benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to give orange-red colored crystals (0.95 g.). IR $\lambda_{max}^{CHCl_3}$ μ: 5.8 (strong). In order to hydrolysis of the acetate, a mixture of the crystals (0.95 g.), MeOH (25 ml.), water (5 ml.), and KOH (1.25 g.) was treated as described above, and chromatographed on active Al_2O_3 (10 g.). The MeOH-ether (3:7) eluate was collected, and evaporated to dryness. The residue was recrystallized from MeOH to give XV (0.35 g.), m.p. 149~151°(alone and mixed with an authentic sample[2]).

The author is grateful to Prof. K. Tsuda of the University of Tokyo, Mr. M. Matsui, Director of this laboratories, and Dr. 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.

Summary

Preparation of 14-hydroxy-halo-codides (II,III), the reactions of II or III with pyrrolidine, and the acetolysis of II, III, or 14-acetoxycodeine 6-tosylate (XVI) were described with regard to steric effects of the 14β-hydroxyl group on these reactions.

(Received July 15, 1965)

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UDC 547.943.07 : 615.783.19

61. Isao Seki: Studies on the Morphine Alkaloids and Its Related Compounds. XIV.*1 Preparation of 6-Amino-hydrophenanthrene Compounds from Hofmann Degradation Products of the Morphine Alkaloids.

(*Central Research Laboratories, Sankyo Co., Ltd.**2)

Although the Hofmann degradation reaction of the morphine alkaloids has been well studied,[1] chemical and pharmacological properties of these products and their various derivatives have been little investigated. 6-Amino-hydrophenanthrenes were prepared from the Hofmann degradation products of the 6-oxomorphine compounds in order to investigate the relationship between pharmacological activity and the position of basic groups in the morphine nucleus. In this paper, the author describes preparation of 6-amino-hydrophenanthrenes (XIV~XX).

6-Oxo-hydrophenanthrenes (I~XIII) were obtained from the 6-oxo-morphines according to the known Hofmann degradation reaction. (Scheme 1) The methine and dihydromethine bases of the 14-hydroxy-compounds (*e.g.* IX, X) formed the corresponding methiodide with much greater ease than the 14-hydroxymorphines (*e.g.* XI, X) as shown in Table I. Both 14-hydroxy-compounds have a hydrogen bond between the 14-hydroxyl group and a lone pair of the nitrogen atom at the 17-position.[2,3] In the methine bases the hydrogen bond forms a seven-membered ring but in the 14-hydroxymorphines a five-membered one. In the former compounds the hydrogen bond must

*1 Part XIII. I. Seki: This Bulletin, **14**, 445 (1966).

*2 1-Chome Hiromachi, Shinagawa-ku, Tokyo (関　功).

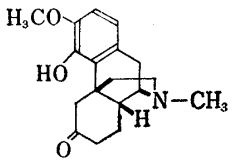
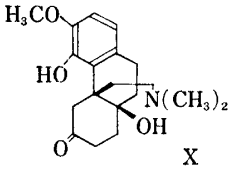
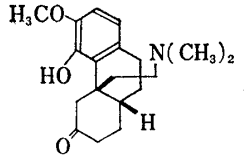
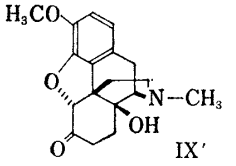
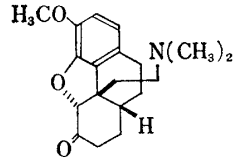
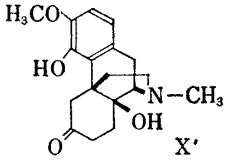
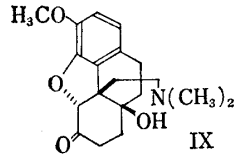
1) K. W. Bentley: "The Chemistry of the Morphine Alkaloids," Oxford (1954), the literature cited in this monograph.

2) I. Seki: Ann. Rept. Takamine Lab., **13**, 67 (1961).

3) *Idem*: Yakugaku Zasshi **85**, 359 (1965).

be less stable and effects of the hydrogen bond should be much smaller than in those of the latter compounds. (Scheme 2) Therefore, the methine and dihydromethine bases are expected to form the corresponding methiodides much more easily. The methiodide of 14-hydroxydihydrothebainone dihydromethine (X) gave dihydrothebaone (XI) when heated with aqueous sodium hydroxide. Since the nitrogen atom is sterically closer to the 14-hydroxyl group than to the 4-hydroxyl group the internal alkylation takes place at the 14-position to afford dihydrothebaone.*3,3)

Table I. Rate of Methiodide Formation

Tertiary bases	Yield of methiodide (% of theor.)a) 4 hr.	50 hr.	Tertiary bases	Yield of methiodide (% of theor.)a) 4 hr.	50 hr.
	82.4	—	 X	—	78.8
	90.2	—	 IX′	—	0.9
	94.5	—	 X′	—	4.8
 IX	42.7	—			

a) A mixture of tertiary base, excess methyl iodide, and benzene was allowed to stand for a described period of time at room temperature, and the crystallized methiodide was weighed.

These 6-oxo-hydrophenanthrenes (I～XIII) were converted to 6-amino-hydrophenanthrenes (XIV～XX) by catalytic reductive amination.4) The amino compounds were also prepared from the enamine derivatives of the oxo-compounds by catalytic reduction, sodium borohydride or formic acid reduction. (Scheme 3) (Table II～V). The chemical behaviors of these 6-oxo-compounds in the reaction and their reactivities for enamine formation with various secondary amines were quite similar to those of 6-oxo-morphines.4,5) Considering the reaction mechanism described in the previous paper,6) the main product of these reduction reactions would be expected to have a 6α-amino group. However, the productive ratio of the 6β-amino isomer

*3 This name will be proposed in place of "Tetrahydro-oxythebaon" that was named by M. Freund [J. prakt. Chem., **99**, 135 (1916)] without the proof of its structure.

4) I. Seki: Yakugaku Zasshi, 84, 626 (1964).
5) *Idem*: *Ibid.*, 84, 621 (1964).
6) *Idem*: *Ibid.*, 84, 631 (1964).

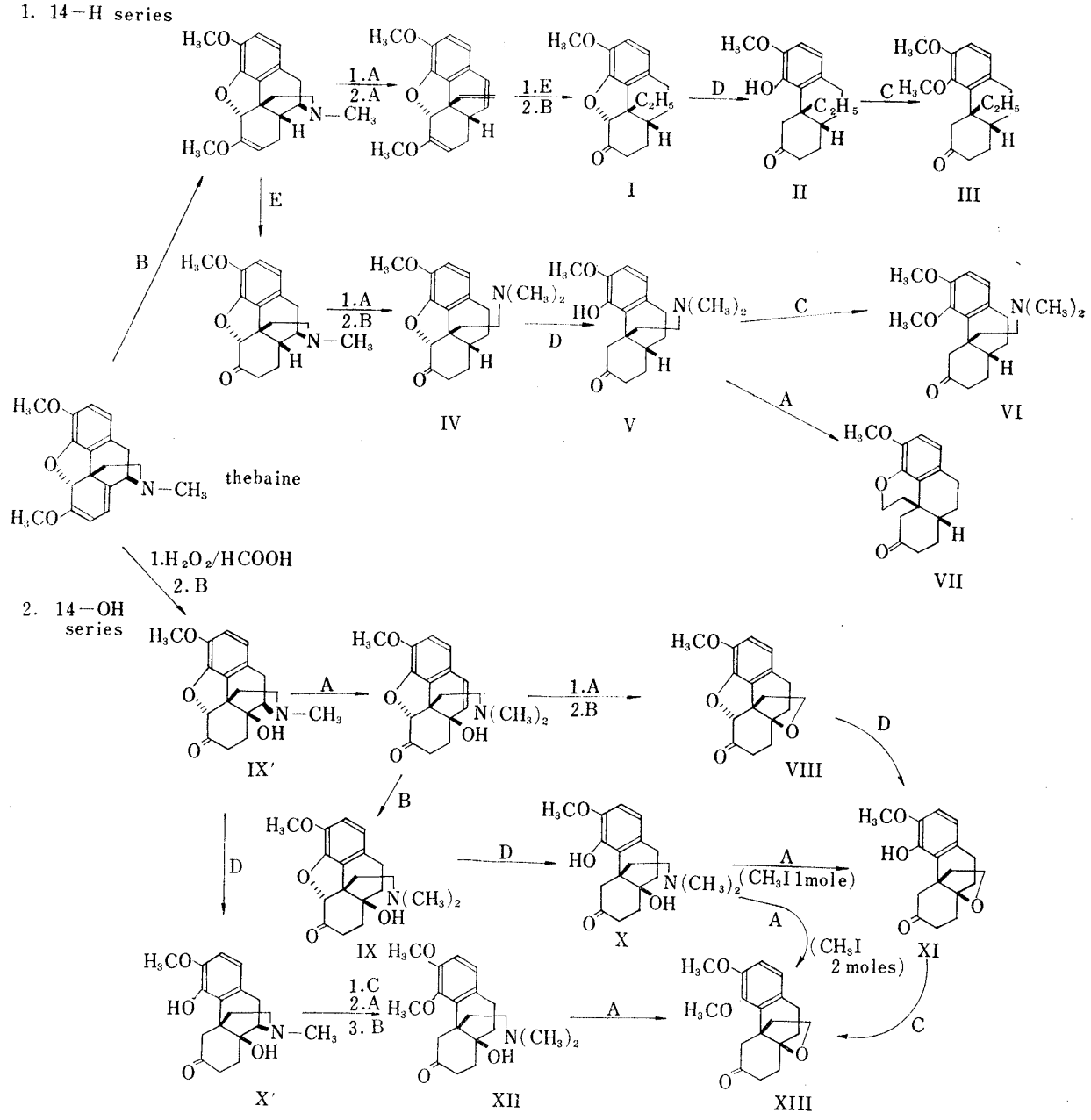


Chart 1.

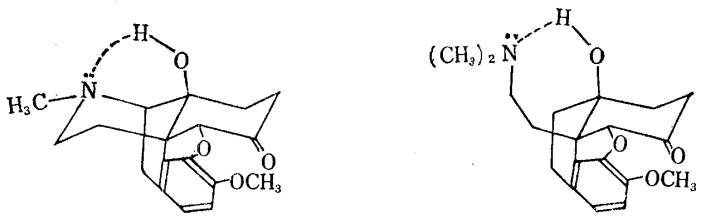


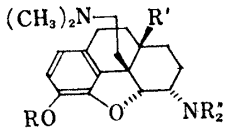
Chart 2.

in the reduction of the enamines of the non-basic 6-oxo-compounds (I, VIII) with formic acid was much greater than in the reduction of the enamines of the basic 6-oxo-compounds (IV, IX) and 6-oxomorphines.[4,6]

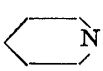
Sargent and Small[7] reported that two 6-amino-epimers were obtained in the proportion of about 2 : 1 by catalytic reduction of the oxime of 3,4-dimethoxy-13-ethyl-

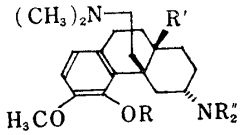
7) L. J. Sargent, L. Small : J. Org. Chem., **16**, 1031 (1951).

TABLE II.

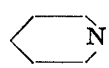


XIV

R	R′	NR_2''	Method[a]	Yield (%)	m.p. (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N
CH_3	H		A B	68 48	249[b]	$C_{35}H_{40}O_{16}N_8$[b]	50.75/50.83	4.87/4.99	13.51/13.31
H	H	〃	—[c]	52	214～219	$C_{22}H_{32}O_2N_2$	74.12/74.01	9.05/8.87	7.86/ 7.95
CH_3	H		A	18	245[b]	$C_{35}H_{40}O_{17}N_8$[b]	49.76/49.58	4.78/4.82	13.27/13.16
〃	〃		〃	38	237～238[b]	$C_{36}H_{42}O_{16}N_8$[b]	51.30/51.35	5.03/4.97	13.30/13.14
〃	〃	$(CH_3)_2N$	〃	25	217～219[b]	$C_{33}H_{38}O_{16}N_8$[b]	49.37/49.34	4.77/4.80	13.97/13.91
〃	OH		A, B	58	152～153	$C_{23}H_{34}O_3N_2$	71.47/71.03	8.87/8.86	7.25/ 7.22
H	〃		—[c]	61	265～270[d]	$C_{22}H_{34}O_3N_2Cl_2 \cdot H_2O$[d]	57.01/57.57	7.82/7.80	6.03/ 6.29

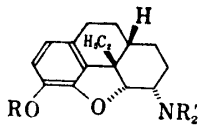


XV

R	R′	NR_2''	Method[a]	Yield (%)	m.p. (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N
H	H		C	70	236～238[b]	$C_{35}H_{42}O_{16}N_8$[b]	50.60/50.51	5.10/5.16	13.49/14.16
〃	〃		〃	41	250[d]	$C_{23}H_{38}O_3N_2Cl_2$[d]	59.85/59.37	8.30/8.73	6.07/ 5.65
〃	〃		〃	33	260[d]	$C_{24}H_{40}O_2N_2Cl_2 \cdot H_2O$[d]	60.35/60.56	8.86/8.60	5.87/ 5.69
CH_3	〃		D	74	236～237[b]	$C_{36}H_{44}O_{16}N_8$[b]	51.18/51.32	5.23/5.28	13.27/13.23
H	OH	〃	〃	71	280[d]	$C_{23}H_{38}O_3N_2Cl_2 \cdot 2H_2O$[d]	55.51/55.69	8.52/8.52	5.63/ 5.68
CH_3	〃	〃	〃	85	265～270[d]	$C_{24}H_{40}O_3N_2Cl_2 \cdot 0.5H_2O$[d]	59.48/59.55	8.54/8.81	5.78/ 5.30
〃	〃		C	34	250[d]	$C_{24}H_{38}O_4N_2Cl_2 \cdot H_2O$[d]	56.79/56.48	7.94/8.67	5.52/ 4.94

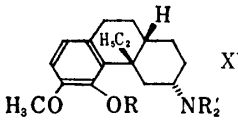
a) A: HCOOH-reduction of enamine B: $NaBH_4$-reduction of enamine C: Catalytic reduction of enamine
D: Catalytic reductive amination of 6-oxo-compound
b) Dipicrate
c) It was prepared from the corresponding 3-methyl ether by demethylation using pyridine hydrochloride.
d) Dihydrochloride

TABLE III.



XVI

R	NR_2'	Method[a]	Yield (%)	m.p. (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N	Cl
CH_3	N(α)	A B	50 75	72～76	$C_{21}H_{29}O_2N$	77.02/77.14	8.93/8.77	4.28/4.59	—
〃	N(β)	A	50	213～220[b]	$C_{21}H_{30}O_2NCl$[b]	—	—	3.85/3.71	9.76/ 9.87
H	N(α)	—[c]	53	169～171	$C_{20}H_{27}O_2N$	76.64/76.45	8.68/8.59	4.47/4.46	—
CH_3	O N	A	18	55～59	$C_{21}H_{29}O_3N$	73.43/72.83	8.51/8.53	4.08/4.37	—
〃	N	〃	5	253～256[b]	$C_{22}H_{32}O_2NCl$[b]	69.90/69.39	8.53/8.48	3.71/3.87	9.39/ 9.59
〃	$(CH_3)_2N$	〃	10	199～202[b]	$C_{19}H_{28}O_2NCl$[b]	67.53/67.21	8.35/8.32	4.15/4.10	10.51/10.68



XVII

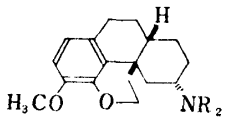
R	NR_2'	Method[a]	Yield (%)	m.p. (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N	Cl
H	N	D	85	125～126	$C_{21}H_{31}O_2N$	76.55/77.14	9.48/9.87	4.25/4.06	—
CH_3	N	〃	72	235～240[b]	$C_{22}H_{34}O_2NCl \cdot 0.5H_2O$[b]	67.92/68.08	9.07/9.49	4.25/4.06	9.13/ 9.01
〃	$(CH_3)_2N$	C	9	277(d)[b]	$C_{20}H_{32}O_2NCl \cdot H_2O$[b,d]	64.57/64.43	9.21/9.75	3.77/3.40	9.54/ 9.07
H	〃	〃	17	126～128	$C_{19}H_{29}O_2N$	75.20/75.13	9.63/9.55	4.62/4.79	—
〃	O N	〃	38	235～240[b]	$C_{21}H_{32}O_3NCl \cdot H_2O$[b]	64.51/64.83	8.51/8.23	3.58/3.77	9.08/ 9.40
〃	N	〃	18	254～256[b]	$C_{22}H_{34}O_3NCl$[b]	69.53/69.21	9.02/8.74	3.69/3.86	9.34/ 9.37

a) A: HCOOH-reduction of enamine B: $NaBH_4$-reduction of enamine C: Catalytic reduction of enamine D: Catalytic reductive amination of 6-oxo-compound

b) Hydrochloride

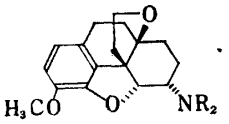
c) It was prepared from the corresponding 3-methyl ether by demethylation using pyridine hydrochloride.

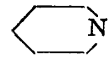
d) Methiodide d.p. 242～243°. cf. lit.[7]: d.p. 242～244°(methiodide of "α-compound")

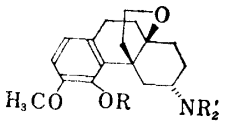
TABLE IV.  XVIII

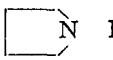
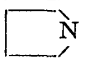
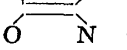
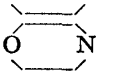
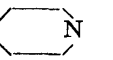
NR_2	Method[a]	Yield (%)	m.p. (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N	Cl
	B	97	190~200(d)[b]	$C_{21}H_{30}O_2NCl\cdot 0.5H_2O$[b]	67.66/68.00	8.38/8.40	3.78/3.69	9.52/ 9.33
	A	36	243~245(d)[b]	$C_{22}H_{32}O_2NCl$[b]	69.90/69.42	8.54/8.50	3.71/3.73	9.38/ 9.41
	〃	87	113~115	$C_{21}H_{29}O_3N$	73.43/73.31	8.51/8.42	4.08/4.18	—
$(CH_3)_2N$	〃	17	248~249(d)[b]	$C_{19}H_{28}O_2NCl$[b]	67.53/66.86	8.35/8.46	4.14/4.42	10.51/10.42

a) A: Catalytic reduction of enamine B: Catalytic reductive amination of thebenone
b) Hydrochloride

TABLE V.  XIX

NR_2	Method[a]	Yield (%)	m.p. (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N	Cl
 (α)	A B	20 40	93	$C_{21}H_{27}O_3N$	73.87/73.68	7.97/7.97	4.10/3.98	—
 (β)	A B	60 40	117~118	$C_{21}H_{27}O_3N$	73.87/73.92	7.97/7.88	4.10/4.16	—
	A	7	244~246(d)[b]	$C_{21}H_{28}O_4NCl$[b]	64.02/63.69	7.16/7.17	3.56/3.77	9.01/ 9.12
	〃	4	265~268(d)[b]	$C_{22}H_{30}O_3NCl$[b]	67.41/66.84	7.71/7.71	3.57/3.43	9.06/ 9.25
$(CH_3)_2N$	〃	9	248~250(d)[b]	$C_{19}H_{26}O_3NCl$[b]	64.48/64.65	7.45/7.37	3.98/3.98	10.09/10.26

 XX

R	NR_2'	Method[a]	Yield (%)	m.p. (°C)	Formula	Analysis (Calcd./Found) (%) C	H	N	Cl
H		D	87	126~128	$C_{21}H_{29}O_3N$	73.43/73.01	8.51/8.40	4.08/4.10	—
CH_3		〃	82	239~244[b]	$C_{22}H_{32}O_3NCl$[b]	67.06/66.59	8.19/8.22	3.56/3.52	9.02/ 8.80
H		C	38	248~250(d)	$C_{21}H_{30}O_4NCl$[b]	63.70/63.77	7.64/7.37	3.54/3.52	8.97/ 9.15
CH_3		〃	50	280~282(d)	$C_{22}H_{32}O_4NCl$[b]	64.45/64.46	7.87/7.83	3.42/3.37	8.66/ 8.84
H		〃	6	238~240[b]	$C_{22}H_{32}O_3NCl\cdot 0.5H_2O$[b]	65.56/65.09	8.26/7.97	3.48/3.13	8.18/ 9.19
〃	$(CH_3)_2N$	〃	22	254~256[b]	$C_{19}H_{28}O_3NCl$[b]	64.48/64.95	7.97/7.37	3.96/3.90	10.03/10.02

a) A: HCOOH-reduction of enamine B: $NaBH_4$-reduction of enamine C: Catalytic reduction of enamine
D: Catalytic reductive amination of 6-oxo-compound
b) Hydrochloride

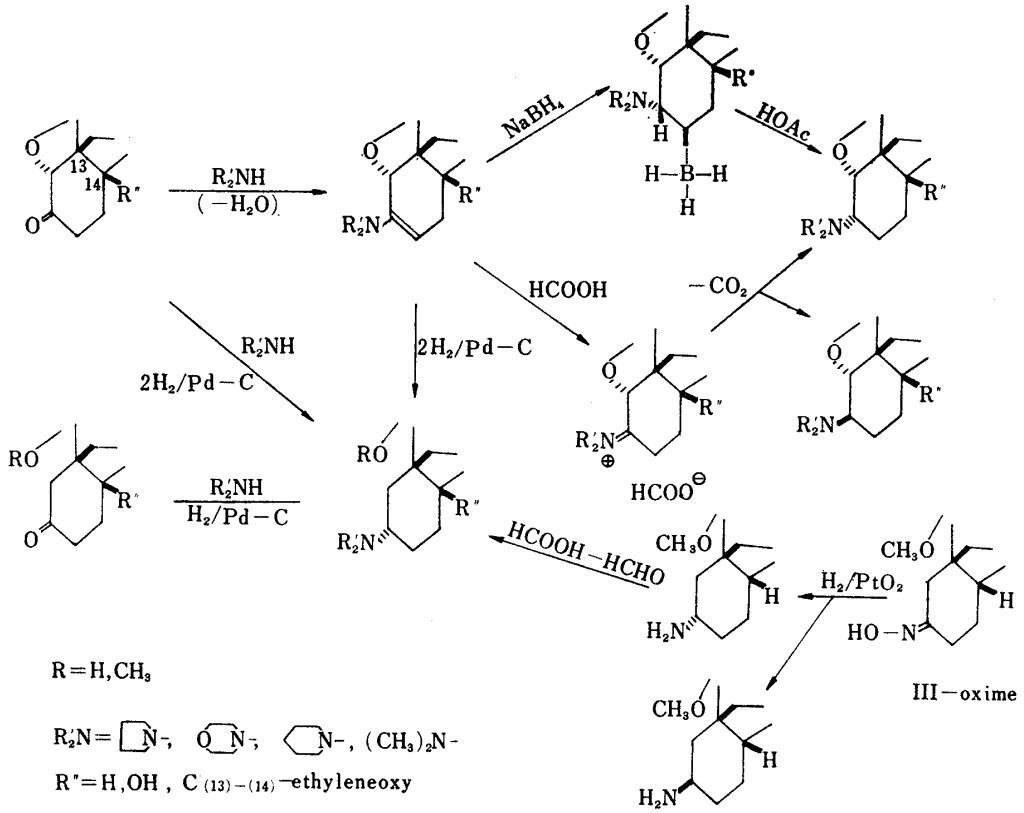


Chart 3.

6-oxo-octahydrophenanthrene (Ⅲ) and each epimer were converted to the corresponding 6-dimethylamino-epimers with the Eschweiler-Clarke reaction. Among these 6-dimethylamino-epimers, the main product [methiodide m.p. 242~244° (decomp.)] which was tentatively named "α-compound" by them without a proof of its conformation was identical with the product [methiodide m.p. 242~244° (decomp.)] obtained by catalytic reductive dimethylamination of the same 6-oxo-compound (Ⅲ). (Scheme 3)

Steric effects on catalytic reduction of alicyclic ketoximes should be similar to that of alicyclic ketones.[8] Since the 6α-alcohol was obtained as a main product by catalytic reduction of 6-oxo-morphines[9] it was also assumed that the main product of catalytic reduction of the corresponding 6-ketoxime should be the 6α-amino compound. Furthermore, the present author previously found that catalytic reduction of the 6-enamine derivatives of morphines gave the corresponding 6α-amino compound.[6] In catalytic reductive amination of the 6-oxo-compound the enamine derivative should be an intermediate.[4,10] The 6-oxo-compounds are thus expected to give the 6α-amino derivatives by this method. In fact, the product obtained by the method was identical with the 6α-amino compound which was prepared from the 6-ketoxime (*e.g.* Ⅲ-oxime) by catalytic reduction as mentioned above.

Experimental*4

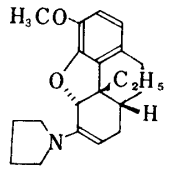
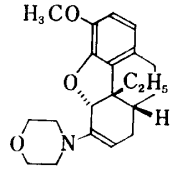
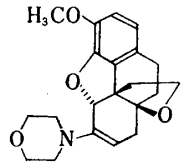
General Method for Preparation of Enamines——A mixture of a 6-oxo-compound (0.01 mole), secondary amine (0.02 mole), and *p*-toluenesulfonic acid (0.3 g.) was heated in benzene (70 ml.) with azeotropic removal

*4 All melting points were uncorrected. Active Al_2O_3 used was the Merck "nach Brockmann" without pre-treatment.

8) D.H.R. Barton: J. Chem. Soc., **1953**, 1029.
9) A. Skita, *et al.*: Ber., **54**, 1560 (1921); L. Small, *et al.*: J. Am. Chem. Soc., **58**, 1458 (1936); D. Elad, D. Ginsburg: *Ibid.*, **78**, 3691 (1956).
10) W.S. Emerson: "Organic Reactions," **4**, 174 (1948), John Wiley & Sons.

of water. The reaction time required was as follows; pyrrolidine : for 1.5～2 hr.; morpholine : for 6～8 hr.; piperidine and dimethylamine : for 8～10 hr. (still not complete). After completion of the reaction, the cooled benzene solution was washed with 10% Na_2CO_3 (two times each 10 ml.) and water (three times each 30 ml.), dried over Na_2SO_4, and evaporated to give the corresponding enamine almost quantitatively. IR λ_{max}^{Nujol} μ : 6.12 (strong), 6.2 (weak). These oily enamines were used for the following reaction without further purification, but some of the enamines crystallized well as shown in Table Ⅵ.

Table Ⅵ. Crystallized Enamines

Enamine	Yield (%)	m.p. (℃) (Solvent)	Formula	Analysis (Calcd./Found) (%) C	H	N
	100	102～104 (EtOH)	$C_{21}H_{27}O_2N$	77.50/77.39	8.36/8.31	4.30/4.29
	97	116～117 (MeOH)	$C_{21}H_{27}O_3N$	73.87/73.80	7.97/8.00	4.10/4.06
	89	131～133 (MeOH–ether)	$C_{21}H_{26}O_4N$	70.96/70.65	7.09/7.06	3.94/4.07

General Method for Reduction of Enamines——1) With $NaBH_4$. To a solution of pyrrolidinyl-enamine (oxo-compound free) (0.005 mole) in MeOH (50 ml.) was added $NaBH_4$ (0.5 g.) within 5～10 min., and it was stirred for 2 hr. at 30～35°. After addition of AcOH (1 ml.), the mixture was refluxed for 3 hr. It was evaporated to dryness *in vacuo*, and the residue was dissolved in dil. HCl. This solution was washed with benzene, made alkaline with NH_4OH, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to give the 6α-pyrrolidinyl compound in 60～80% yield.

2) With HCOOH. A mixture of enamine (0.01 mole) and HCOOH (0.012 mole) was heated for one hour at 100～110° (inner temperature). After completion of the reaction, the cooled reaction mixture was dissolved in dil. HCl. This solution was washed with benzene, made alkaline with NH_4OH, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and evaporated to dryness. The product obtained by the reduction of the pyrrolidinyl-enamines was dissolved in *n*-hexane, and chromatographed on active Al_2O_3. The *n*-hexane eluate was collected and evaporated to give the 6α-amino compound which was identical with $NaBH_4$ reduction product of the same enamine. Then, the benzene eluate was collected and evaporated to give the 6β-isomer. The total yield of the amines was 60～70% and proportion of the two isomers was about 6α 2:6β 1 in the reduction of the enamine derived from the basic 6-oxo-compound (*e.g.* Ⅳ, Ⅸ). But, in the case of reduction of the enamine derived from the non-basic 6-oxo-compound (*e.g.* Ⅰ, Ⅷ), the 6β-isomer as well as an equal amount of 6α-isomer were produced. On the other hand, when a benzene solution of the product obtained by reduction of morpholino-, piperidino-, and dimethylamino-enamines was decolorized with charcoal and active Al_2O_3, and evaporated, only the 6α-amino compound was obtained in 5～40% yield.

3) Catalytic reduction. A mixture of enamine (0.01 mole), 10% Pd-C (3 g.), and MeOH (100 ml.) was shaken under hydrogen atmosphere at normal pressure and room temperature for 3～6 hr. After filtration, the filtrate was evaporated to dryness *in vacuo*, and the residue was dissolved in dil. HCl. This solution was washed with benzene, made alkaline with NH_4OH, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, decolorized with active Al_2O_3, and evaporated to give only the 6α-amino compound in 5～80% yield.

In these reduction reactions, the benzene extracts obtained by the reduction of the morpholino-, piperidino-, and dimethylamino-enamine of the basic 6-oxo-compounds were treated with NH_2OH-HCl (0.02 molar equivalents) in warm water for 30 min. in order to remove contaminated 6-oxo-compound. Then, the mixture was made alkaline with NH_4OH, and extracted with benzene. The benzene solution was washed with water, dried over Na_2SO_4, and chromatographed on active Al_2O_3 (ten times of the solute). The benzene eluate was collected and evaporated to give a pure sample of the 6-amino compound.

General Method for Catalytic Reductive Amination of 6-Oxo-compound——A mixture of 6-oxo-compound (0.01 mole), secondary amine (0.01 mole), 10% Pd-C (3 g.), and MeOH (100 ml.) was treated as described in the case of catalytic reduction of enamines. This method is particularly suitable for preparation of the pyrrolidino-derivatives.

The author is grateful to Prof. K. Tsuda of the University of Tokyo, Mr. M. Matsui, Director of this laboratories, and Dr. 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 spectra.

Summary

Preparation of 6-amino-hydrophenanthrene compounds from the 6-oxo-hydrophenanthrene compounds derived by the Hofmann degradation reaction of the 6-oxo-morphine alkaloids was described. There have been used catalytic reductive amination of the 6-oxo-compounds and catalytic, sodium borohydride, and formic acid reductions of their enamine derivatives. Behaviors of the 6-oxo-compounds in the described reactions were quite similar to those of the 6-oxo-morphines reported previously.

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[Chem. Pharm. Bull. 14(5) 461~466 (1966)] UDC 615.771.7 : 547.722.5.09

62. Toshimitsu Ujiie : Experimental Anticancer Studies. XXVIII.*1 Anticancer Activity of Some Nitrofuran Derivatives.*2

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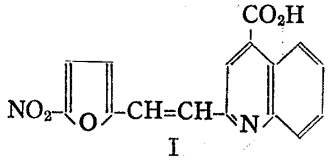
It was reported in the previous paper[1] that 2-[2-(5-nitrofuryl)vinyl]-4-quinoline-carboxylic acid (I) showed moderate prolongation of life span of mice implanted with Ehrlich ascites carcinoma cells. Meanwhile, Miura, *et al.*, who examined a variety of analogous nitrofuran derivatives, found that 2-[2-(5-nitrofuryl)vinyl] quinoline was similarly effective.[2]



I

The results of anticancer experiments with some of the Schiff base compounds of 2,4-dihydroxy-5-*n*-hexylbenzaldehyde were already reported elswhere.[3]

*1 Part XXVII. Japan. J. Exptl. Med., **35**, 249 (1965)

*2 A part of this paper was presented at the 44th Meeting of Juzen Medical Society (Kanazawa) on February 27, 1965.

*3 Takara-machi, Kanazawa (氏家俊光).

1) T. Ujiie : Ann. Rep. Tbc. Kanazawa, **21**, (3), 363 (1964).

2) K. Miura, M. Ikeda, T. Oohashi, I. Okada, Y. Igarashi : Yakugaku Zasshi, **84**, 341 (1964); *Idem* : *Ibid.*, **84**, 537 (1964).

3) R. Koshiura, Y. Kagotani, T. Ujiie : This Bulletin, **10**, 528 (1962); T. Ujiie, Y. Kagotani, S. Koshimura : Presented at the 82nd Annual Meeting of the Pharmaceutical Society of Japan (Shizuoka), 1962.