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Utilization of Protopine and Related Alkaloids. V.[1] The Adduct of Photoproduct of Anhydromethylberberine with Dimethyl Acetylenedicarboxylate

MASAYUKI ONDA, KYOKO YONEZAWA, KAORU ABE,[2a)]
HIROSHI TOYAMA, and TERUO SUZUKI[2b)]

School of Pharmacy, Kitasato University[2a)] *and Japan Electron Optics Laboratory Co., Ltd.*[2b)]

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The adduct of photoproduct of anhydromethylberberine with dimethyl acetylenedicarboxylate has been investigated by means of the nuclear magnetic resonance spectroscopyand the nuclear Overhauser effect measurements to establish the structure, in which the B/C ring juncture is *cis* and the conformation of B ring is a flattened boat form. Theselective reduction of adduct with lithium aluminum hydride and the reduction of adduct with hydrazine in the presence of oxygen are studied.

In a previous paper[1] we described anhydroprotopine (Ia) and anhydromethylberberine (Ib) photocyclized to yield 5,6,11,12-tetrahydrosanguinarine (IIa) and 5,6,11,12-tetrahydrochelerythrine (IIb), respectively. If this photocyclization can be regarded as the electrocyclic reaction of hexatriene, the primary photoproduct must be 5,6,10b,11-tetrahydro-compound (III) which immediately rearranges to II. An adduct, $C_{27}H_{27}O_8N$, which was obtained on irradiation of Ib in the presence of dimethyl acetylenedicarboxylate, was found to be 4b, 12-dicarbomethoxyetheno-compound (IV) by means of the infrared (IR), the nuclear magnetic resonance (NMR) and the mass spectroscopy, while the irradiation of IIb in the presence of dimethyl acetylenedicarboxylate afforded no adduct. These facts support the above deduc-

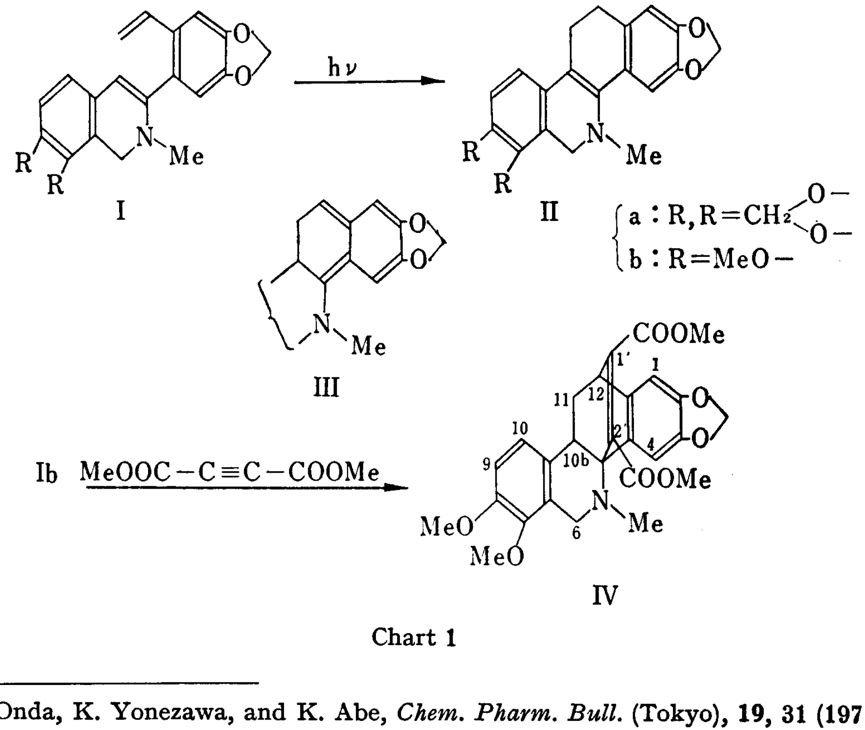

Chart 1

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[1] Part IV: M. Onda, K. Yonezawa, and K. Abe, *Chem. Pharm. Bull.* (Tokyo), **19**, 31 (1971).

[2] Location: *a) Minato-ku, Tokyo; b) Akishimashi, Tokyo.*

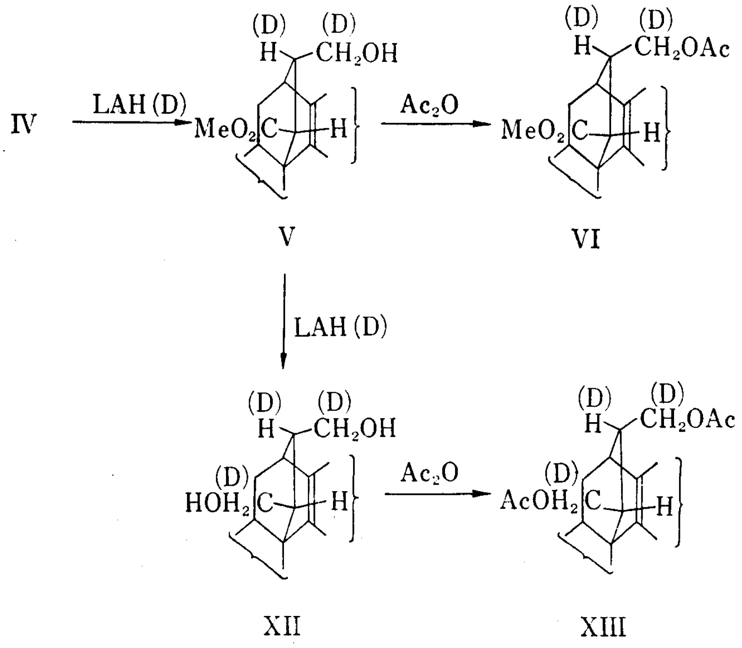

Chart 2

tion to be correct. This paper is concerned with the structures of the adduct (IV) and its derivatives, and also some reactions of IV.

IV was reduced with lithium alminum hydride (LAH) to yield the compound(V), mp 203—204°, $C_{26}H_{29}O_7N$. Its IR spectrum shows the absorption bands at 3500 cm^{-1} corresponding to OH and at 1735 cm^{-1} corresponding to COOMe. V afforded the acetate (VI), mp 181—182°, $C_{28}H_{31}O_8N$. Also, the compound, mp 202—204°, which was derived from IV by the reduction with lithium aluminum deuteride (LAD), was shown to be V-d_3 by the mass spectroscopy. V-d_3 afforded the acetate (VI-d_3), mp 180—182°. These facts indicate that the double bond and one carbomethoxyl group in IV were reduced with LAH (D).

Recently, the investigations³⁾ on the relationship between the nuclear Overhauser effect (NOE) and the internuclear distance for the protons in question have been reported. As shown in Fig. 1, when V-d_3 was irradiated at 5.26 τ (the signal attributed to C_6-H_A) an increase in area of 18% was observed for the signal at 2.88 τ corresponding to C_4-H. From the investigation of Dreiding model, the structures (VII and VIII), in which the B/C ring juncture is *trans*, exhibit that C_4-H is too far away from C_6-H_A to interact mutually. The structure (IX), in which the B/C ring juncture is *cis* and the conformation of the B ring is the half-chair form, seems to be able to explain the existence of the NOE between C_4-H and C_6-H_A.

Now, the IR spectrum of V in a dilute carbontetrachloride solution shows the absorption band at 3620 cm^{-1} attributed to $OH\cdots\pi$ intramolecular hydrogen bond and no strong intramolecular hydrogen bonds which are expected from $OH\cdots N$ and/or $OH\cdots O{=}\overset{|}{C}{-}OMe$ (Fig. 2). The absence of the intramolecular hydrogen bonds attributed to $OH\cdots N$ and/or $OH\cdots O{=}\overset{|}{C}{-}OMe$ indicates that CH_2OH locates at C_1' and orientates *trans* to COOMe. At this moment, it can be easily seen that the carbomethoxyl group at C_1' in IV was reduced with LAH (D) and the other at C_2' remained unchanged. The presence of the intramolecular hydrogen bond attributed to $OH\cdots\pi$ indicates that C_1'-CH_2OH orientates *cis* to the D ring. Among several possible structures, only IX, which contains C_1'-*syn*⁴⁾-CH_2OH and C_2'-*anti*⁴⁾-COOMe, can reasonably account for the IR data of V.

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3) R.A. Bell and J.K. Saunders, *Can. J. Chem.*, **48**, 1114 (1970); J.K. Saunders, R.A. Bell, and C.Y. Chen, *ibid.*, **46**, 2876 (1968).

4) *syn* and *anti* are referred to the D ring.

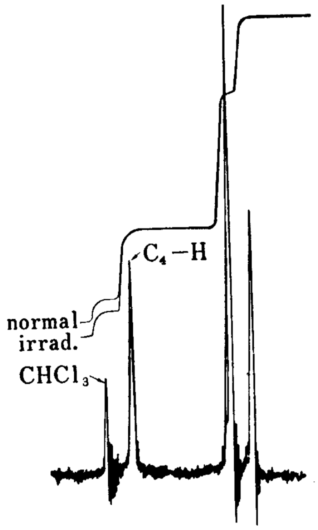


Fig. 1. The NOE's Result of V-d_3

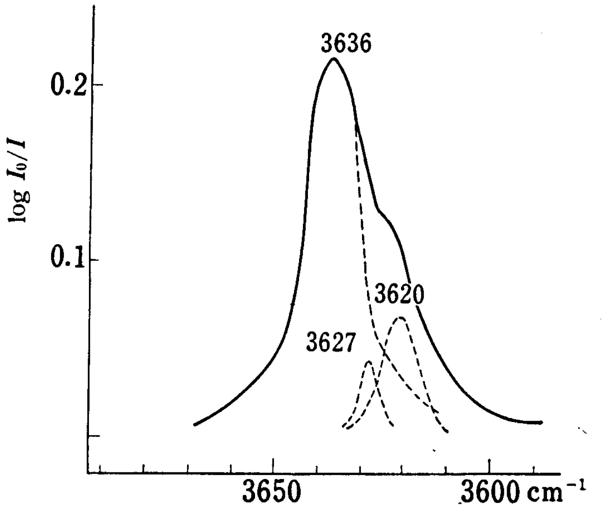
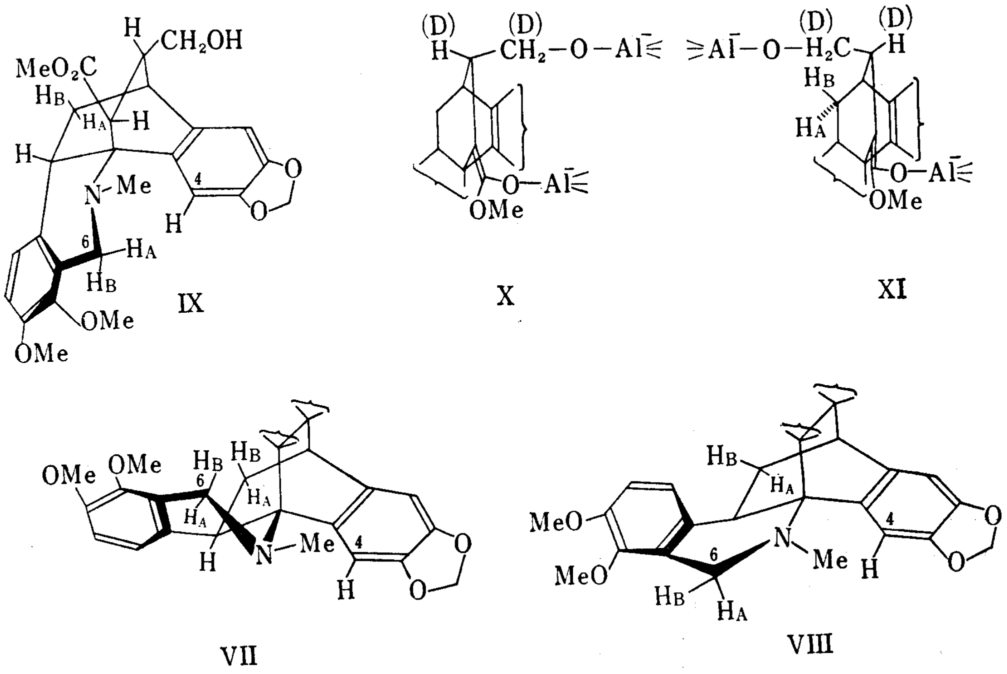


Fig. 2. IR Spectrum of V in CCl_4
0.0003 mole/liter, 20 mm cell



IX

X

XI

VII

VIII

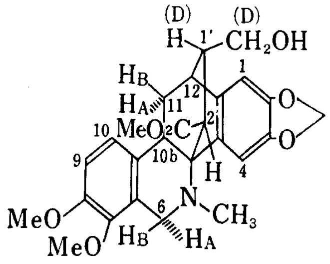
Chart 3

From the comparison of the NMR spectra of V and V-d_3, the structure, which contains C_1'-*syn*-CD_2OH and C_1'-*anti*-D, is assigned to V-d_3. This fact exhibits that the double bond in IV was attacked at C_1' from *anti* side to the D ring. The selective reduction of the double bond and one carbomethoxyl group in the dimethyl maleate seems to be unusual. The primary product precipitated from the ethereal solution is probably the aluminate complex (X) which converts to V with H_2O. The preferential attack of reagent at C_1' from *syn* side to the D ring is predicted from steric hindrance, giving the alternative complex (XI) which contains C_1'-*syn*-H and C_1'-*anti*-CH_2OAl. Taking into account the interaction between C_{11}-H_A and the substituent at C_1', X is more stable than XI. Accordingly, the reduction of IV gave exclusively V *via* X, apparently under "product development control".

On reduction with LAH in a tetrahydrofuran solution, V was converted to the diol (XII), mp 217—219°, $C_{25}H_{29}O_6N$, whose IR spectrum showed no longer the absorption band corresponding to COOMe. XII afforded the diacetate (XIII), mp 187—188°, $C_{29}H_{33}O_8N$, whose IR spectrum showed the absorption band at 1735 cm^{-1} corresponding to OAc. These facts indicate that the other carbomethoxyl group at C_2' in V can also be reduced under slightly drastic condition. Also, the treatment of V-d_3 with LAD gave the diol (XII-d_5), mp 217°, which was converted to the diacetate (XIII-d_5), mp 185—187°, by acetylation. In order to confirm the structure the NMR spectra of these compounds were taken with a 100 Mc instrument (Table I—IV). The fact that the signals for C_6-HA and C_6-HB remain essentially unchanged regardless of the anti-substituents at C_2' shows that these protons orientate not to be affected by the substituent[5a)] and the half-chair conformation deduced from the NOE measurements is favorable for the B ring.

Here, the structure for IV is examined on the basis of that of V. From the NMR spectra of IV and V, it can be easily seen that the chemical shift of C_{11}-HB is more influenced by the double bond than that of C_{11}-HA. This observation supports that C_{11}-HA in IV orientates *syn* and C_{11}-HB *anti* to the D ring. The NMR spectra of bicyclo[2.2.2]octanes, in general, show that the values of vicinal coupling constants for *cis* protons (J_{cis}) larger than that for *trans* protons (J_{trans}) in accord with the Karplus rule.[5b)] As shown in Fig. 3 and Table V, the NMR spectrum of IV shows $J_{10b,11A}=7$ cps and $J_{10b,11A}=10$ cps. Since the vicinal coupling constants corresponding to dihedral angles of approximately 130° and 10° are found to be 6.8 cps and 9.5 cps, respectively, the studies on the coupling cnstants, also, probably support the above deduction that C_{11}-HA is *syn* and C_{11}-HB *anti*. If the B ring exists in the half-chair form (XIV), the signals for C_4-H and C_6-HA in IV will appear in the nearly same as that in V.

TABLE I.



V

	N-Me	O-Me	$CH_2\langle^O_O$	CO_2Me	C_1-H	C_4-H	C_9-H	C_{10}-H	OH
H	7.32	6.25 6.27	4.12d 4.17d $J\approx1$	6.45	3.39s	2.88s	3.30s	3.30s	7.90
D	7.32	6.25 6.27	4.12d 4.17d $J\approx1$	6.46	3.39s	2.88s	3.30s	3.30s	8.0

	C_6-HA	C_6-HB	C_{10b}-H, C_{11}-HB C_{12}-H	C_{11}-HA	C_1'-H	C_2'-H	C_1'-CH_2OH
H	5.26d $J=17.5$	6.07d	6.77—7.05	8.34oct $J=2.3$, 7.5 and 12.5	7.97m	7.25d $J=5$	*ca.* 6.2
D	5.26d $J=17.5$	6.07d	6.8 — 7.1	8.34oct $J=2.3$, 7.5 and 12.5		7.26s	

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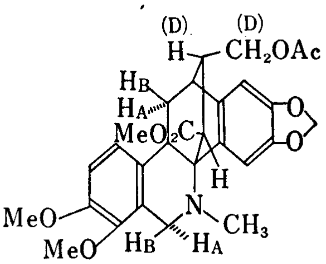
5) *a)* L.M. Jackman and S. Sterhnell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N.Y., 1969, p. 71; *b) Idem, ibid.*, 1969, p. 288.

TABLE II.

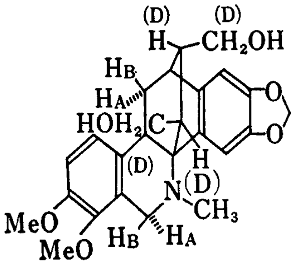


VI

	N-Me	O-Me	$CH_2\langle^{O}_{O}$	CO_2Me	$-O-\overset{O}{\overset{\parallel}{C}}-CH_2$	C_1-H	C_4-H	C_9-H	C_{10}-H
H	7.33	6.26 6.27	4.14d 4.19d $J\approx1$	6.47	7.94	3.39s	2.87s	3.31s	3.31s
D	7.34	6.26	4.14d 4.19d $J\approx1$	6.47	7.94	3.39s	2.87s	3.30s	3.30s

	C_6-H_A	C_6-H_B	C_{10b}-H, C_{11}-H_B, C_{12}-H	C_{11}-H_A	C_1'-H	C_2'-H	C_1'-C$\underline{H}_2$OAc
H	5.29d $J=18$	6.07d	6.76—7.22	8.28m	7.86m	7.23d $J=5$	5.77q $J=2$ and 7
D	5.29d $J=18$	6.08d	6.73—7.2	8.28m		7.24s	

TABLE III.

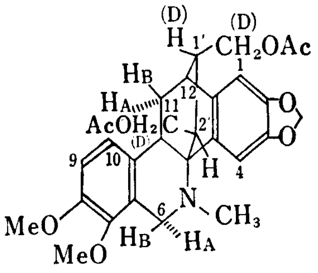


XII

	N-Me	O-Me	$CH_2\langle^{O}_{O}$	C_1-H	C_4-H	C_9-H	C_{10}-H
H	7.40	6.25 6.27	4.14d 4.18d $J\approx1$	3.41s	2.84s	3.30s	3.30s
D	7.40	6.25 6.27	4.15d 4.17d $J\approx1$	3.40s	2.84s	3.29s	3.29s

	C_6-H_A	C_6-H_B	C_{10b}-H, C_{11}-H_B, C_{12}-H, C_2'-CH_2OH	C_{11}-H_A	C_1'-H	C_2'-H	C_1'-C$\underline{H}_2$OH
H	5.31d $J=18$	6.09d	6.8—7.3	8.43 oct $J=2.5$ 7.5 and 12.5	8.85m	7.85m	*ca.* 6.2
D	5.31d $J=18$	6.08d	6.8—7.3	8.44 oct $J=2.5$ 7.5 and 12.5		7.86s	

TABLE IV.

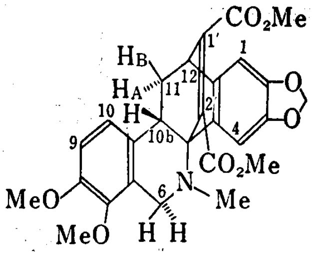


XIII

	N-Me	O-Me	$CH_2{<}^{O}_{O}$	–OAc	C_1-H	C_4-H	C_9-H	C_{10}-H
H	7.42	6.24	4.15d 4.19d $J\approx1$	7.87 8.02	3.38s	2.88s	3.28s	3.28s
D	7.43	6.25	4.15d 4.19d $J\approx1$	7.93 8.06	3.38s	2.88s	3.28s	2.28s

	C_6-H_A	C_6-H_B	C_{10b}-H, C_{11}-H_B, C_{12}-H, C_2'-H	C_{11}-H_A	C_1'-H	C_1'-CH_2OAc, C_2'-CH_2OAc
H	5.35d $J=17.5$	6.07d	6.75—7.22	8.2—8.48	8.2—8.48	5.55—5.77
D	5.35d $J=17.5$	6.07d	6.75—7.22	8.43m		

TABLE V.



IV

N-Me	O-Me	$CH_2{<}^{O}_{O}$	COOMe	C_1-H	C_4-H	C_9-H
7.04	6.17 6.19	4.21d 4.23d $J\approx1$	6.22	3.27s	3.27s	3.48d $J=8$

C_{10}-H	C_6-H_2	C_{10b}-H	C_{11}-H_A	C_{11}-H_B	C_{12}-H
3.38d $J=8$	5.65s	6.75q	8.30 oct	7.68 oct	5.58q

$J_{11AB}=12$ $J_{10b,11A}=7$ $J_{10b,11B}=10$ $J_{12,11A}=2.5$ $J_{12,11B}=4$
(130°, calcd. 6.8) (10°, calcd. 9.5)

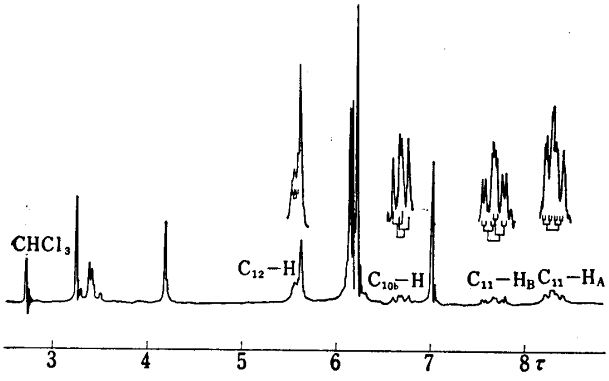
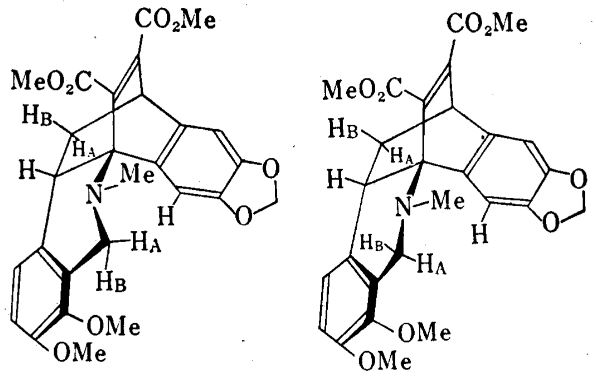


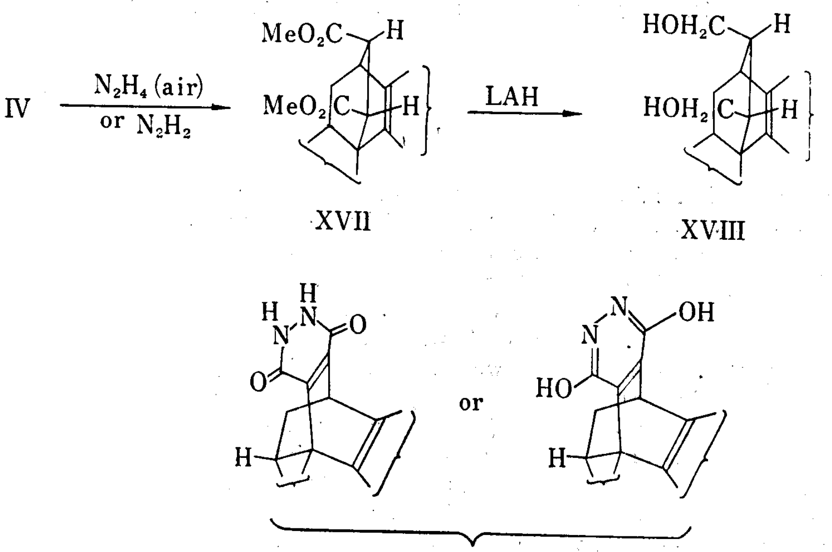
Fig. 3. NMR Spectrum of IV (100 Mc)



XIV XV

Chart 4

The signals for C_4-H and C_6-H$_A$ in IV shift higher by 0.39 ppm compared with that in V. Since the conformation of B ring in IV was assumed to be same as that in V, the NOE between C_4-H and C_6-H$_A$ is also expected. The irradiation at 5.65 τ did not affect the signal at 3.27 τ. From the above observation it seems likely that the conformation of B ring in IV is different from that in V. Although the boat conformation for the B ring can explain the absence of the NOE between C_4-H and C_6-H$_A$, the serious interaction[5a)] of N-Me with C_4-H will cause a significant down field shift in the resonance of C_4-H. Eventually, the correlation with the NMR data leads to a flattened boat conformation (XV) close to the 1,3-diplanar form[6)] for the B ring, in which all interactions mentioned above are released. Also, XV can explain that the two protons at C_6 are magnetically equivalent and the signals for the two protons appear at 5.65 τ as a singlet. From the examination of Dreiding model, it is obvious that there is a difference between the angular distortions in the bicyclo[2.2.2]octadiene and bicyclo[2.2.2]octene system. As a result, the ring fused with these systems may be subjected



XVII XVIII

XVI

Chart 5

[6)] N.L. Allinger and E.L. Eliel, "Topics in Stereochemistry," Vol. 2, John Wiley and Sons, Inc., New York, N. Y., 1967, p. 161.

to the conformationally different effect. This would be a cause that the B rings in IV and V exist in the different conformation.

Next, the treatment of IV with hydrazine for the purpose of obtaining the pyridazine derivative (XVI), contrary to expectation, afforded the dihydro-compound (XVII), mp 179—181°, $C_{27}H_{29}O_8N$. XVII was characterized by the IR (1710 cm^{-1}; COOMe), the NMR (6.28 and 6.30 τ, 2×COOMe), and the mass spectrum (M$^+$, 495.1908; MW,[7] 495.1893 for $C_{27}H_{29}O_4N$). There have been a few studies[8] on the reduction of double bond with hydrazine in the presence of oxygen or air. It seems probably that diimide, which resulted from the oxydation of hydrazine with oxygen in air, reacts as the reducing reagent. The proposal of this reaction pathway was confirmed by the treatment of IV with diimide. The stereostructure of XVII was determined from the investigation of the diol (XVIII) which was provided from the LAH reduction of XVII. As shown in Fig. 4, the IR spectrum of XVIII in a dilute carbontetrachloride solution shows the absorption band at 3500 cm^{-1} attributed to OH···N and/or OH···O intramolecular hydrogen bond. If either C_1'-CH_2OH or C_2'-CH_2OH orientates *cis* to the D ring a weak intramolecular hydrogen bond due to OH···π must appear at around 3620 cm^{-1} as in the IR spectrum of IX. From the absence of the intramolecular hydrogen bond due to OH···π it is considered that both C_1'- and C_2'-CH_2OH in XVIII probably orientate *trans* to the D ring. This consideration naturally leads to the structure for XVII, in which both C_1'- and C_2'-COOMe orientate *trans* to the D ring. Although XVII must be sterically unfavorable compared with other isomers, if the *cis* attack and the less hindered side attack of diimide on the double bond are taken into account, the formation of XVII is considered to be reasonable. Although Ib was irradiated in the presence of dimethyl maleate in order to confirm the structure of XVII, there was unfortunately obtained no adduct.

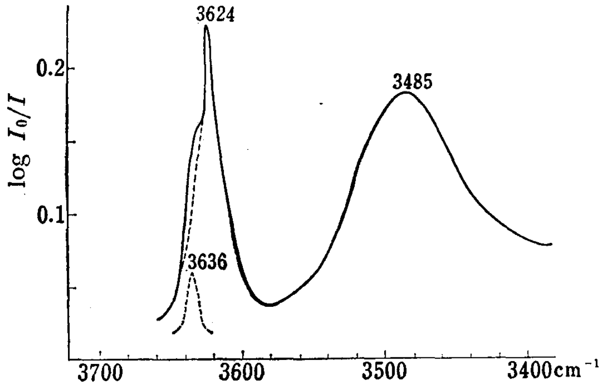


Fig. 4. IR Spectrum of XVIII in CCl_4
0.0007 mole/liter, 20 mm cell

Experimental

Melting points were determined on a micro hot-stage and were uncorrected. Infrared spectra were measured in $CHCl_3$ with a JASCO Model IR-S and intramolecular hydrogen bond was measured with a JASCO Model DS-403G. Nuclear magnetic resonance spectra and nuclear Overhauser effect were measured in $CDCl_3$ with a JEOL's JNM-4H-100 spectrometer (100 Mc). For nuclear Overhauser effect measurements, a 6 w/v% solution of the sample in $CDCl_3$ was degassed. Degassing was carefully done by repeated freezing, and melting under high vacuum. Each peak was integrated repeatedly with no irradiated power and optimum irradiated power. Mass spectra were measured with a JEOL's JMS-O1S.

Reduction of 4b,12-Dicarbomethoxyetheno-4b,5,6,10b,11,12-hexahydrochelerythrine (IV) with $LiAlH_4$ and $LiAlD_4$——a) To a solution of $LiAlH_4$ (164 mg) in dry ether (5 ml) was added dropwise a solution of IV (425 mg) in dry ether (20 ml) at room temperature with stirring. The stirring was continued for 1.5 hr. The precipitate was collected, suspended in ether and treated with H_2O in usual ways. The residue (302 mg) was chromatographed over silicagel (40 g) by using benzene–AcOEt (1:1 v/v) as eluent to afford colorless needles (V) (112 mg), mp 203—204°, which showed same melting point on recrystallization from acetone–ether. Mass Spectrum Calcd. for $C_{26}H_{29}O_7N$: MW, 467.1944. Found: M$^+$, 467.1918. *Anal.* Calcd. for $C_{26}H_{29}O_7N$: C, 66.80; H, 6.25; N, 3.00. Found: C, 66.49; H, 6.38; N, 3.01. Acetate (VI): colorless plates, mp 181—182° (from *n*-hexane–acetone). Mass Spectrum Calcd. for $C_{28}H_{31}O_8N$: MW, 509.2049. Found:

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[7] MW: molecular weight.

[8] E.J. Corey, W.L. Mock, and D.J. Pasto, *Tetrahedron Letters*, **1961**, 347, 353.

M+, 509.2017. Picrate of VI: pale yellow needles, mp 200—202°. *Anal.* Calcd. for $C_{34}H_{34}O_{15}N_4$: C, 55.35; H, 4.65; N, 7.60. Found: C, 55.56; H, 4.75; N, 7.56.

b) The same procedure was carried out except for replacement of $LiAlH_4$ with $LiAlD_4$. There was obtained colorless needles (V-d_3), mp 202—204° (from acetone–ether). Acetate (VI-d_3): colorless plates, mp 180—182° (from *n*-hexane–acetone).

Reduction of 4b,12-(1′-*syn*-Hydroxymethyl-2′-*anti*-carbomethoxy)ethano-4b,5,6,10b,11,12-hexahydrochelerythrine (V) with $LiAlH_4$——To a solution of $LiAlH_4$ (30 mg) in dry ether (20 ml) was added dropwise a solution of V (335 mg) in dry tetrahydrofuran (14 ml) at room temperature with stirring. The stirring was continued for 1.5 hr. The reaction mixture was treated in usual ways. The residue (305 mg) was chromatographed over Al_2O_3 (grade III) (30 g). The first fraction of benzene–AcOEt (4:1 v/v) afforded starting material (V) (92 mg) and the second of EtOH–AcOEt (1:9 v/v) afforded colorless needles (XII) (110 mg), mp 217—218°, which showed same melting point on recrystallization from *n*-hexane–acetone–$CHCl_3$. Mass Spectrum Calcd. for $C_{25}H_{29}O_6N$: MW, 439.1990. Found: M+, 439.1970. *Anal.* Calcd. for $C_{25}H_{29}O_6N$: C, 68.32; H, 6.65; N, 3.19. Found: C, 68.83; H, 6.50; N, 3.49. Diacetate (XIII): colorless prisms, mp 187—188° (from *n*-hexane–acetone). *Anal.* Calcd. for $C_{29}H_{33}O_8N$: C, 66.53; H, 6.35; N, 2.68. Found: C, 66.62; H, 6.35; N, 2.67.

Reduction of V-d_3 with $LiAlD_4$——The same procedure was carried out except for replacement of $LiAlH_4$ with $LiAlD_4$ as mentioned above. There was obtained colorless needles (XII-d_5), mp 217° (from *n*-hexane–acetone–$CHCl_3$). Diacetate (XIII-d_5): colorless plates, mp 185—187° (from *n*-hexane–acetone).

4b,12-(1′,2′-*anti*-Dicarbomethoxy)ethano-4b,5,6,10b,11,12-hexahydrochelerythrine (XVII)——a) A solution of IV (49 mg) and 80% of $N_2H_4 \cdot H_2O$ (20 mg) in MeOH (4 ml) was refluxed for 48 hr. After cooling, the precipitate was collected and recrystallized from MeOH–acetone to give colorless plates (12 mg), mp 179—181°. Mass Spectrum Calcd. for $C_{27}H_{29}O_8N$: MW, 495.1893. Found: M+, 495.1908.

b) To a suspension of IV (1.0 g) and potassium azodicarboxylate (0.8 g) in MeOH (30 ml) was added dropwise AcOH (0.5 ml) at room temperature with stirring. After stirring for 30 min, the reaction mixture was filtered. The filtrate was evaporated *in vacuo*, made alkaline with 10% ammonia and then extracted with benzene. The residue was chromatographed over Al_2O_3 (grade III) (70 g) by using benzene as eluent to afford colorless plates (255 mg), mp 179—181°, which was identified with the compound described above by the IR, the NMR spectra and the mixed melting point.

4b,12-(1′,2′-*anti*-Dihydroxymethyl)ethano-4b,5,6,10b,11,12-hexahydrochelerythrine (XVIII)——To a solution of $LiAlH_4$ (24 mg) in dry ether (5 ml) was added dropwise a solution of XVII (78 mg) in dry ether (75 ml) at room temperature with stirring. After stirring for 6 hr, the reaction mixture was worked up in usual ways. The residue (68 mg) was chromatographed over Al_2O_3 (grade III) (8 g) by using MeOH–AcOEt (1:9 v/v) to afford a syrup (56 mg). Mass Spectrum Calcd. for $C_{25}H_{29}O_6N$: MW, 439.1990. Found: M+, 439.2020.

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