Summary

2-Ethyleneiminomethyl-4-nitroquinoline-N-oxide was prepared by the reaction of 2-chloromethylquinoline-N-oxide with potassium nitrate and sulfuric acid, followed by treatment with ethyleneimine. Nitration of 2-ethyleneiminomethylquinoline-N-oxide with potassium nitrate and sulfuric acid to 2-ethyleneiminomethyl-4-nitroquinoline-N-oxide was failed.

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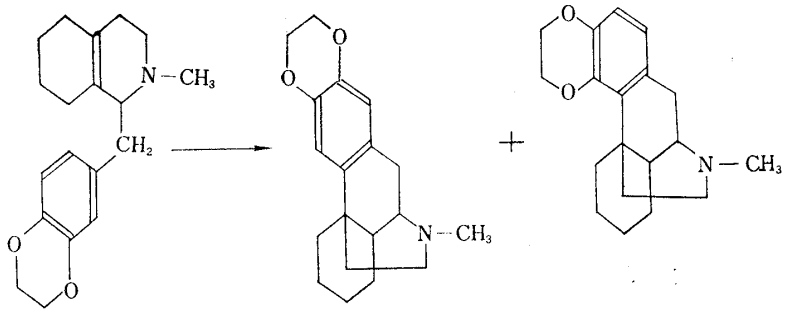
Masuko Akagawa, Mitsuo Sasamoto*1, and Masayuki Onda*2 : Synthesis in the Morphinan Group. VI.*3 Further Supports for the Structure of 2,3-Ethylenedioxy- and 3,4-Ethylenedioxy-N-methylmorphinan.

(*Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd.**1)

In this series, one of us (M. S.) reported synthesis of morphinan derivatives by the Grewe cyclization of 1-(3,4-ethylenedioxybenzyl)-2-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline (I) and separation of two isomers, from which phenanthrene derivatives obtained by the Hofmann degradations were identified with authentic samples to assign their structures (II and III).



I II III

Chart 1.

At that time, however, purities of the isomers were just confirmed by comparison of melting points of their derivatives and not checked by the tools of physical chemistry. Accordingly there has been remaining a slight doubt whether the recrystallization method was suitable to separate the isomers or not. We reinvestigated this problem by means of thin-layer chromatography (TLC), gas chromatography (GC) and nuclear magnetic resonance spectroscopy (NMR), and obtained new findings.

TLC——Rf-values were listed in Table I~III. II and III showed almost same Rf-values. On examining a mixture of II and III with the solvents which gave slightly

*1 Toda-machi, Kita-adachi-gun, Saitama-ken (赤川真寿子, 笹本光雄).

*2 Present addres : School of Pharmacy, Kitazato Memorial University, Shirogane Sanko-cho Shiba, Minato-ku, Tokyo (恩田政行).

*1 Part V. M. Sasamoto : This Bulletin, 8, 980 (1960).

different values, there was obtained only a single spot. This fact indicates that TLC is not suitable to identify II and III.

Table I.

	A	B	C	D	E
II	0.37	0.64	0.22	0.40	0.2
III	0.37	0.68	0.18	0.37	0.2

A: acetone, B: MeOH, C: $CHCl_3$, D: AcOEt, E: ether

Table II.

	F	G	H	I
II	0.49	0.38	0.15	0.27
III	0.49	0.36	0.13	0.25

F: $CHCl_3$-acetone=5:4
G: $CHCl_3$-AcOEt=5:4
H: $CHCl_3$-benzene=4:1
I: benzene-AcOEt=2:1

Table III.

	J	K	L	M
II	0.93	0.86	0.88	0.64
III	0.93	0.86	0.88	0.62

J: $CHCl_3$-acetone-$NHEt_2$=5:4:1
K: $CHCl_3$-AcOEt-$NHEt_2$=5:4:1
L: $CHCl_3$-benzene-$NHEt_2$=80:20:1
M: $CHCl_3$-$NHEt_2$=99:1

GC——As shown in Fig. 1, II and III exhibited a single peak, respectively, with retention times of 8.4 min. and 6.2 min., indicating that the two isomers are purely separated from each other.

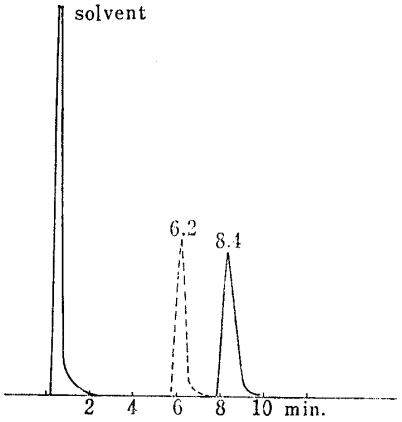


Fig. 1. Gas Chromatograms of II and III
——— II ----- III

NMR——The NMR spectra of II and III are shown in Fig. 2 and 3. The main differences between the spectra of II and III are the signals appearing at near 3.6 τ corresponding to two protons and near 6.9 τ corresponding to one proton. Firstly, aromatic protons in II exhibited two singlets at 3.53 τ and 3.67 τ due to the nonequivalent para-protons and, unfortunately, aromatic protons in III, whose AB-type signals were expected, overlapped in a singlet at 3.64 τ. As reported by Okuda, *et al.*,[1] there are many cases in which aromatic *ortho*-protons show a singlet instead of a pair of AB-doublets. The compound (III) probably belongs to the same category.

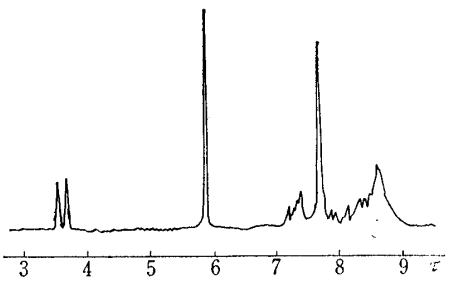


Fig. 2. Nuclear Magnetic Resonance Spectrum of II

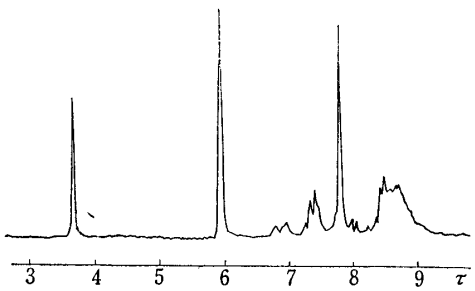


Fig. 3. Nuclear Magnetic Resonance Spectrum of III

Secondly, there was a broad doublet corresponding to one proton at 6.85 τ (J=10.5 c.p.s.) in III and no signal in this region in II. This discrepancy should be undoubtedly due to the difference between the effects of the ethylenedioxy group on a ring proton in II and III. On examining Dreiding models of II and III (Fig. 4), C_5-H_α in III is stereochemically close to the ethylenedioxy group which gives the anisotropic effect.

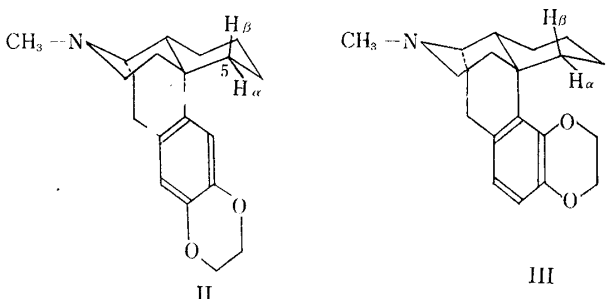


Fig. 4.

1) S. Okuda, S. Yamaguchi, Y. Kawazoe, K. Tsuda: This Bulletin, **12**, 104 (1964).

Accordingly the signal at 6.85 τ in III corresponds to C_5-H_α which shifts down-field by spatial deshielding effect of the ether group.[2] The C_5-H_α in II is too far from the ethylenedioxy group to be affected magnetically and it is very reasonable that no signal is shown in this area.

Experimental

Samples——II and III were synthesized as reported in the preceding paper[3] of this series. II; syrup. III; m.p. 122~124°.

TLC——TLC was carried out on Alumina G (Merck) plates (0.25 mm.) at 22~24°. The plates were activated at 105~110° for 30 min. Dragendorff reagent was employed for coloration.

GC——A Shimadzu Seisakusho instrument of Model GC-1B (hydrogen flame detector, dual column. differential flame) was employed in this study. A stainless steel column of 150 cm. (U-shaped, 75 cm. × 2) × 6 mm. i. d. was packed with 1.5% SE-30 (G. E. methyl silicone gum) on Chromosorb W (60~80 meshes, acid washed and silanized). The operating conditions were as follows : sensitivity 1000, range 3.2, column temp. 198°, detector temp. 230°, sample heater temp. 280°, supply of carrier gas N_2 75 ml./min. Samples were 2~3 μl. of 0.5% solutions of the compounds in acetone.

NMR——The spectra were measured on a JNM C-60 spectromenter (Japan Electron Optics Laboratory Co., Ltd.), operating at 60 Mc. with high resolution. The compounds were examined in a 10~15% solution in carbon tetrachloride. The chemical shifts were given in τ values and tetramethylsilane was used as an internal standard.

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Summary

The morphinan derivatives (II and III) were examined by means of thin-layer chromatography, gas chromatography and nuclear magnetic resonance spectroscopy. Their purities were certainly confirmed by gas chromatography and nuclear magnetic resonance spectroscopy, but thin-layer chromatography was not suitable for this purpose.

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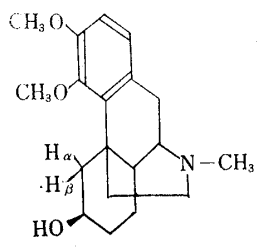
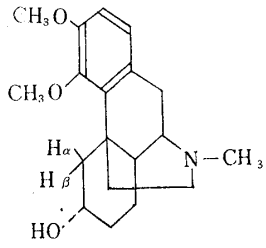
2) According to personal communication from Dr. S. Okuda, University of Tokyo, the same conclusion was obtained in the following situation :



C_5 —Hα: 6.9τ (J_{gem} ~14c.p.s.)



C_5 —Hα: 6.8τ (J_{gem} ~14c.p.s.)

3) M. Sasamoto : This Bulletin, 8, 324 (1960).