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Studies on the Morphine Alkaloids and Its Related Compounds. XVII.[1] One-Step Preparations of Enol Ether and Pyrrolidinyl Dienamine of Normorphinone Derivatives[2]

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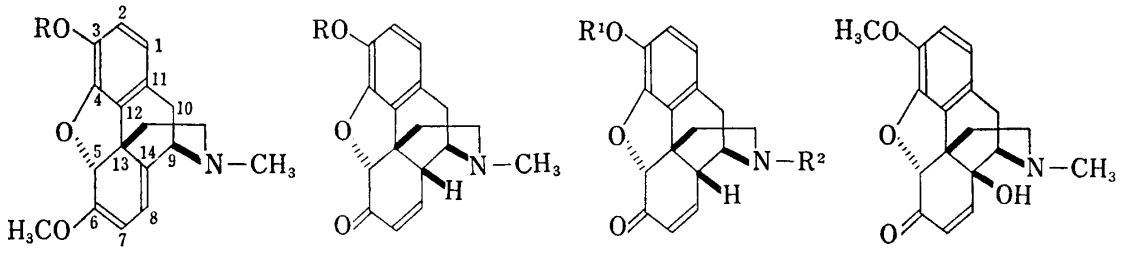
One-step preparation of the pyrrolidinyl dienamine and the enol ethers including thebaine, which is only known $\Delta^{6,8}$-diene compound in the morphine alkaloids, from O,N-disubstituted-normorphinones including codeinone were described. The $\Delta^{6,8}$-diene compounds were oxidized to O,N-disubstituted-14-hydroxy-normorphinones with 30% hydrogen peroxide in formic acid.

It has been shown that thebaine (Ia) and oripavine (Ib) are the enol methyl ether of codeinone (IIa) and morphinone (IIb), respectively, and Ia is an important starting material for various interesting reactions in the morphine alkaloids.[4] However, one-step preparations of the such $\Delta^{6,8}$-diene compounds from the α,β-unsaturated ketones such as codeinone (IIa) have never been accomplished.[5] Accordingly, the author commenced a study on the syntheses of $\Delta^{6,8}$-diene compounds from O,N-disubstituted-normorphinones (III). It is the purpose of this paper to report on one-step preparations of the pyrrolidinyl dienamine and the enol ethers from III.



Ia : R=CH_3
Ib : R=H

IIa : R=CH_3
IIb : R=H

III

IV

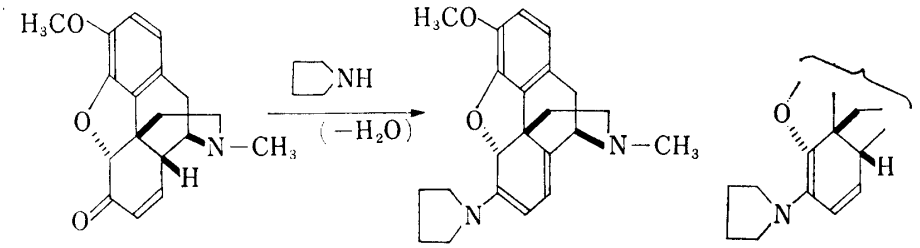
Chart 1

(1) Preparation of Pyrrolidinyl Dienamine

As reported previously, in the reaction of α,β-unsaturated ketones such as codeinone (IIa) or 14-hydroxy-codeinone (IV) with secondary amines an 1,4-addition of amines to the conjugated system occurred preferably, while only the reaction of IIa with pyrrolidine was much complication.[6] From the results of detailed survey of this reaction under various

1) Part XVI: I. Seki and H. Takagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 1555 (1969).
2) This work was presented at the Meeting of Kinki Branch, Pharmaceutical Society of Japan, Kyoto, Nov. 1968.
3) Location: *1-Chome Hiromachi, Shinagawa-ku, Tokyo.*
4) *e.g.*, L. Small, H. Fitch, and W.E. Smith, *J. Am. Chem. Soc.*, **58**, 1457 (1936); K.W. Bentley and D.G. Hardy, *ibid.*, **89**, 3267, *et seq.* (1967); I. Seki, *Ann. Sankyo Res. Lab.*, **12**, 52 (1960).
5) Recently, the synthesis of thebaine (Ia) from codenione (IIa) *via* multiple-steps was reported by H. Rapoport, C.H. Lovell, H.R. Reist, and M.E. Warren, Jr,. *J. Am. Chem. Soc.*, **89**, 1942 (1967).
6) I. Seki, *Yakugaku Zasshi*, **84**, 621, 626 (1964).

conditions, it was found that codeinone pyrrolidinyl dienamine (V) produced in over 90% yield by heating a mixture of IIa and pyrrolidine (each one mole) with or without catalytically amounts of *p*-toluenesulfonic acid in inert solvent such as benzene or chloroform under azeotropic removal of water formed. The reaction proceeded rapidly (0.5—1.5 hours) under above conditions, and the glassy product isolated from reaction mixture was readily converted to pale yellow crystallized substance having mp 126—128° by treatment with isopropanol. The elemental analysis of this substance agreed with the formula V.



IIa V V'

Chart 2

In comparison with UV spectra of codeine (λ_{max}^{EtOH} 286 mμ, ε 1550), thebaine (λ_{max}^{EtOH} 285 mμ, ε 7330) and dihydrocodeinone pyrrolidinyl enamine (*e.g.*, VI), marked bathochromic shift (*ca.* 50 mμ) was observed in that of the substance (λ_{max}^{EtOH} 336 mμ, ε 8450) as shown in Fig. 1. In the IR spectrum of the substance very strong absorption at 1582 cm^{-1} was observed, and in the NMR spectrum a signal due to the 5β-proton was shown at 5.47 ppm as singlet. On the basis of above spectroscopic observations it was concluded that the substance having mp 126—128° is a dienamine which has linear conjugated system in the structure as shown in formula V and not cross conjugated dienamine like formula V'.[7,8]

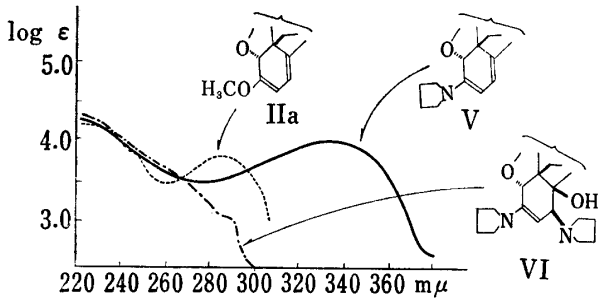


Fig. 1

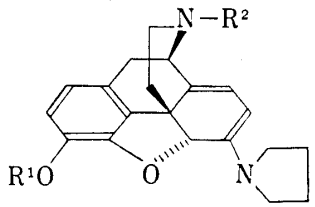
Codeinone pyrrolidinyl dienamine (V) was oxidized to 14-hydroxy-codeinone (IV) with 30% hydrogen peroxide in formic acid but its yield was low (30—40%) comparing with the case of thebaine (80—85%). This fact can be attributed to high sensibility of the dienamine to acids because in mineral acids the dienamine immediately decomposed and even the salts with organic acids such as bitartrate changed slowly to a reddish resinous substance in air.

The O,N-disubstituted-normorphinone pyrrolidinyl dienamines (VII) (Table I) were prepared from corresponding ketones under the conditions mentioned above, and these dienamines were converted to O,N-disubstituted-14-hydroxy-normorphinones (VIII) (Table II) by 30% hydrogen peroxide in formic acid.

7) A.I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, N.Y., 1964, p. 26,45,50; J. Szumuszkovicz, "Enamines" in "Advances in Organic Chemistry Method and Results," Vol. 4, ed. by R.A. Raphael, E.L. Taylor, and H. Wynberg, Interscience Publishers, N.Y., 1963, p. 1,98.

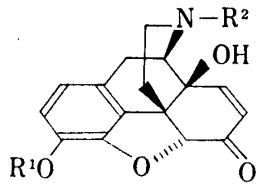
8) The preparation of codeinone dienamines was found in *Chem. Abstr.*, 67, 82295 V (1967) (Neth. Pat. 6610236 (1967)). But this method is different from our one-step method with respect to use of two-steps *via* 8-aminodihydrocodeinone enamines, and consequently, yield of dienamine is low comparing with the result by our method.

Table I. O,N-Substituted-normorphinone Pyrrolidinyl Dienamines (VII)



R^1	R^2	mp (solvent) (C°)	$[\alpha]_D^{21.5}$ ($CHCl_3$)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Methyl	methyl	126—128 (iso-PrOH)	−192.2	$C_{22}H_{26}O_2N_2$	75.40	7.48	7.99	75.14	7.74	7.90
Allyl	methyl	glassy solid		$C_{24}H_{28}O_2N_2$	76.56	7.50	7.44	76.68	7.83	7.55
Methyl	allyl	glassy solid		$C_{24}H_{28}O_2N_2$	76.56	7.50	7.44	76.88	7.37	7.24
Methyl	phenethyl	153.5—155.5 (iso-PrOH)	−247.2	$C_{29}H_{32}O_2N_2$	79.06	7.32	6.36	78.99	7.33	6.25
Benzyl	methyl	glassy solid		$C_{28}H_{30}O_2N_2$	78.84	7.09	6.57	78.95	7.17	6.34

Table II. O,N-Substituted-14-hydroxy-normorphinones (VIII)



R^1	R^2	mp (solvent) (C°)	$[\alpha]_D^{21.5}$ ($CHCl_3$)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Ethyl	methyl	236—237 ($CHCl_3$–MeOH)	+20.5	$C_{19}H_{21}O_4N$	69.70	6.47	4.28	69.84	6.37	4.25
n-Propyl	methyl	237—239 ($CHCl_3$–MeOH)	+244.4	$C_{20}H_{23}O_4N$	70.36	6.79	4.10	70.29	6,71	4.23
Iso-propyl	methyl	218—219 ($CHCl_3$–MeOH)	−15.1	$C_{20}H_{23}O_4N$	70.36	6.79	4.10	70.46	6.79	4.33
Allyl	methyl	222—223 ($CHCl_3$–MeOH)	+14.0	$C_{20}H_{21}O_4N$	70.78	6.24	4.13	70.81	6.14	4.22
Benzyl	methyl	244—245 ($CHCl_3$–MeOH)	−3.1	$C_{24}H_{23}O_4N$	74.02	5.95	3.60	73.62	6.41	3.58
Methyl	allyl	133—135 ($CHCl_3$–MeOH)	−28.2	$C_{20}H_{21}O_4N$	70.78	6.24	4.13	70.58	6.46	4.07
Methyl	phenethyl	198(decomp)[a]		$C_{29}H_{31}O_{10}N \cdot 0.5H_2O$[a]	61.91	5.73	2.49	61.86	6.22	2.41

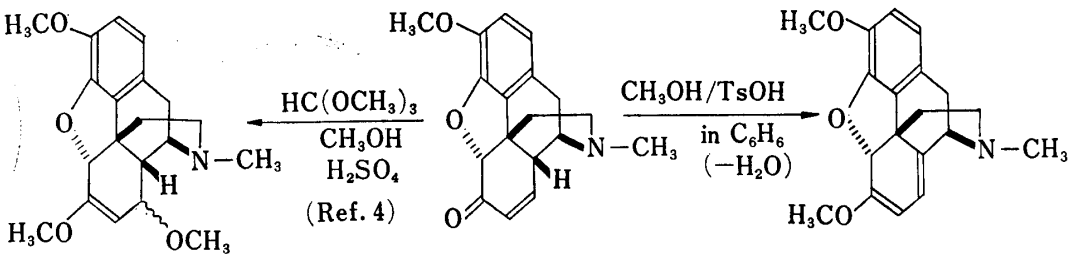
a) bitartrate

(2) Syntheses of Enol Ethers

For the preparation of enol ether or ketal of α,β-unsaturated ketone various methods has been presented.[9] Although it was reported recently that the ketalization of codeinone (IIa) with trimethyl orthoformate, which is used generally, was unsuccessful because of the formation of 8-methyl-Δ^6-dihydrothebaine (IX),[5] there is little work with other reagents in the morphine

9) *e.g.*, C. Djerassi, "Steroid reactions," Holden-Day Inc., SanFrancisco, 1963, p. 42.

alkaloids. The author examined on the possibility of one-step formation of enol ether from IIa with alcohol under the presence of *p*-toluenesulfonic acid.

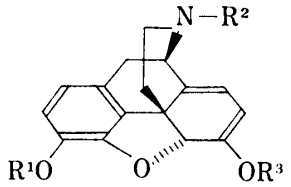


IX IIa Ia

Chart 3

Codeinone (IIa) was added to the mixture of *p*-toluenesulfonic acid dehydrated prior to the reaction, absolute methanol, and dried benzene, and the solution was refluxed for 3 hours under azeotropic removal of water formed. When the reaction mixture purified by washing with diluted sodium hydroxide solution followed by chromatography on active alumina, the crystals having mp 190—193° were obtained. By direct comparison with an authentic sample isolated from opium this crystals were shown to be thebaine (Ia). The maximum yield (26.8%) of Ia was achieved by use of 1.1—1.5 molar equivalents of *p*-toluenesulfonic acid to codeinone. In this reaction, it was observed that 1,4-addition of methanol to the conjugated system like the reaction with orthoformate[5] or secondary amines[6] is principal by-reaction and this occurs considerably even under room temperature. Other catalysts such as boron trifluoride or trifluoroformic acid were uneffective as recovered starting materials and use of higher boling solvent such as toluene resulted a decomposition of the ketones.

Table III. O,N-Substituted-normorphinone Enol Ethers (X)



R¹	R²	R³	Yield (%)	mp (solvent) (C°)	$[\alpha]_D^{21.5}$ ($CHCl_3$)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Methyl	methyl	methyl	26.8	190—193[a] (EtOH)								
Methyl	methyl	ethyl	22.8	123—124 (80% EtOH)	− 6.0	$C_{20}H_{23}O_3N$	73.82	7.12	4.30	73.93	7.19	4.31
Methyl	methyl	*n*-propyl	45.4	155.5—156.5 (EtOH)	− 2.5	$C_{21}H_{25}O_3N$	74.31	7.42	4.13	74.14	7.50	3.72
Methyl	methyl	iso-propyl	38.1	131—132 (EtOH)	−221.1	$C_{21}H_{25}O_3N$	74.31	7.42	4.13	74.26	7.40	4.36
Methyl	methyl	*n*-butyl	25.5	103—104 (EtOH)	+ 19.9	$C_{22}H_{27}O_3N$	74.75	7.70	3.96	74.63	7.78	3.94
Methyl	methyl	methoxy-methyl	30.3	140—142 (EtOH)	−237.9	$C_{21}H_{25}O_4N$	70.96	7.09	3.94	70.50	7.28	3.85
Benzyl	methyl	*n*-propyl		118—123[b] (95% EtOH)		$C_{31}H_{35}O_9N \cdot 1.5H_2O$[b]	62.83	6.46	2.36	62.95	6.48	2.23

a) Alone and mixed with an authentic sample isolated from opium. *b*) bitartrate

According to above reaction conditions, O,N-disubstituted-normorphinone enol ethers (X) (Table III) were prepared from corresponding ketones. *n*-Amyl and benzyl ethers were not obtained for decomposition of the ketones under the higher boiling medium, and *t*-butyl ether was also not obtained because of lower solubility of materials. Oxidation of these enol ethers with 30% hydrogen peroxide in formic acid gave O,N-disubstituted-14-hydroxy-normorphinones (VIII) in 60—70% yield (Table II).

Details on the 1,4-addition of nucleophiles to the conjugated system of codeinones will be reported in following paper.

Experimental[10]

Codeinone Pyrrolidinyl Dienamine (V)——The mixture of codeinone[11] (IIa; 9 g), pyrrolidine (3 ml), TsOH–H_2O (0.3 g), and benzene (80 ml) was refluxed for 1.5 hours under azeotropic removal of water formed. After cooling, the solution was washed with 10% Na_2CO_3 (10 ml×2) and then with water, dried over Na_2SO_4, evaporated to dryness *in vacuo*. Pale red residue (10.95 g) was chromatographed on active alumina (30 g) and benzene eluates were collected to give codeinone pyrrolidinyl dienamine (9.8 g; 92.3%) as pale orange-yellow substance. This substance was converted to pale yellow crystals having mp 124—126° by treatment with iso-PrOH. Crystals were recrystallized from iso-PrOH for analysis. mp 126—128°. $[\alpha]_D$ −192.2° (c=2.01). UV λ_{max}^{EtOH} mμ (ε): 336 (8450). IR ν_{max}^{Nujol} cm^{-1}: 1637, 1582. NMR ppm: 5.60 (1H, doublet, J=6.5 cps, 7-H), 5.47 (1H, singlet, 5β-H), 4.47 (1H, doublet, J=6.5 cps, 8-H). *Anal.* Calcd. for $C_{22}H_{26}O_2N_2$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.14; H, 7.74; N, 7.90.

O,N-Disubstituted-normorphinone pyrrolidinyl dienamines (VII) were prepared from corresponding ketones under above conditions (Table I).

Codeinone Enol *n*-Propyl Ether (X; $R^1=R^2=CH_3$, $R_3=n$-C_3H_7)——TsOH·H_2O (1.6 g) was dehydrated in boiling benzene for 2 hours under azeotropic removal of water, and to the cold benzene solution *n*-PrOH (10 ml) was mixed and then codeinone (IIa; 2 g) was added slowly into the mixture. This procedure must be observed to avoid decomposition of codeinone. The mixture was refluxed for 4 hours under azeotropic removal of water formed. After cooling, the solution was washed with 10% NaOH (10 ml×2) and then with water, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The orange-red residue (2.7 g) was chromatographed on active alumina (27 g), and the benzene eluates were evaporated to dryness *in vacuo*. Pale orange residue (1.5 g) was dissolved in EtOH (6 ml), and the solution was treated with NH_2OH–HCl (0.2 g) and water (2 ml) at 80° for 10 min. The mixture was made weak acidic with 10% AcOH (4 ml) and removed EtOH by evaporation *in vacuo*. The residue was dissolved in water, and the solution was made alkaline 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*. Pale orange-red residue (1.3 g) was chromatographed on active alumina (10 g), and benzene eluates were collected to give codeinone enol *n*-propyl ether having mp 152—155° as white crystals (1 g). The crystals were recrystallized from EtOH for analysis. mp 155.5—156.5°. $[\alpha]_D$ −2.5° (c=2.04). UV λ_{max}^{EtOH} mμ (ε): 286 (7870). IR ν_{max}^{Nujol} cm^{-1}: 1672, 1634, 1610. *Anal.* Calcd. for $C_{21}H_{25}O_3N$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.14; H, 7.50; N, 3.92.

O,N-Disubstituted-normorphinone enol ethers including thebaine were prepared from corresponding ketones under above conditions (Table III).

14-Hydroxy-codeinone (III)——1) From codeinone pyrrolidinyl dienamine (V). V (2.5 g) was dissolved in 98—100% HCOOH (5.5 ml) at 5—10°. The solution was mixed with 30% H_2O_2 (1 ml) at 30° and the mixture was allowed to stand for 1 hour holding reaction temperature at 50—55°. After cooling to room temperature, the mixture was diluted with water (20 ml), made alkaline with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried over Na_2SO_4, decolorized by chromatography on active alumina (10 g). The $CHCl_3$ eluates were collected and evaporated to dryness *in vacuo*. The crystalline residue (1.2 g) was washed with cold MeOH to give 14-hydroxy-codeinone (0.94 g). mp 276—279° (alone and mixed with an authentic sample prepared from thebaine).

2) From codeinone enol *n*-propyl ether (X; $R^1=R^2=CH_3$, $R^3=n$-C_3H_7). The enol ether (5.2 g) was dissolved in the mixture of 85% HCOOH (2.55 ml) and water (6.6 ml) at room temperature. The solution was treated with 30% H_2O_2 (2.2 ml) for 1.5 hours at 60°. After dilution with water (20 ml), the mixture was made alkaline with NH_4OH, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water,

10) All mp were uncorrected. Active alumina for chromatography was used Merck's "nach Brockmann" without pre-treatment. The NMR-data were measured by a Varian A60 at 60 Mc in $CDCl_3$ and used Me_4Si as internal standard. Optical rotations were measured in $CHCl_3$ at 21.5° by a Perkin-Elmer model 141 automatic polarimeter.

11) Yield of codeinone have improved markedly (over 90%) by refluxing of a mixture of each one equivalents of codeine, cyclohexanone, and aluminum isopropoxide in benzene for about 1 hour.

evaporated to dryness *in vacuo*. The crystalline residue (4.7 g) was washed with cold MeOH to give 14-hydroxy-codeinone (3.6 g). mp 276—279° (alone and mixed with an authentic sample prepared from thebaine).

O,N-Disubstituted-14-hydroxy-normorphinones as shown in Table II were prepared from enol ethers or pyrrolidinyl dienamine of O,N-disubstituted-normorphinones under above conditions.

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