[Chem. Pharm. Bull. 12 (1) 104 ~ 112]

UDC 547.943 : 615.783.19

16. Shigenobu Okuda,*1 Sadao Yamaguchi,*2 Yutaka Kawazoe,*3 and Kyosuke Tsuda*1 : Studies on Morphine Alkaloids. I. Nuclear Magnetic Resonance Spectral Studies on Morphine Alkaloids. (I).

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Extensive chemical and physical studies of morphine alkaloids have been carried out.[1] However nuclear magnetic resonance, one of the most powerful tools for structural determination problems, has not been applied to stereochemical assignments of these alkaloids. The present study of nuclear magnetic resonance spectra of the various (−)-morphine type alkaloids was initiated with the hope that the spectra obtained would assist in the structural elucidation of unknown derivatives of these alkaloids.

Experimental

All spectra were obtained by a Varian Associates DP 60 NMR spectrometer, operating at 60 Mc.p.s. with high resolution. The compounds were examined in a 2~10% solution in $CHCl_3$. The chemical shifts are given in τ values calibrated by cyclohexane as an internal standard ($\tau_{cyclohexane}=8.564$).

The compounds studied here were synthesized from (−)-thebaine and (−)-codeine according to the methods described in the literature[1,2] and their purities were carefully checked by their physical constants.

Results and Discussion

1. Spectral Assignments and General Features

Many distinct absorptions could be found in the spectra of morphine alkaloids.

In general the C_3-methoxy and N-methyl groups exhibited sharp singlet signals at about 6.15 and 7.55 τ, respectively. The aromatic protons at C_1 and C_2 gave those of AB type at about 3.40 τ in which A and B were almost equivalent.

The $C_{5\beta}$-proton of 6-keto compounds, XV to XX, showed a singlet and that of XXI and XXII, possessing two protons at C_6, a diffuse triplet. In the case of a 6-monosubstituted compound, such as I, II and IV to XII, the $C_{5\beta}$-proton signal appeared as a doublet whose $J_{5,6}$ yielded instructive information about the ring C conformation (cf. section 2).

The ethylenic protons in ring C gave various absorption patterns depending on their position and enviroment as follows:

a) The C_7- and C_8-protons of 6α-monosubstituted Δ^7-compounds, I, II, and IV, whose C_6-protons were β, exhibited absorption pattern similar to that of AB type because of the small couplings with the protons at $C_{6\beta}$ and $C_{14\beta}$.

b) The C_7- and C_8-protons of Δ^7-6-keto derivatives, XVI and XVII, gave AB type quartets when the $C_{14\beta}$-proton was absent. When it was present, the signals of XV were an ABX type octet.

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1) K. W. Bentley, "The Chemistry of the Morphine Alkaloids" Oxford, The Clarendon Press, 1954; H. L. Holmes and G. Stork, "The Morphine Alkaloids" in "The Alkaloids" edited by R. H. Manske and H. L. Holmes, Academic Press, Vol. 2, p. 1 and p. 162 (1952), Vol. 6, p. 219 (1960); the literature sited in these monographs.
2) S. Okuda, K. Tsuda, S. Yamaguchi : J. Org. Chem., **27**, 4121 (1962).

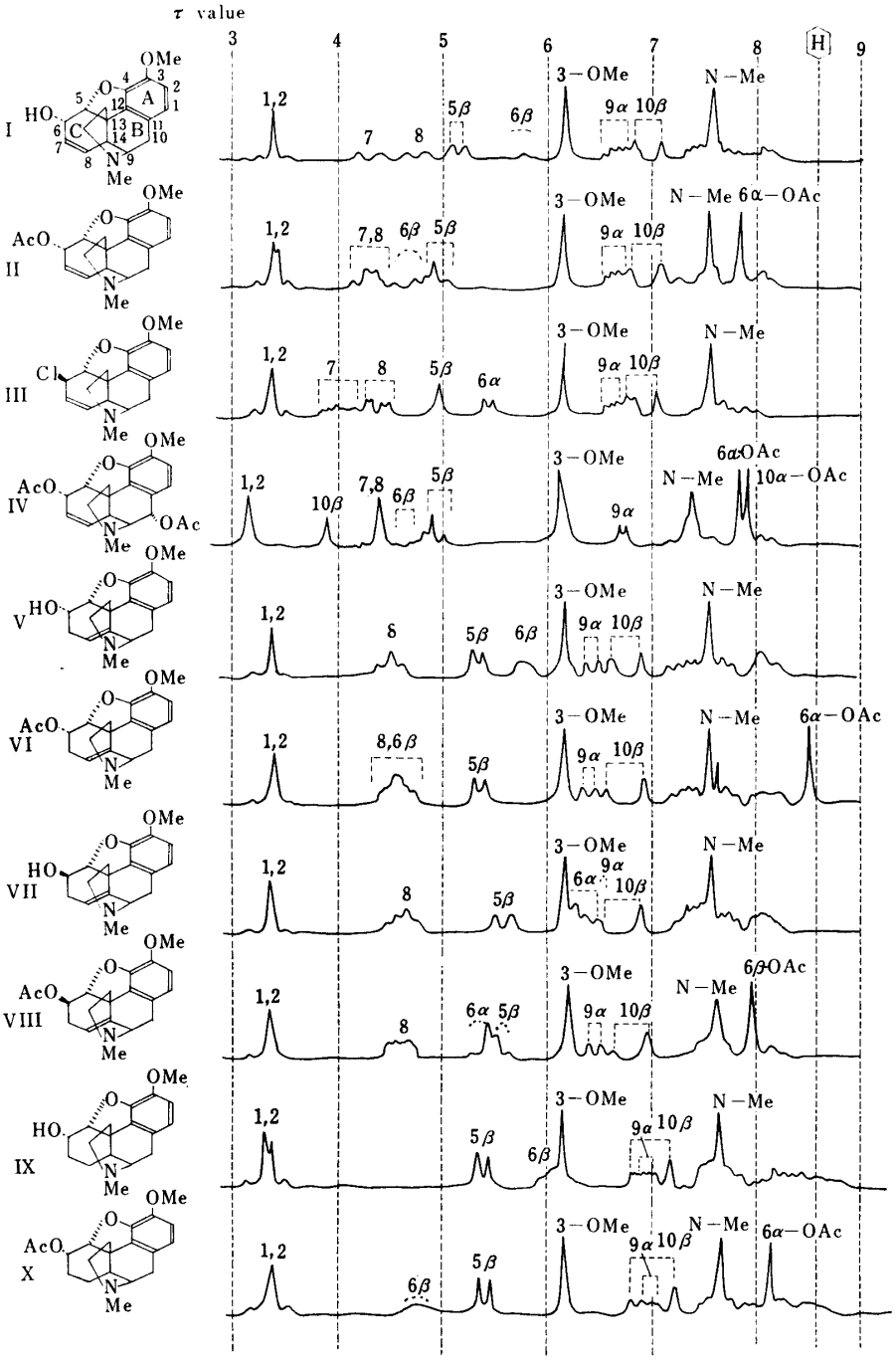


Fig. 1 (a).

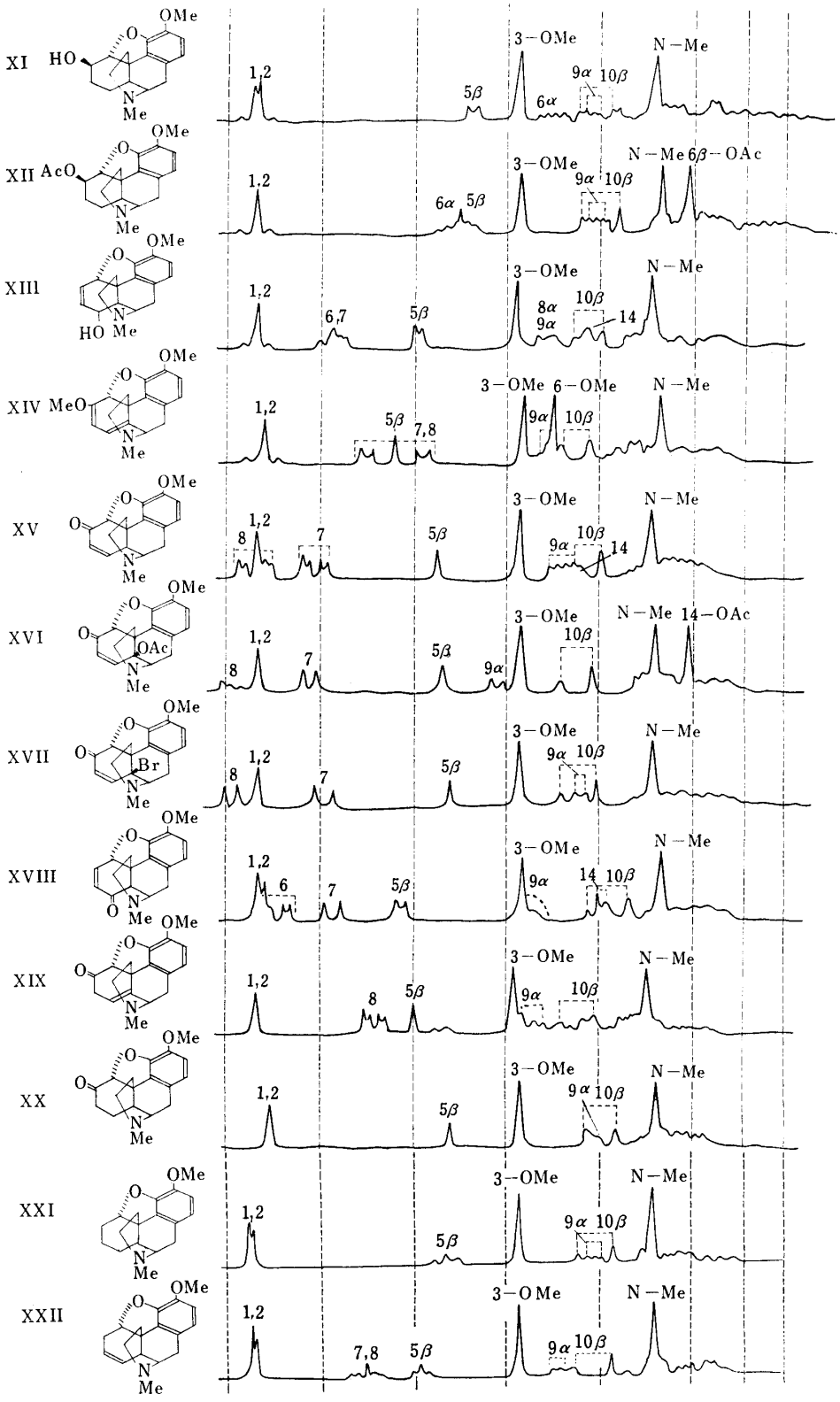


Fig. 1 (b).

TABLE I.

	1,2-H[a)]	3-OMe	5β-H	6-H	7-H	8-H	9α-H	10β-H	N-Me	etc.
Codeine (I)	3.40	6.16	5.15 $J_{6\beta}$-6.4	5.84(β)	4.29 J-9.6	4.74 J-9.6	6.63 J_{14}-3.2 $J_{10\alpha}$-5.6	6.92 $J_{10\alpha}$-18.4	7.56	
Acetylcodeine (II)	3.33	6.15	4.98 $J_{6\beta}$-6.7	ca. 4.9 (β)	4.38 J-9.9	4.64 J-9.9	6.64 J_{14}-3.3 $J_{10\alpha}$-5.7	6.92 $J_{10\alpha}$-18.6	7.57	6α-OAc 7.85
α-Chlorocodide (III)	3.39	6.16	4.96	5.48(α) J_7-5.7	4.02 J_8-9.7 $J_{6\alpha}$-5.7 J_{14}-2.4	4.38 J_7-9.7 J_{14}-1.6	6.63 J_{14}-3.3 $J_{10\alpha}$-5.6	6.88 $J_{10\alpha}$-18.0	7.53	
10α-Acetoxy-acetylcodeine (IV)	3.29	6.14	4.95 $J_{6\beta}$-6.7	ca. 4.8 (β)	4.41(eq.)		6.71 J_{14}-3.1	3.92	7.39	6α-OAc 7.85 10α-OAc 7.92
Neopine (V)	3.39	6.14	5.36 $J_{6\beta}$-4.6	5.78(β)		4.52	6.43 $J_{10\alpha}$-6.1	6.73 $J_{10\alpha}$-17.9	7.55	
Acetylneopine (VI)	3.41	6.15	5.34 $J_{6\beta}$-4.5	ca. 4.6 (β)		4.56	6.41 $J_{10\alpha}$-6.0	6.72 $J_{10\alpha}$-18.1	7.56	6α-OAc 8.51
Isoneopine (VII)	3.37	6.16	5.54 $J_{6\alpha}$-7.4	ca. 6.3 (α)		4.60	6.38 $J_{10\alpha}$-6.5	6.71 $J_{10\alpha}$-17.7	7.53	
Acetylisoneo-pine (VIII)	3.38	6.17	5.42 $J_{6\alpha}$-7.5	ca. 5.4 (α)		4.59	6.46 $J_{10\alpha}$-6.5	6.78 $J_{10\alpha}$-17.8	7.58	6β-OAc 7.90
Dihydrocode-ine (IX)	3.32	6.12	5.42 $J_{6\beta}$-5.1	ca. 6.0 (β)			6.95 J_{14}-2.6 $J_{10\alpha}$-5.8	7.01 $J_{10\alpha}$-18.1	7.61	
Acetyldihydro-codeine (X)	3.39	6.14	5.41 $J_{6\beta}$-5.7	ca. 4.8 (β)			6.90 J_{14}-2.5 $J_{10\alpha}$-5.6	6.96 $J_{10\alpha}$-18.2	7.61	6α-OAc 8.19
Dihydroiso-codeine (XI)	3.34	6.14	5.66 $J_{6\alpha}$-6.0	ca. 6.5 (α)			6.92 J_{14}-2.4 $J_{10\alpha}$-5.6	7.00 $J_{10\alpha}$-18.1	7.57	
Acetyldihydro-isocodeine (XII)	3.37	6.17	5.57 $J_{6\alpha}$-6.3	ca. 5.5 (α)			6.93 J_{14}-2.5 $J_{10\alpha}$-5.6	7.00 $J_{10\alpha}$-18.0	7.61	6β-OAc 7.93
Pseudocodeine (XIII)	3.37	6.17	5.09	4.18(eq.)		ca. 6.4 (α)	6.52 J-?	6.91 $J_{10\alpha}$-18.0	7.62	14β-H 6.84
Thebaine (XIV)	3.40	6.17	4.75		5.02 J_8-6.6	4.49 J_7-6.6	ca. 6.4 J-?	6.67 $J_{10\alpha}$-17.7	7.54	6-OMe 6.41
Codeinone (XV)	3.35	6.15	5.31		3.94 J_{14}-2.3 J_8-10.4	3.31 J_{14}-1.7 J_7-10.4	6.57 J_{14}-3.3 $J_{10\alpha}$-5.4	6.85 $J_{10\alpha}$-18.0	7.54	14β-H ca. 6.8
14β-Acetoxy-codeinone (XVI)	3.39	6.17	5.27		3.93 J_8-10.5	2.93 J-?	5.94 $J_{10\alpha}$-5.7	6.70 $J_{10\alpha}$-18.5	7.62	14-OAc 7.92
14β-Bromo-codeinone (XVII)	3.36	6.13	5.41		4.05 J_8-9.3	3.08 J_7-9.3	6.74 $J_{10\alpha}$-5.4	6.74 $J_{10\alpha}$-18.1	7.52	
Pseudo-codeinone (XVIII)	3.37	6.18	4.83 J_6-3.1	3.50 $J_{5\beta}$-3.1 J_7-10.5	4.06 J_6-10.0		ca. 6.2	7.02 $J_{10\alpha}$-17.9	7.57	14β-H 7.00 J_9-3.1
Neopinone (XIX)	3.31	6.11	5.00			4.56 $J_{7\beta}$-1.63 $J_{7\alpha}$-4.08	6.35 $J_{10\alpha}$-6.5	6.72 $J_{10\alpha}$-18.0	7.51	
Dihydro-codeinone (XX)	3.46	6.15	5.42				6.90 J-?	7.00 $J_{10\alpha}$-18.0	7.60	
Dihydrodeo-xycodeine D (XXI)	3.39	6.20	5.49 $J_{6\alpha}$-8.2 $J_{6\beta}$-7.2				6.90 J-?	7.03 $J_{10\alpha}$-17.5	7.65	
Deoxycodeine E (XXII)	3.43	6.13	5.16		ca. 4.3～5.0		6.53 J-?	6.96 $J_{10\alpha}$-18.1	7.55	

a) The center between the chemical shifts of C_1 and C_2 protons.

c) The C_7- and C_8-protons of a $\Delta^{6,8}$-compound such as XIV appeared as an AB type quartet.

d) The C_8-proton of the Δ^8-series, V to VIII and XIX, exhibited an ABX type quartet.

e) the octet signal of the C_7-proton of III, whose C_6-proton is α, could be explained by its coupling with the $C_{6\alpha}$-, C_8- and $C_{14\beta}$-protons, and the quartet of the C_8-proton by its coupling with the C_7- and $C_{14\beta}$-protons.

f) The absorption of the C_6-proton in XVII appeared as a quartet coupled with the protons at $C_{5\beta}$ and C_7, and that of C_7-proton as a doublet coupled with the C_6-proton.

The $C_{6\beta}$-proton, alpha to hydroxyl and acetoxyl of I, II, and IV to XII, was found to have a weak and diffuse signal because of the coupling with at least two other protons. On the other hand, the $C_{6\alpha}$-proton alpha to the chloro of III, showed a doublet because the coupling between $C_{6\alpha}$- and C_7-proton was observed but that between $C_{5\beta}$-and $C_{6\alpha}$-proton was not. Accordingly the signal of the $C_{5\beta}$-proton of this compound was a singlet and these results tended to indicate that the dihedral angle between $C_{5\beta}$- and $C_{6\alpha}$-proton was about 90° and that the conformation of ring C should be a half chair (cf. section 2).

The absorptions of $C_{9\alpha}$- and $C_{10\beta}$-protons were also discernible in many cases and the details of their assignment will be discussed in section 4.

The $C_{14\beta}$-proton signal was generally difficult to distinguish because of its overlapping with other signals such as those of N-methyl, N-methylene and probably of $C_{10\alpha}$-proton. However in the case of XIII, XV, and XVIII, the signals in question were shifted down-field by the electronic and spatial interaction of the double bond and substituent in ring C, and thus were distinguishable.

The absorption of the other protons, *i.e.* those at $C_{10\alpha}$, C_{15}, and C_{16}, could not be assigned because of their complicated couplings and overlappings.

The nuclear magnetic resonance spectra measured were presented in Fig. 1, and in Table I the chemical shifts which were directly obtained from the peak positions without any analytical treatment.*[4]

2. The Conformational Analysis of Ring C

The crystallographic analysis of morphine hydrobromide[3] has shown its three dimensional structure to be I, as illustrated in Fig. 2, in which ring B is rigidly held in a strongly distorted form and ring C and D take a half boat and a chair form respectively. The conformations of ring B and D in this type skeleton, which possesses a C_4-C_5 ether bridge, are generally not changeable. However, the conformation of ring C is dependent on whether a double bond is present or not and its position.

Ring C in the Δ^7-series, such as I to IV, can only take a half boat form in which the $C_{6\alpha}$ substituent is in a bowsprit orientation. On the other hand, those of the saturated compounds, IX to XII, XX, and XXI, can exist either in a chair or boat form and their chemical behavior indicated that the preferential conformation of ring C is the former in which the $C_{6\alpha}$ substituent is axial (cf. Fig. 3).[4] Furthermore ring C of the Δ^8-series, V to VIII, can also have either a half-chair or half-boat form (cf. Fig. 4), but the preferential conformation of ring C has not been elucidated.

Accordingly it was of interest to determine whether the theoretical relationship between the coupling constants and the corresponding dihedral angles can be safely applied for the conformational analysis of ring C in the various morphine type alkaloids. For this reason the observed coupling constants between $C_{5\beta}$- and $C_{6\alpha}$- or $C_{6\beta}$-proton were compared with the expected values which were obtained from the corresponding dihedral angles measured with Dreiding models and the Karplus's theoretical curve.*[5,6]

*[4] Therefore in some cases the values thus obtained are little different from the true ones.

3) M. Mackay, D.C. Hodgkin : J. Chem. Soc., **1955**, 3261.

4) D. Elad, D. Ginsburg : J. Am. Chem. Soc., **78**, 3691 (1956).

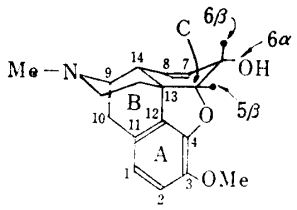
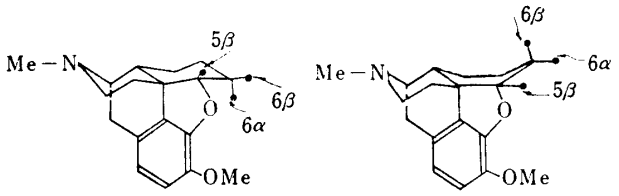


Fig. 2.

Table II.

	(Dihedral angle) Expected J	Observed J
(5β-6β) $J_{5\beta-6\beta}$	(25～30) 6.0～6.7	(I) 6.4 (II) 6.7
(5β-6α) $J_{5\beta-6\alpha}$	(90～95) 0～0.1	(III) 0

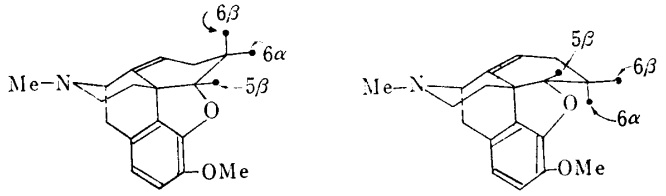


ring C: chair form ring C: boat form

Fig. 3.

Table III.

	(Dihedral angle) Expected J		Observed J
	Chair form	Boat from	
(5β-6β) $J_{5\beta-6\beta}$	(30～35) 5.3～6.0	(45～50) 3.5～4.1	(IX) 5.1 (X) 5.7
(5β-6α) $J_{5\beta-6\alpha}$	(150～155) 6.9～7.5	(70～75) 0.2～0.5	(XI) 6.0 (XII) 6.3



ring C: half boat ring C: half chair

Fig. 4.

Table IV.

	(Dihedral angle) Expected J		Observed J
	Half boat	Half chair	
(5β-6β) $J_{5\beta-6\beta}$	(75～80) 0.3～0.1	(40～45) 4～5	(V) 4.6 (VI) 4.5
(5β-6α) $J_{5\beta-6\alpha}$	(40～45) 4.1～5.0	(160～165) 8.0～8.5	(VII) 7.4 (VIII) 7.5

*5 Recently several workers suggested that the coefficient value in Karplus's equation should be modified according to the nature of the substituents on $-\overset{H}{\underset{|}{C}}-\overset{H}{\underset{|}{C}}-$ (K. Tori, T. Tomita, H. Itazaki, M. Narisada, W. Nagata: This Bulletin, **11**, 956 (1963); the literature cited therein). However Karplus's curve was used in the present study because this seemed to be suitable for a qualitative investigation.

5) N. Karplus: J. Chem. Phys., **30**, 11 (1959).

As shown in Table II and III, the observed $J_{5\beta,6\alpha}$ or $J_{5\beta,6\beta}$ of Δ^7-derivatives were in comparatively good agreement with the expected ones. Those of the saturated series also supported the chemical proof of the preferential ring C conformation. In the case of Δ^8-compounds, the results given in Table IV clearly showed that ring C in these compounds took a half chair form.

3. The Relationship between the Chemical Shift of C_6-Acetoxyl Methyl and the Conformation of Ring C

As seen in Table V, the acetoxyl methyl signals of II, IV, VIII, and XII appeared at 7.85~7.97 τ and on the other hand those of VI and X at 8.19~8.51 τ. These differences are mainly*[6] due to the geometrical relationship between the acetoxyl methyl and the aromatic ring A, which gives the diamagnetic anisotropy effect to the proton located near the perpendicular axis of the benzene ring.

Table V.

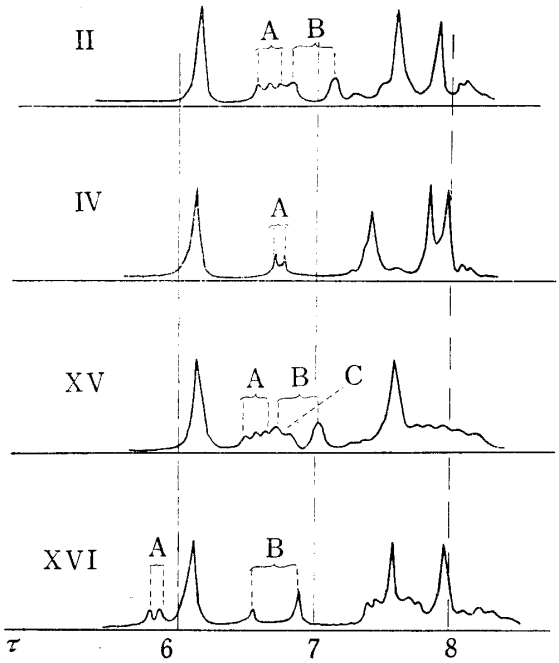
II	IV	VI	VIII	X	XII
6α, 7.85	6α, 7.85	6α, 8.51	6β, 7.90	6α, 8.19	6β, 7.93

The examination of the conformation of these compounds with Dreiding models and the nuclear megnetic resonance spectral data resulted in the same conclusions concerning the ring C conformation as those obtained in section 2:

a) The conformation of ring C in Δ^7-series, II and IV, is a half-boat.
b) That of Δ^8-series, VI and VIII, is a half-chair.
c) That of the saturated series, X and XII, is a chair.

4. The Assignment of $C_{9\alpha}$- and $C_{10\beta}$-Protons

Morphine type compounds generally showed characteristic absorption in the region 6.5~7.3 τ, which corresponded two or three protons, as illustrated in Fig. 5. In the



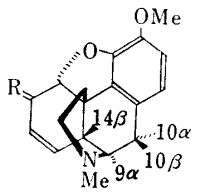


Fig. 5.

*[6] The double bond in ring C and the C_4-C_5 ether bridge might also affect this acetoxyl methyl signal, but these influences would be small.

case of IV and XVI, the absorption patterns in this region were much simpler than those of the other compounds. A comparison of the spectra of II and IV showed that the introduction of an acetoxyl group at $C_{10\alpha}$ gave rise to the following changes :
a) Although II exhibited signals corresponding to two protons (A and B in Fig. 5) in this region, IV exhibited only a doublet due to one proton (A).
b) In IV, a new singlet due to one proton appeared at 3.92 τ (cf. Fig. 1).

Trerefore the signal at 3.92 τ of IV would correspond to $C_{10\beta}$-proton, whose signal should be shifted down-field by the introduction of the $C_{10\alpha}$-acetoxyl. The coupling between $C_{9\alpha}$- and $C_{10\beta}$-proton was not observed because the corresponding dihedral angle was about 90°. The signal B of this compound was due to the $C_{9\alpha}$-proton, whose $J_{9\alpha,14\beta}$ was 3.1 c.p.s.

Furthermore XV showed signals corresponding to three protons (A, B, and C*[7]) in the above mentioned region whereas XVI showed a doublet due to only a single proton (B). In the latter case, a new doublet due to one proton (A) appeared at 5.94 τ. Since the $C_{14\beta}$-acetoxyl was expected to cause the signal of $C_{9\alpha}$-proton to exhibit a greater down-field shift as compared to that of the $C_{10\beta}$-proton, the signal B (6,70 τ, $J_{9\alpha,10\beta}$:0, $J_{10\alpha,10\beta}$: 18.5 c.p.s.) of XVI should correspound to the $C_{10\beta}$-proton and the signal A (5.94 τ, $J_{9\alpha,10\alpha}$: 5.7 c.p.s.) to the $C_{9\alpha}$-proton.

Therefore it was expected that the signals of $C_{9\alpha}$- and $C_{10\beta}$-protons*[8] appeared in the region 6.5~7.3 τ and $J_{9\alpha,10\alpha}$, $J_{9\alpha,10\beta}$, $J_{9\alpha,14\beta}$, and $J_{10\alpha,10\beta}$ were respectively about 5, 0, 3, and 18 c.p.s. The chemical shifts of the $C_{9\alpha}$- and $C_{10\beta}$-protons, which were assigned on the basis of the above discussion, are given in Table I. This data suggested new proposals about the magnetic anisotropy of the double bond and the cyclic tertiary amine nitrogen,[6] the details of which will be discussed in a series of papers on the nuclear magnetic resonance spectral studies of morphine alkaloids.

Conclusion

It was concluded that the observed value of $J_{5\beta,6\alpha}$ or $J_{5\beta,6\beta}$ and the chemical shifts of C_6-acetoxyl methyl could be utilized for the conformational analysis of ring C in this type of compounds. Consequently the preferential conformation of ring C in Δ^8-series, V to VIII, was shown to be a half-chair.

The authors are indebted to Drs. O. Yamamoto and T. Suzuki of the Government Chemical Industrial Research Institute of Tokyo for making a NMR spectrometer available for the present work. They are also grateful to Dr. I. Iwai and Mr. I. Seki of Sankyo Co. Ltd. for the starting material.

Summary

The nuclear magnetic resonance spectra of twenty two morphine type derivatives were measured and their characteristic signals of the aromatic protons, N-methyl, acetoxylmethyl, the ethylenic protons in ring C, the protons alpha to hydroxyl, acetoxyl and C_4-C_5 ether bridge, and those of $C_{9\alpha}$, $C_{10\beta}$, and $C_{14\beta}$ were assigned.

The observed values of $J_{5\beta,6\alpha}$ or $J_{5\beta,6\beta}$ and the chemical shifts of C_6-acetoxylmethyl yielded information about the ring C conformation.

(Received September 6, 1963)

*[7] This signal could be assigned to that of $C_{14\beta}$-proton from the date examined here.
*[8] Because the $C_{10\beta}$-proton was strongly affected by the magnetic anisotropy of cyclic tertiary amine nitrogen, this resonated at much lower field than was expected.
6) S. Yamaguchi, S. Okuda, N. Nakagawa : This Bulletin, **11**, 1465 (1963).

〔Added after submitting paper〕 This paper was read at the 82th Annual Meeting of Pharmaceutical Society of Japan (Shizuoka : Nov. 3, 1962. cf. the abstract of the 82th Annual Meeting of Pharmaceutical Society of Japan, p. 96～102).

After submission of this paper, the report of the nuclear magnetic resonance spectra of morphine type alkaloids (T. Rüll : Bull. Soc. chim. France, **1963** (3), 586.) was seen. In this report the spectra of eleven compounds, including I, V, IX, XI, XIV, XV, XVII, XIX, and XX, were measured and the C ring conformations of these compounds were discussed.

〔Chem. Pharm. Bull. 12 (1) 112～118〕 UDC 547.655.1.07

17. Hiromu Mori,*1 Vipichandra S. Gandhi,*2 and Erwin Schwenk : Mannich Compounds of 2-Naphthol Derivatives.[1]

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The introduction by Mannich reactions[2] of alkylating grouping like bis-(2-chloroethyl)aminomethyl- or the aziridinomethyl group into estrone occurred exclusively in the 2-position of aromatic ring, even when a large excess of reagents over the theoretically necessary was used. Substitution in 4-position could be enforced only when the 2-position was blocked by a methyl group. The results confirmed observations made earlier by Patton[3] who found that estrone or estradiol would react in the Mannich reaction only to give 2-aminomethyl derivatives while from equilenine exclusively 4-substituted substances were obtained. Because of the formal similarity of these aromatic steroids with 5,6,7,8-tetrahydro-2-naphthol and 2-naphthol respectively a study of the Mannich reaction with these two substances and some of their derivatives were undertaken.

It is known from a paper by Shriner, *et, al.*[4] that 2-naphthol (I) itself reacts with formaldehyde and morpholine exclusively in the 1-position giving 1-(morpholinomethyl)-2-naphthol (II). When, however, 5,6,7,8-tetrahydro-2-naphthol (XVI) was submitted to the same reaction only 3-(morpholinomethyl)-5,6,7,8-tetrahydro-2-naphthol (XV) was isolated, in agreement with Cohen, *et al.*[5] who condenced XVI with formaldehyde and piperidine and obtained 3-(piperidinomethyl)-5,6,7,8-tetrahydro-2-naphthol. It was now found that it is possible to prepare the isomer (XI) of compound (II) by an indirect route. From 2-hydroxy-3-naphthoic acid (VI) the acid chloride was obtained with thionyl chloride and then reacted with morpholine. The carbonyl group in the morpholide thus prepared was easily reduced as in other amides[6] with lithium aluminum hydride to a methylene group and 3-(morpholinomethyl)-2-naphthol (XI) isomeric to the Mannich compound from 2-naphthol was obtained. A similar sequence of reactions carried out with 3-hydroxy-

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1) This work was supported by Grant No. 4550 of the U.S. Public Health Service, an Institutional Grant No. EIN-56 of the American Cancer Society and a Grant from the Massachusetts Division of the American Cancer Society.

2) V.S. Gandhi, E. Schwenk : to be published.
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