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69. **Shojiro Uyeo, Akira Koshiro, Hiroshi Irie, and Kenji Yamamoto** : The Structure of the Rearrangement Product obtained by a Prévost-Woodward Reaction on 14-Hydroxydeoxydihydrocodeine Methine.

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The chemical evidence for structure II assigned previously to the product obtained by treatment of 14-hydroxydeoxydihydrocodeine methine with silver acetate and iodine followed by potassium hydroxide under the Prévost-Woodward reaction conditions is presented.

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In a previous communication[1] we have pointed out that the structure (II) should be assigned to the product formed as a result of a Prévost-Woodward reaction with 14-hydroxydeoxydihydrocodeine methine (I). This was based on an interpretation of its ultraviolet, infrared, nuclear magnetic resonance and mass spectra, and its combustion values were also in better agreement with the formula $C_{18}H_{23}O_4N$ than the previously assigned $C_{17}H_{21}O_4N$.[2] We now present the chemical evidence for structure (II). This has been provided by its transformation to III also obtainable from 14-hydroxydeoxydihydrocodeine methine by an unambiguous sequence of reactions.

Reduction of the keto-aldehyde (II) under the Huang-Minlon conditions gave the ketone (IV), only the aldehyde group in II being reduced to the methyl group without affecting the sterically hindered ketonic function. In confirmation of this structure no aldehyde system conjugated with the benzene ring was detected in the UV spectrum (λ_{max}^{EtOH} mμ 225, 293), while an isolated carbonyl band was observed at 1700 cm^{-1} in the IR spectrum. Treatment of IV in *t*-butanol with amyl nitrite in the presence of potassium *t*-butoxide afforded the isonitroso compound (V), the structure of which was supported by its elemental analysis, infrared absorptions at 3500 and 3200 cm^{-1}, and the solubility in aqueous alkali.

An attempt was made to carry out a second order Beckmann rearrangement on V by treatment of its alkaline solution with tosyl chloride. However, the reaction gave a mixture of products from which we failed to isolate the desired nitrilecarboxylic acid.

An alternative attempt involved the benzylic acid rearrangement of the α-diketone (VI), which was obtained from IV either by treatment with pyruvic acid or hydrochloric acid in acetone, or acid hydrolysis. It was an oil which was characterized as its perchlorate. Treatment of VI with potassium ethoxide in ethanol gave the α-hydroxy carboxylic acid (VII), isolated as its hydrochloride which exhibited infrared bands at 3500~2250 (OH, COOH, N^+H), and 1710 cm^{-1} (CO).

Reduction of the hydrochloride with lithium aluminum hydride in N-ethyl morpholine afforded the oily amino-diol (VIII). It exhibited strong hydroxy bands at 3550 and 3400 cm^{-1} in the infrared spectrum, and its periodic acid oxidation gave, along with formaldehyde, the six-membered ketone (III). The former was characterized as its dimedone adduct and the latter was identical in every respect with the compound prepared by osmium tetroxide oxidation of 14-hydroxydeoxydihydrocodeine methine (I) followed by periodide oxidation and subsequent Huang-Minlon reduction.

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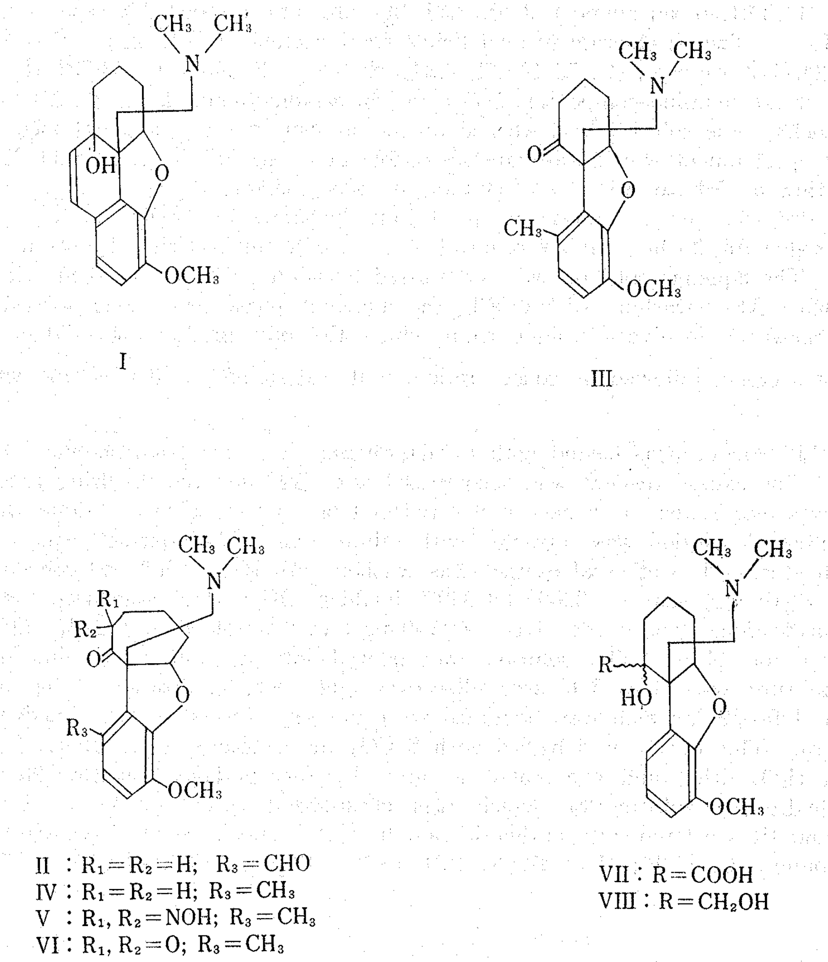
1) I. Iwai, A. Koshiro, M. Kurabayashi, H. Mishima, S. Uyeo, K. Yamamoto: Chem. Comm., **1965**, 118.

2) H. Mishima, M. Kurabayashi, I. Iwai: J. Org. Chem., **28**, 2621 (1963).

Thus the structure of the product of Prévost-Woodward reaction with 14-hydroxydeoxydihydrocodeine methine (I) was conclusively established as represented by formula II assigned before.



I

III

II : $R_1=R_2=H$; $R_3=CHO$
IV : $R_1=R_2=H$; $R_3=CH_3$
V : $R_1, R_2=NOH$; $R_3=CH_3$
VI : $R_1, R_2=O$; $R_3=CH_3$

VII : R=COOH
VIII : R=CH_2OH

Chart 1.

Experimental

Wolff-Kishner Reduction of the Ketoaldehyde (II)——A mixture of II (2.40 g.), diethylene glycol (150 ml.), 80% hydrazine hydrate (12.5 ml.), and KOH (7.5 g.) was heated at 100~110° for 1 hr. and then kept at 165~175° for 3 hr. After cooling, the reaction mixture was extracted with benzene. The benzene extract was washed with saline water, dried and evaporated to give an oil which was chromatographed in benzene over alumina. Elution with benzene gave the ketone (III) (1.20g.) which crystallized from hexane as prisms, m.p. 76~77°. *Anal.* Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.16; H, 8.70; N, 4.60. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 1700 (C=O). UV λ_{max}^{EtOH} mμ (log ε) : 293 (3.48). NMR ($CDCl_3$, τ): 7.97 (3H, $C\underline{H}_3$ -phenyl, singlet), 7.82 (6H, N-$\underline{Me}_2$, singlet), 6.10 (3H, $C\underline{H}_3$-O-, singlet), 5.11 (1H, -$\overset{|}{C}\underline{H}$-O-, doublet, J=6.5 c.p.s.), 3.43, 3.22 (2H, aromatic protons, AB type quartet, J_{AB}=8 c.p.s.).

Oximation of the Ketone (IV)——A solution of the ketone (IV) (200 mg.) and *t*-BuOK (1.033 g.) in *t*-BuOH (10 ml.) was stirred at room temperature for 1 hr. Isoamyl nitrite (1.2 ml.) was added dropwise into the solution and stirring was continued at room temperature for 40 hr. The resulting orange-colored mixture was diluted with ice-H_2O (40 ml.), and the aqueous solution was saturated with NH_4Cl and extracted with $CHCl_3$. The extract was washed with aqueous $NaHCO_3$ and with H_2O, dried and evaporated to give the oximino-compound (V) (180 mg.) which crystallized from EtOH as prisms, m.p. 204~205° (decomp.). *Anal.* Calcd. for $C_{19}H_{26}O_4N_2$: C, 65.87; H, 7.57; N, 8.09. Found : C, 66.13; H, 7.72; N, 7.88. IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3500, 3200 (OH), 1695 (C=O).

Hydrolysis of the Oximino-compound (V)——1) A mixture of the oximino-compound (V) (50 mg.), pyruvic acid (0.5 ml), AcOH (6 ml.) and H_2O (2 ml.) was heated under reflux for 12 hr. The mixture was concentrated under reduced pressure to a small volume, diluted with H_2O, basified with K_2CO_3 and extracted with ether. The ethereal extract was washed with H_2O, dried and evaporated to give an oil which was chromatographed in $CHCl_3$ over SiO_2 gel. Elution with $CHCl_3$-MeOH (9:1) gave the yellow oily α-diketone (VI) (15 mg.). IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 3450 (OH), 1725 shoulder, 1715 and 1680 shoulder (C=O). NMR ($CDCl_3$, τ): 7.85 (3H, $C\underline{H}_3$-phenyl, singlet), 7.78 (6H, $N\underline{Me}_2$, singlet), 6.16 (3H, CH_3-O- singlet), 4.94 (1H, $-\overset{|}{C}\underline{H}-O$ doublet, J=6 c.p.s.), 4.18 (1H, $O\underline{H}$, broad singlet), 3.40, 3.21 (2H, aromatic protons AB type quartet, $J_{AB}=9$ c.p.s.), 3.32 (1H, $=C\underline{H}-CH_2-$). The perchlorate formed flakes from acetone-EtOH, m.p. 205∼206°. *Anal.* Calcd. for $C_{19}H_{25}O_4N \cdot HClO_4 \cdot 1/2$ acetone: C, 53.42; H, 6.34; N, 3.04. Found: C, 53.33; H, 6.42; N, 3.19.

2) A solution of the oximino-compound (V) (70 mg.) in acetone (5 ml.) and 2*N* HCl (5 ml.) was refluxed for 8 hr. After cooling, the solution was worked up in the same manner as mentioned above to give the α-diketone, the IR spectrum of which was superimposable upon that of the compound (VI) obtained above.

Ring Contraction of VI to VII——A solution of the α-diketone (VI) (160 mg.) in anhydrous EtOH (7 ml.) was added dropwise to a solution of potassium (200 mg.) in EtOH (3 ml.). The mixture was refluxed under nitrogen for 26 hr. After removal of the EtOH under reduced pressure, the residue was taken up in H_2O. The aqueous solution was neutralized by adding dry-ice, washed with $CHCl_3$ and acidified with dilute HCl. After washing with $CHCl_3$, the aqueous phase was concentrated to dryness under reduced pressure below 40° to give a residue from which the oily product (VII) (130 mg.) was obtained by extraction with hot acetone, followed by concentration. It had IR $\nu_{\max}^{\mathrm{Nujol}}$: 3500∼2250 $\mathrm{cm^{-1}}$ (COOH, $-\overset{|}{\underset{|}{N}}{}^{+}-H$, OH), 1710 (C=O).

This product (VII) (90 mg.) was heated with $LiAlH_4$ (40 mg.) in N-ethyl-morpholine (30 ml.) under nitrogen at 100° for 15 hr. The excess reagent was decomposed with H_2O and the resulting precipitate was filtered off. The filtrate was evaporated to dryness under reduced pressure to give a residue which was taken up in ether and the ethereal solution was extracted with dilute HCl. The extract was basified with K_2CO_3 and extracted with ether. The ethereal extract was washed with H_2O, dried and concentrated to give the glycol (VIII) (40 mg.) (IR $\nu_{\max}^{\mathrm{CHCl_3}}$ $\mathrm{cm^{-1}}$: 3550 and 3400 shoulder (OH)) which was used for the next reaction without further purification. The crude glycol (VIII) (40 mg.) was dissolved in 0.27*M* HIO_4 (2 ml.) and kept at room temperature for 24 hr. The solution was poured into a solution of dimedone (40 mg.) in H_2O (40 ml.) and the mixture was allowed to crystallize overnight. Recrystalization of the product from EtOH gave needles, m.p. 189∼191°, which were identical with authentic formaldehyde dimedone adduct in mixed m.p. and IR spectra. The filtrate was baified with K_2CO_3 and extracted with ether. The ethereal solution was washed with H_2O, dried and evaporated to give 1-oxo-6-methoxy-9-methyl-9b-dimethylaminoethyl-1,2,3,4,4a,9b-hexahydro-dibenzofuran (III), which was crystallized from hexane as prisms, m.p. 79∼81°, identical in m.p. and IR spectrum with authentic sample (III).[*2] *Anal.* Calcd. for $C_{18}H_{25}O_3N$: C, 71.25; H, 8.31; N, 4.62. Found: C, 71.46; H, 8.29; N, 4.94. $[\alpha]_D^{23}$ +211° (c=1.06, $CHCl_3$). IR $\nu_{\max}^{\mathrm{KBr}}$ $\mathrm{cm^{-1}}$: 1698 (C=O).

[*2] We are grateful to Dr. I. Iwai, Sankyo Co., Tokyo, for a generous supply of an authentic sample of III.