was recrystallized from benzene. mp 218—221° [alone and mixed with III (R=CH_3, R'=H) prepared by Beckmann rearrangement].

Acknowledgement The author is grateful to Dr. G. Sunagawa, Director, and I. Iwai, Assistant Director, of this laboratories for their advice and encouragement throughout this work. Thanks are also due to the members of analytical and physical measuring section in this laboratories for the micro-analysis and measuring of IR and NMR spectra.

[Chem. Pharm. Bull. 18(6)1273—1276(1970)]

UDC 547.834.2.07

Hofmann Degradation of Quinolizidine (Synthesis of Quinolizine Derivatives. XXII[1])

KAZURO SUGIMOTO, KYOICHIRO OHME,[2a] MITUO AKIBA and SADAO OHKI[2b]

Technical Research and Development Institute, Japan Defence Agency,[2a] and Tokyo College of Pharmacy[2b]

(Received October 15, 1969)

In the work reported earlier,[3] the Hofmann degradation of sparteine was tried and des-N-methyloxysparteine (II) was obtained as the sole product from 17-oxysparteine methiodide (I), and α-des-N-methylsparteine (IV) and β-des-N-methylsparteine (V) in approximately 2:1 ratio from sparteine methiodide (III). Since the A—B ring juncture of sparteine is *trans* and C—D ring juncture is *cis*, the degradation of I corresponds to the Hofmann degradation of *trans*-quinolizidine methiodide (VI) and that of III to *cis*-quinolizidine methiodide (VII). Schofield[4] reported that the Hofmann degradation of VI afforded a large amount of N-methylazocyclodecene (VIII) and a small amount of N-methylpiperidylbutene (IX) in approximately 90:5 ratio, and that a small amount of VIII and a large amount of IX in approximately 5:90 ratio were obtained from VII.

Comparison of this result with the degradation of I and III shows that the formation of II alone from I is in parallel with the degradation of VI, but the formation of a large amount of IV and a small amount of V from III is rather a reverse of the degradation of VII.

In order elucidate this problem, Hofmann degradation of *trans*- (VI) and *cis*-quinolizidine methiodide (VII) was reexamined to compare its result with that of Schofield.

The starting compound, quinolizidine methiodide was synthesized by the method of Clemo and others[5] for the *trans* compound (VI) and by that of Moynehan and others[6] for the *cis* compound (VII). Authenticity of these compounds was proved by the analytical values and the data of their derivatives agreeing with those listed in the literature.

Hofmann degradation of VI and VII was carried out under identical condition by treatment with silver oxide and an oily product was obtained in 81.8 and 16.7% yield, respectively. These two substances were separated into two sharp peaks each in gas chromatogram but

---

1) Part XXI: S. Ohki and M. Akiba, *Chem. Pharm. Bull.* (Tokyo), **17**, 2484 (1969).
2) Location: *a*) *Ikejiri 1-2-24, Setagaya-ku, Tokyo, 154, Japan*; *b*) *Ueno Sakuragi 1-10-19, Daito-ku, Tokyo, 110, Japan.*
3) K. Sugimoto, N. Shibata, and S. Ohki, *Yakugaku Zasshi*, **88**, 903 (1968).
4) K. Schofield and R.J. Wells, *Chem. Ind.* (London), **1963**, 572.
5) G.R. Clemo, G.R. Ramage, and R. Raper, *J. Chem. Soc.*, **1932**, 2959.
6) T.M. Moynehan, K. Schofield, R.A.Y. Jones, and A.R. Katritzky, *J. Chem. Soc.*, **1962**, 2637.

NII-Electronic Library Service