[Chem. Pharm. Bull. 15(8)1247~1250(1967)] UDC 547.943.07

Tadashi Sasaki and Ken Kanematsu : Studies on Morphine-like Compounds. VI.*[1] Transformation of Thebaine to Benzomorphan Analogues by Ozonolysis.

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(Received August 29, 1966)

The feasibility of ring C in the morphine-like compounds towards oxidative cleavage is well known, which was demonstrated, for the first time, by Pshorr and Einbeck[1] who carried out ozonolysis of thebaine (I). Later Wieland and Small[2] reported its ozonolyzed product being α-thebaizone (IIa), $C_{19}H_{21}O_5N$, melting at 123~125°, but no detailed description. Recently May, *et al.*[3] reported some benzomorphan analogues with potent analgesic effectiveness and with minimum addiction liability and toxicity which enforced the present authors to reinvestigate ozonolysis of thebaine to benzomorphan analogues. This paper described the results of the ozonolysis and the structural elucidation of the products.

Ozonolysis of thebaine gave three basic products, A, B, and C in yields of 3, 14, and 34%, respectively. Separation of these products was carried out successfully by using their solubility differences and by column chromatography on silica gel.

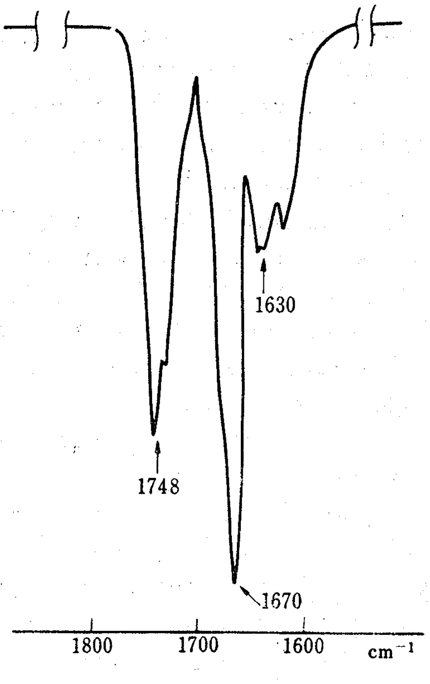

Fig. 1. Infrared Absorption Spectrum of Compound B (in $CHCl_3$)

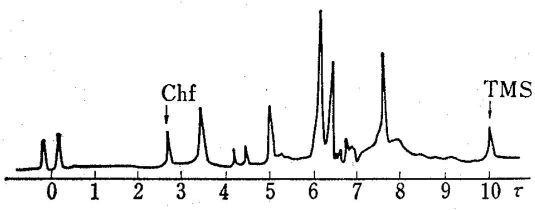

Fig. 2. NMR Spectrum of Compound B (in $CDCl_3$ at 60 Mc)

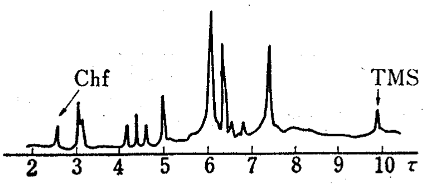

Fig. 3. NMR Spectrum of III (in $CDCl_3$ at 60 Mc)

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*[1] Part V. T. Sasaki, K. Kanematsu : J. Med. Chem., **9**, 857 (1966).

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1) R. Pshorr, H. Einbeck : Chem. Ber., **40**, 365 (1901).

2) H. Wieland, L.F. Small : Ann., **467**, 17 (1928).

3) E.L. May, L.J. Sargent : "Morphine and Its Modification," in Medicinal Chemistry, **5**, 145 (1965). Academic Press, New York.

Compound A, $C_{18}H_{19}O_4N$, m.p. 279~281°(decomp.), colorless plates from EtOH, was assumed to be 14-hydroxycodeinone by its comparison with an authentic specimen prepared by the known method of peroxide-oxidation of thebaine.4) This assignment was confirmed by its infrared absorption- and nuclear magnetic resonance spectrum; the former showed sharp bands at 3360, 1680, and 1640 cm^{-1} owing to the presence of a hydroxyl, an ethylenic, and an α,β-unsaturated carbonyl group, respectively and the latter manifested the olefinic protons at $3.84\,\tau$ (1H, doublet, J=10 c.p.s.) and $3.35\,\tau$ (1H, doublet, J=10 c.p.s.).

Compound B, $C_{19}H_{21}O_5N$, m.p. 149~150°, yellow prisms from MeOH, showed sharp absorptions at 1748 (an ester group), 1670 and 1630 cm^{-1} (an α,β-unsaturated carbonyl group) in the infrared absorption (IR) spectrum as shown in Fig. 1 and the absorption maximum at 278 mμ (log ε 3.32) in the ultraviolet spectrum. Its nuclear magnetic resonance (NMR) spectrum as shown in Fig. 2 showed signals at $6.23\,\tau$ (3H, singlet, $-COOC\underline{H}_3$), $4.04\,\tau$ (1H, doublet, J=7.0 c.p.s., $\rangle C{=}C\underline{H}-$) and $0.00\,\tau$ (1H, doublet, J=7.0 c.p.s., $-C\underline{H}O$).

The existence of an aldehyde group in compound B was demonstrated by formation of the 2,4-dinitrophenylhydrazone and by its positive reactions with such reagents as Fehling's and Tollen's solutions. Holmes4) describes that the remaining double bond in such a compound as B exhibits striking reactivity towards catalytic hydrogenation and therefore, reduction of an aldehyde group in compound B was carried out with $NaBH_4$ in MeOH to give an alcohol (Ⅲ), $C_{19}H_{23}O_5N$, m.p. 130~131°, colorless prisms from MeOH, which lacked clearly an aldehyde absorption band in the infrared spectrum. As shown in Fig. 3, its nuclear magnetic resonance spectrum showed an olefinic proton at $4.45\,\tau$ (1H, triplet, J=7.0 c.p.s.). Further reduction of the remaining carboxyl group in Ⅲ was accomplished by using $LiAlH_4$ in tetrahydrofuran to give a diol (Ⅳ), $C_{18}H_{23}O_4N$, m.p. 178~179°, colorless needles from EtOH.

It is known that α-thebaizone, m.p. 123~125° is isomerized at 200° to its β-isomer of m.p. 151°.[2,3] Considering from its reductivity, its melting point and its empirical formula, compound B might be presented as β-thebaizone.*3

Compound C, $C_{18}H_{21}O_6N \cdot H_2O$, m.p. 174~175°, colorless prisms from H_2O, showed the infrared absorption bands at 3400 (-OH), 1730 (broad, -COOH), 1720 (shoulder, -COOH) and 1650 cm^{-1} ($\rangle C{=}C\langle$). Disappearance of the IR absorption bands corresponding to carboxylic acid in $CHCl_3$ was observed by addition of Et_3N as shown in Fig. 4, which shows clearly the existence of -COOH groups. By its pKa values being 4.30 and 6.82 in 80% methylcellosolve solution at 25°, compound C should be dibasic acid, in which one of the two carboxylic groups shows stronger acidity, presumably owing to the presence of its conjugation with an olefinic linkage. This

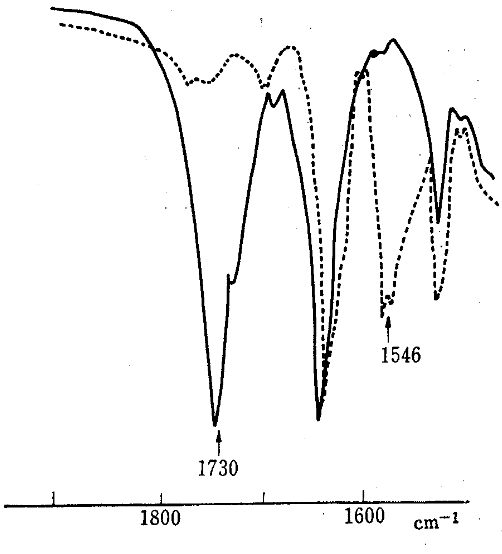

Fig. 4. Infrared Absorption Spectra of Compound C

——— in KBr
-------- in $CHCl_3$ added Et_3N

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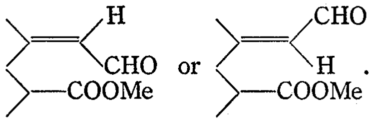
*3 Further investigation is necessary for determination of each absolute configuration,



4) H. Holmes; "The Morphine Alkaloids" in R. H. F. Manske, H. Holmes: "The Alkaloids," Vol. 2, 92 (1952). Academic Press.

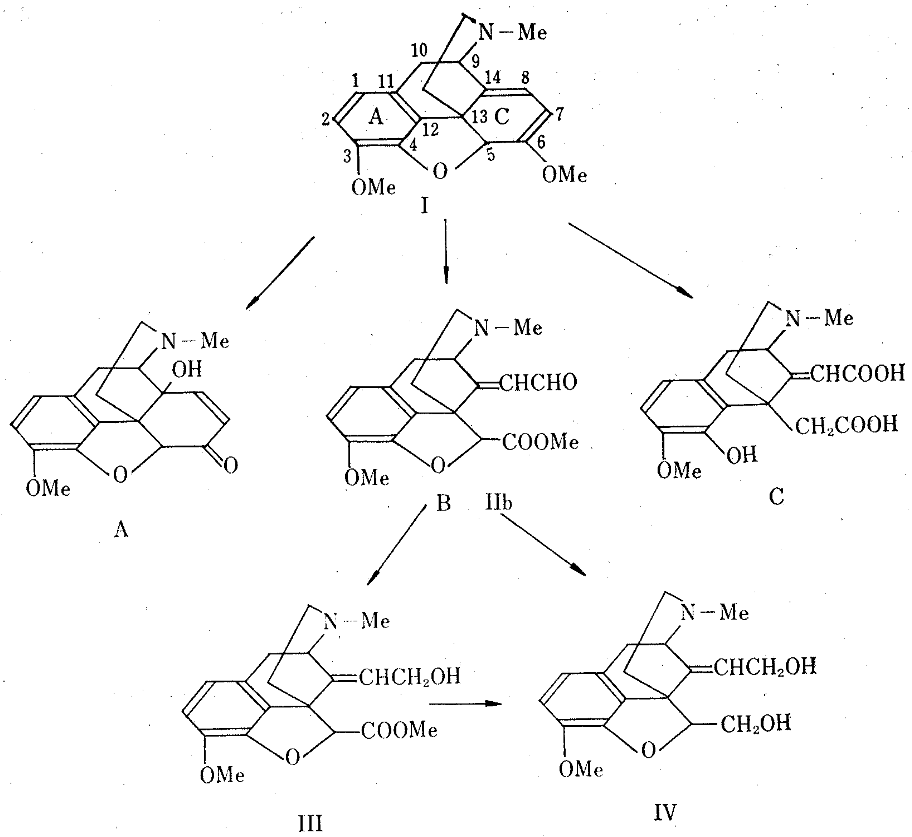


Chart 1.

compound also gave strongly positive reactions with diazotized sulfanilic acid reagent, ferric chloride test and Gibb's reagent. These are all characteristic reactions of the morphine alkaloids with a free phenolic hydroxyl group. Any other attempt for further structural elucidation was unsuccessful, but from its IR data, pKa values and its empirical formula, compound C might be described as shown in Chart 1.*[4]

Experimental

All melting points are uncorrected. The infrared spectra were measured with a Nippon Bunko IR-S infra code. The ultraviolet spectra measurements were performed with a Nippon Bunko Model ORS/UV-5 spectrophotometer. All NMR spectra were determined with a Varian A-60 recording spectrometer in deuteriochloroform with tetramethylsilane as an internal standard and the peak positions are given in τ-values. The microanalyses were carried out with a C. H. N. Coder MT-1 type. An ozonater used in this work is a Nippon Ozone Company Model O-1-2 and ozone concentrations were determined with a Nippon Ozone Company Model ozone meter.

Ozonolysis of Thebaine——A solution of 10 g. of purified thebaine in a mixture of 20 ml. of water and 20 ml. of 1*N* HCl was treated with ozone at a rate of 40 L./hr., at 0° for 3 hr. After flushing with dry oxygen, the reaction mixture was evaporated to dryness under reduced pressure. The oily residue was poured into 20 ml. of water, suspended with 3 g. of zinc powder. After the solution was kept at room temperature overnight, the reaction mixture was filtered to remove syrupy zinc powder. To this filtrate was added 20 ml. of 10% aq. Na_2CO_3 and the mixture was extracted with $CHCl_3$. The chloroform extract was purified by column chromatography on silica gel and separated into two fractions. From the first fraction was separated compound A after removal of the solvent, m.p. 279~281°(decomp.), recrystallized from EtOH. Yield 3%. *Anal.* Calcd. for $C_{18}H_{19}O_4N$: C, 68.99; H, 6.11; N, 4.47. Found : C, 68.84; H, 6.32; N, 4.95. $[\alpha]_D^{25.4}$ $-218°$(c=1.2, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1} : 3360 (OH), 1680 (C=O), 1640 (C=C). UV λ_{max}^{EtOH} 280 mμ (log ε 3.25). NMR ($CDCl_3$) τ : 7.56 (3H, singlet, N-C$\underline{H}_3$), 6.17 (3H, singlet, O-C$\underline{H}_3$), 5.32 (1H,

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*[4] K. W. Bentley describes the related structures of [XIX]~[XXX] in his book ("The Chemistry of the Morphine Alkaloids," p. 189~191 (1954), Clarendon Press, Oxford), but none of them is in good accordance with C in its melting point and its chemical formula.

singlet, $O\overset{|}{C}\underline{H}$–), 3.84 (1H, doublet, J=10 c.p.s., $\rangle C{=}\overset{|}{C}\underline{H}$), 3.35 (1H, doublet, J=10 c.p.s., $\underline{H}\overset{|}{C}{=}C\langle$), 3.33 (2H, overlapped singlet,[*5] aromatic H).

From the second fraction was separated compound B, m.p. 149~150° after recrystallization from MeOH. Yield 14%. *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.46; H, 6.16; N, 4.08. Found : C, 66.39; H, 6.15; N, 4.10. IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 1748 ($COOCH_3$), 1670 (CHO), 1630 (C=C). UV $\lambda_{\max}^{MeOH}$ 278 mμ (log ε 3.32). NMR ($CDCl_3$) τ : 7.54 (3H, singlet, $N{-}C\underline{H}_3$), 6.23 (3H, singlet, $COOC\underline{H}_3$), 6.13 (3H, singlet, $OC\underline{H}_3$), 5.00 (1H, singlet, $-O\overset{|}{C}\underline{H}-$), 4.04 (1H, doublet, J=7.0 c.p.s., $\rangle C{=}C\underline{H}-$), 3.28 (2H, overlapped singlet,[*5] aromatic $\underline{H}$), 0.00 (1H, doublet, J=7.0 c.p.s., $-C\underline{H}O$).

The Na_2CO_3–H_2O layer, with chloroform non-extracted, was neutralized with 1*N* HCl and water was removed under reduced pressure. The residue was extracted with 90% EtOH to give a crude compound C which was purified by recrystallization from water, m.p. 174~175°. Yield 34%. *Anal.* Calcd. for $C_{18}H_{21}O_6N \cdot H_2O$: C, 59.18; H, 6.33; N, 3.83. Found : C, 59.20; H, 5.80; N, 3.87. $[\alpha]_D^{25.4}$ +293.6°(c=0.55, H_2O). IR $\nu_{\max}^{CHCl_3}$ cm^{-1} : 3400 (OH), 1730 (COOH, broad), 1720 (COOH, shoulder), 1650 (–C=C). The NMR measurement was unsuccessfull on account of the absence of the suitable solvents.

Sodium Borohydride Reduction of Compound B——To a solution of 0.2 g. of Ⅱb in 20 ml. of MeOH was added 0.1 g. of $NaBH_4$ with stirring at room temperature. The reaction mixture was stirred at 20° for 5 hr., followed by careful decomposition of the excess hydride with 15 ml. of water and extracted with $CHCl_3$. The chloroform layer was evaporated *in vacuo* and the residue was recrystallized from MeOH to give colorless prisms of Ⅲ, m.p. 130~131°. Yield 92%. *Anal.* Calcd. for $C_{19}H_{23}O_5N$: C, 66.07; H, 6.71; N, 4.06. Found : C, 66.22; H, 6.90; N, 4.26. IR $\nu_{\max}^{KBr}$ cm^{-1} : 3380 (OH), 1748 (COOMe), 1630 (C=C). NMR ($CDCl_3$) τ : 7.58 (3H, singlet, $N{-}C\underline{H}_3$) 6.32 (3H, singlet, $COOC\underline{H}_3$), 6.13 (3H, singlet, $OC\underline{H}_3$), 4.98 (1H, singlet, $-O\overset{|}{C}\underline{H}$), 4.45 (1H, triplet,[*6] J=7.0 c.p.s., $\rangle C{=}C\underline{H}{-}CH_2OH$), 3.28 (2H, overlapped singlet,[*5] aromatic $\underline{H}$).

Lithium Aluminum Hydride Reduction of Compound B——To a solution of 0.5 g. of Ⅱb in 10 ml. of absolute ether was added 0.05 g. of $LiAlH_4$ with stirring at 5° and the mixture was stirred at 10° for 5 hr. The reaction mixture was added with 20 ml. of water and extracted with ether. The organic layer was evaporated *in vacuo* and the residue was recrystallized from MeOH to give Ⅳ as colorless prisms, m.p. 178~179°. Yield 90%. *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.12; H, 7.31; N, 4.41. Found : C, 67.84; H, 7.33; N, 4.51.

Lithium Aluminum Hydride Reduction of III——To a solution of 0.1 g. of Ⅲ in 10 ml. of absolute ether was added 0.01 g. of $LiAlH_4$ with stirring at 5° and the reaction mixture was stirred at 10° for 5 hr. This mixture was worked up as before. The crystals thereby separated out were collected by filtration and recrystallized from MeOH to give Ⅳ as colorless prisms, m.p. 178~179°, which showed no depression on admixture with Ⅳ by the preceding procedure. Yield 89%.

The authors are much indebted to the Research Laboratory of the Takeda Pharmaceutical Industries Co., Ltd. for a kind supply of some starting materials and the NMR measurements.

[*5] S. Okuda, *et al.* (This Bulletin, **12**, 104 (1964)) reported on the NMR behaviors of morphine alkaloids, in which the aromatic protons at C_1 and C_2 in ring A gave those of a AB type at about 3.40 τ, but on account of A and B being almost equivalent, the observed signal was often singlet, for which this expression was used.

[*6] It is to be noted here that a doublet at 4.04 τ in Ⅱb was changed into a triplet at 4.45 τ in Ⅲ by reduction. This is a good evidence that reduction has occurred as the following scheme :

$$\underset{\text{Ⅱb}}{\rangle{=}C\underline{H}CHO} \longrightarrow \underset{\text{Ⅲ}}{\rangle{=}C\underline{H}CH_2OH}$$