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Stereochemistry of 3-Methylhexahydrophthalide[1]

Yasuhiro Fujiwara, Shoshichiro Kimoto and Masao Okamoto

Kyoto College of Pharmacy[2]

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Four stereoisomers of 3-methylhexahydrophthalide (IVa, IVb, IVc, and IVd) were synthesized. The stereochemical correlations including the ring juncture and the configurations of methyl groups of these compounds and also the conformations of the methyl groups were investigated by chemical means and by proton magnetic resonance and mass spectrometry.

In the preceding paper[3] the authors described the catalytic hydrogenation of methyl *cis*-2-azidoacetylcyclohexanecarboxylate. In order to clarify the configuration of *cis*-hexahydrophthalydylmethylamine which was obtained as a by-product in the reaction, four stereoisomers (IVa, IVb, IVc and IVd)[4] of 3-methylhexahydrophthalide were synthesized according to the scheme illustrated in Chart 1 and the configurations of these lactones were clarified on the basis of the isomerization, the reactivity with hydrazine and the physicochemical analyses with proton magnetic resonance (PMR) and mass spectra.

Starting from *trans*-2-methoxycarbonylcyclohexanecarboxylic acid *via* acid chloride and diazo ketone, the corresponding ω-chloro ketone (I-1)[5], mp 62°, was prepared and converted by dechlorination over Pd-C catalyst to methyl *trans*-2-acetylcyclohexanecarboxylate (II-1), bp 99—100°/4 mmHg. Hydrolysis of the ester in a usual manner gave the corresponding carboxylic acid (III), mp 133—134.5°, which was esterified with diazomethane to give the original ester (II-1). Hydrogenation of II-1 over platinum oxide as a catalyst in ethanol afforded a mixture of two stereoisomers of 3-methyl-*trans*-hexahydrophthalide in a ratio[6] of IVa: IVb=1: 5. Separation of the isomers was effected by the solubility difference of the corresponding hydrazides in ethanol.[7] Thus, the mixture was treated with hydrazine hydrate and the precipitated hydrazide (Vb), mp 195—196°, was collected by filtration, and the other hydrazide (Va), mp 132—133°, was obtained by concentration of the filtrate. The original lactones IVb, bp 92°/3.5 mmHg, and IVa, mp 43—44° were reproduced in the pure state on hydrolysis of these hydrazides with conc. hydrochloric acid, respectively. On the other hand, reduction of II-1 with sodium borohydride in methanol gave a mixture of IVa and IVb in the ratio 2: 3.

Two stereoisomers of 3-methyl-*cis*-hexahydrophthalide (IVc and IVd) were obtained in a similar manner as above. Thus, methyl *cis*-2-acetylcyclohexanecarboxylate (II-2), bp 98—99°/4 mmHg, was prepared from *cis*-2-methoxycarbonylcyclohexanecarboxylic acid *via* the ω-chloro ketone (I-2),[8] bp 115—117°/4 mmHg. The ω-chloro ketone (I-2) was readily

1) Communication: Y. Fujiwara, S. Kimoto, and M. Okamoto, *Chem. Pharm. Bull.* (Tokyo), **21**, 1166 (1973). A part of mass spectrometry was presented at the 8th Symposium of Mass Spectrometry for Organic Compounds (Nov. 1973 at Hiroshima).
2) Location: *Nakauchi-cho, Yamashina-Misasagi, Higashiyama-ku, Kyoto.*
3) S. Kimoto, Y. Fujiwara, M. Okamoto, and K. Nakamura, *Yakugaku Zasshi*, **93**, 939 (1973).
4) P. Kolsaker, *Acta Chem. Scand.*, **16**, 1056 (1962).
5) S. Kimoto, M. Okamoto, M. Uneo, S. Ohta, M. Nakamura, and T. Niiya, *Chem. Pharm. Bull.* (Tokyo), **18**, 2141 (1970).
6) The product ratio was determined by gas–liquid chromatography (GC) throughout the work.
7) The separation of isomers described in the previous communication[1] has been amended as described here.
8) S. Kimoto, M. Okamoto, M. Nakamura, and T. Baba, *Yakugaku Zasshi*, **90**, 1538 (1970).

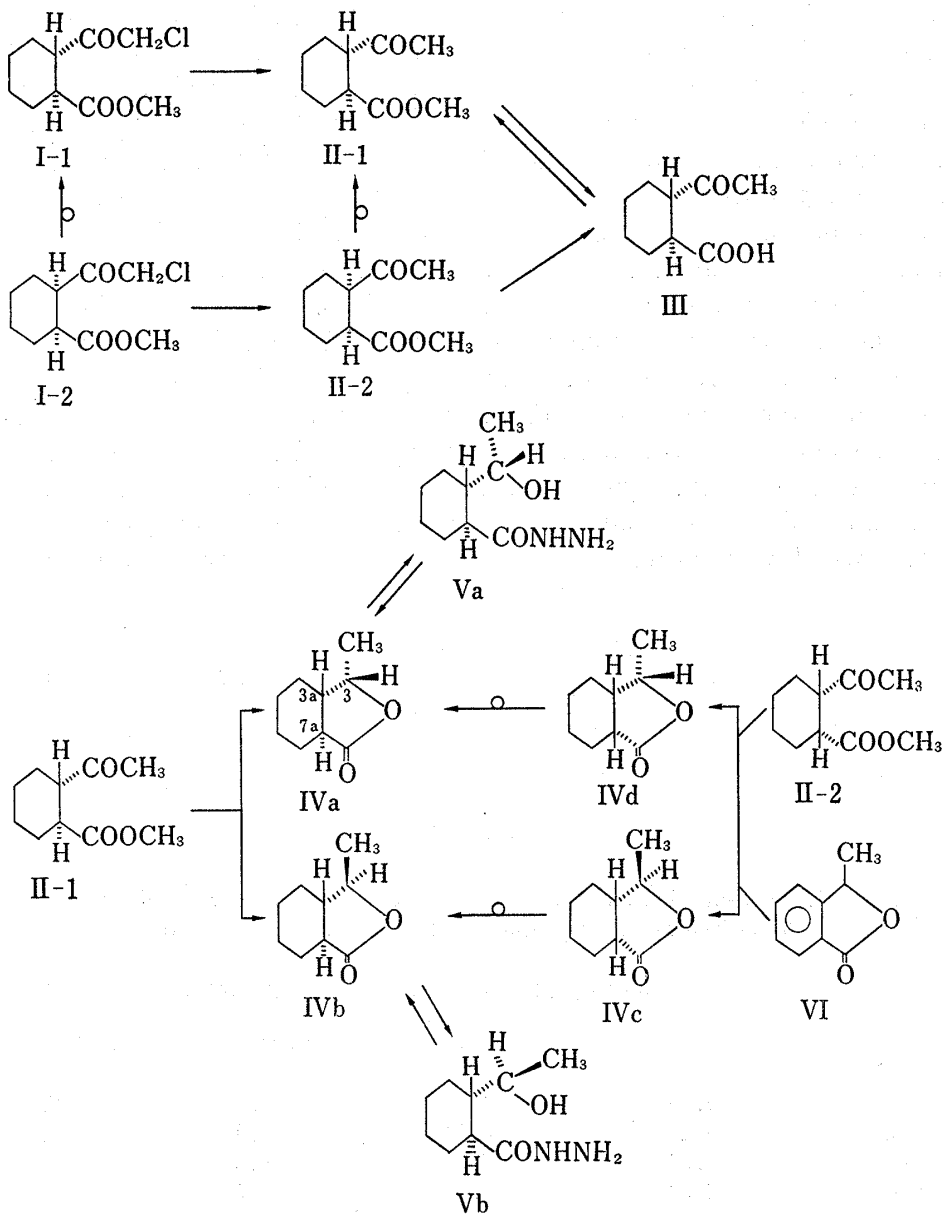
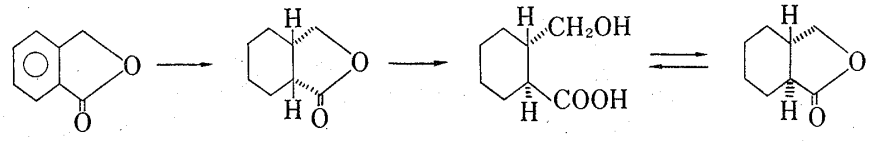


Chart 1

isomerized to I-1 on treatment with aqueous sodium carbonate while the ketone (II-2) was isomerized to II-1 with dil. hydrochloric acid. Hydrolysis of II-2 with aqueous sodium hydroxide solution under reflux resulted in the formation of the *trans* carboxylic acid (III), while reduction of II-2 with sodium borohydride gave a mixture of the lactones IVc and IVd in the ratio 3: 2. On the other hand, as the hydrogenation of II-2 over platinum oxide proceeded very slow, 3-methylphthalide (VI) was hydrogenated over the same catalyst in acetic acid according to Kolsaker's method[4] to yield a mixture of IVc and IVd in the ratio 1: 13. Separation of the mixture of IVc and IVd by means of the above mentioned hydrazide formation was without success, however it was found that the rate of lactone-ring opening of IVd with an aqueous sodium hydroxide solution was slower than that of IVc. Therefore, the mixture of IVc and IVd was added to an aqueous 1.5% solution containing 0.8 molar equivalent of sodium hydroxide, and the resulting mixture was stirred for a few minutes and divided into an oily layer (containing IVd in a rich amount) and an aqueous layer, which on acidification gave another oil (containing a rich amount of IVc). The foregoing oily layer and the oil obtained by acidification of the aqueous layer were respectively treated again with aqueous

alkali. After repetition of the procedure, IVd, bp 94°/3 mmHg, and IVc, bp 86°/4 mmHg, were isolated in the almost pure state. Based on the fact that IVd was obtained exclusively in the case of hydrogenation of VI, it was reasonably presumed that the hydrogens at C-3a and C-7a should be *cis*. Moreover, IVc and IVd, when boiled with a 10% sodium hydroxide solution, were converted to the corresponding *trans* lactones IVb and IVa with the concomitant inversion of the configuration at C-7a. From these evidences, the stereochemical correlation of these four stereoisomers are summarized as follows: i) IVa and IVb should have the *trans* ring-fusion and IVc and IVd have the *cis* fusion. ii) IVa and IVd, and IVb and IVc, should have respectively the same configurations at C-3 position. It follows therefore that the precise configurations of these four isomers will be defined if the relative configurations of C-3 and C-3a positions are clarified. For this purpose, PMR spectrometry was applied.

As the reference compounds for the PMR analysis on the protons at C-3 and C-3a of four stereoisomers, the known *trans*- and *cis*-hexahydrophthalides (VIII-1 and VIII-2)[9] became necessary and were prepared through a new route as shown in Chart 2. Thus, catalytic hydrogenation of phthalide (VII) over platinum oxide or Raney nickel gave in a good yield the *cis* lactone (VIII-2), which was hydrolysed with alkali to give the corresponding *trans* carboxylic



VII VIII-2 IX VIII-1

Chart 2

Table I. Proton Magnetic Resonance Data[a] of the Four Stereoisomers of 3-Methylhexahydrophthalide (IVa, IVb, IVc, and IVd)

	Chemical shift (δ)		Coupling constant (Hz)	
	CH_3	H(3)	J CH_3–H(3)	J H(3)–H(3a)
IVa	1.34	4.65	6.7	6.7
IVb	1.28	4.14	6.1	9.7
IVc	1.31	4.30	6.4	4.2
IVd	1.34	4.44	6.5	3.6

a) Measurements were carried out in deuteriochloroform solutions of 0.5—0.7 mole concentration with Varian HA-100D Analytical Spectrometer.

Table II. Proton Magnetic Resonance Data[a] of *trans*- and *cis*-Hexahydrophthalides (VIII-1 and VIII-2)

	Chemical shift (δ)		Coupling constant (Hz)		
	H(3α)	H(3β)	J H(3a)–H(3α)	J H(3a)–H(3β)	J H(3α)–H(3β)
VIII-1	3.85	4.37	10.6	6.2	8.2
VIII-2	3.97	4.20	1.3	4.8	8.8

a) Deuteriochloroform solutions of 0.22 mole concentration were used.

acid (IX), mp 106—109°, with the concomitant inversion of the configuration at C-7a and the acid (IX) was then heated to give the *trans* lactone (VIII-1). Thus prepared two hexahydro-

9) H. Christol, A. Donche, and F. Plenat, *Bull. Soc. Chim. France*, **1966**, 2535.

phthalides (VIII-1 and VIII-2) were identified by conversion to the known *trans*-and *cis*-2-hydroxymethylcyclohexanecarbohydrazides, the melting points of which agreed with the reported values,[9] respectively.

The PMR data of the lactones (IVa, IVb, IVc and IVd) and the hexahydrophthalides (VIII-1 and VIII-2) are listed in Table I and II, respectively. As shown in Table I, the coupling constants JH(3)-H(3a) of the *trans* lactones (IVa and IVb) are 6.7 and 9.7 Hz which are consistent, on the basis of Dreiding model examination and the Karplus rule,[10] with the pre-

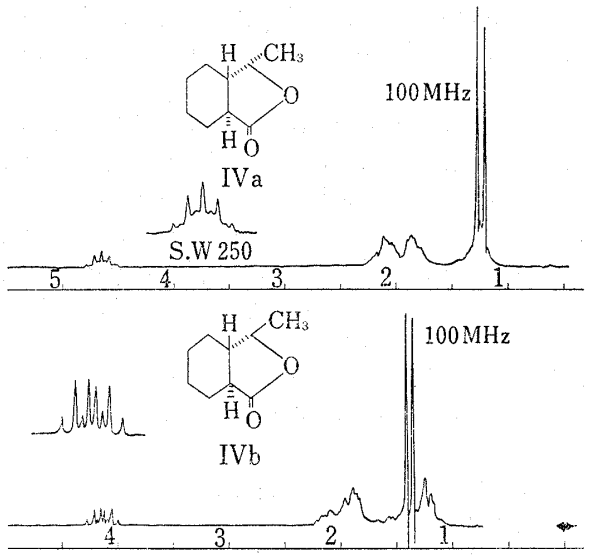


Fig. 1. PMR Spectra of 3-Methyl-*trans*-hexahydrophthalides (IVa and IVb)

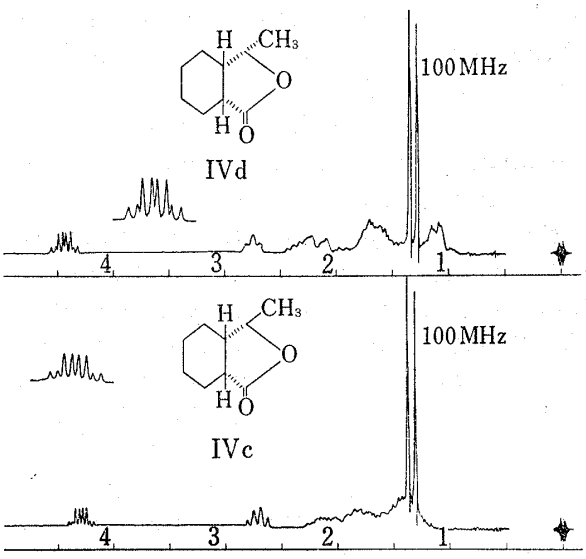


Fig. 2. PMR Spectra of 3-Methyl-*cis*-hexahydrophthalides (IVc and IVd)

sumpion that IVa and IVb possess an axial-like α-methyl group and an equatorial-like β-methyl group respectively as depicted in Chart 1. The similar magnitude of the coupling constant is observed in VIII-1: JH(3a)$-$H(3β)$=$6.2 Hz and JH(3a)$-$H(3α)$=$10.6 Hz as shown in Table II. On the other hand, the corresponding J values of *cis* lactones (IVc and IVd) are 4.2 and 3.6 Hz and the difference of both values appears to be not so large enough to discriminate IVc and IVd.[11]

As shown in the above conversion, IVd possesses an α-methyl group at C-3 as in IVa, and

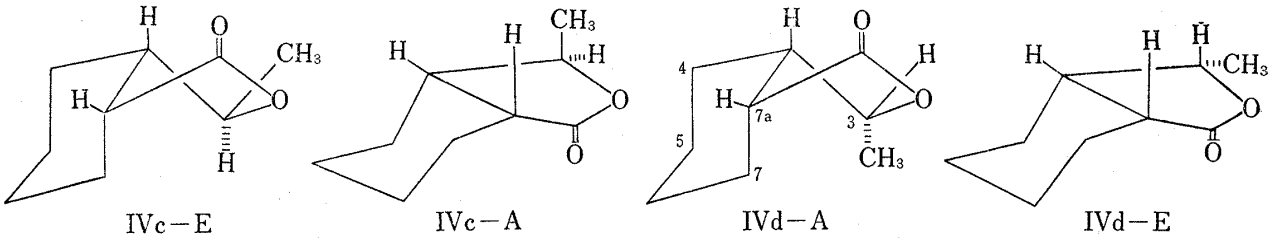


Chart 3

two alternative conformers (IVd-E and IVd-A) illustrated in Chart 3 are considered possible as the stereostructure of IVd. To make the definite choise of two, the coupling constant of H(3)-H(3a) (J=3.6 Hz) is of no use, since the dihedral angles between the protons at C-3 and C-3a in IVd-E and IVd-A are alike each other.

10) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

11) In order to obtain more informations, PMR spectra of VIII-1 and VIII-2 were measured using Eu(DPM)$_3$ as a shift reagent, but the conclusive evidence could not be drawn.

However, the conformation of IVd-E seems to be preferable for IVd rather than that of IVd-A, because the latter appears to suffer the unfavorable spacial interaction between an axial-like α-methyl group and α-hydrogen at C-5.

For the conformation of IVc, IVc-A (with slightly deformed lactone ring) seems to be preferable rather than IVc-E, since in IVc-E the larger J value of H(3)-H(3a) (4.2 Hz in IVc) would be observed as in case of IVb (9.7 Hz) and VIII-1 (10.6 Hz).

In addition, a one-proton signal characteristically observed at *ca.* 2.7 (δ) in IVd and IVc (Fig. 2) is presumably assignable to H(7a) of each and the downward shift is probably due to the anisotropic effect of the carbonyl function and the cyclohexane ring.[12] The difference of the coupling pattern of H(7a) could be attributable to the slight difference in the ring conformation of IVd and IVc.

It should be pointed out here that the experimental findings previously obtained in hexahydrophthalydylmethylamine[3] are also consistent with the discussion described above.

Although a great deal of mass spectral data regarding lactones have been reported,[13a-e] little has been known about the relationship between the configuration and the fragmentation pattern in the mass spectra. We examined the mass fragmentation patterns of above described four lactones and two hexahydrophthalides, and obtained the interesting results (Table III, Fig. 3 and 4) which are summarized below.

i) The fragment ion peaks observed at m/e 67, 54, 41 and 39 in the mass spectra of VIII-1 and VIII-2 are very similar including the peak intensities to those observed in the case of

Table III. Base Peaks and Intensity Ratio $[M\text{-}15^+]/[M^+]$ in the Mass Spectra of the Lactones, VIII-1, VIII-2, IVa, IVb, IVc, and IVd

	Base peak (m/e)	Intensity ratio $[M\text{-}15^+]/[M^+]$		Base peak (m/e)	Intensity ratio $[M\text{-}15^+]/[M^+]$
VIII-1	67	——	VIII-2	81	—
IVa	67	1.86	IVc	81	1.81
IVb	67	0.56	IVd	81	0.29

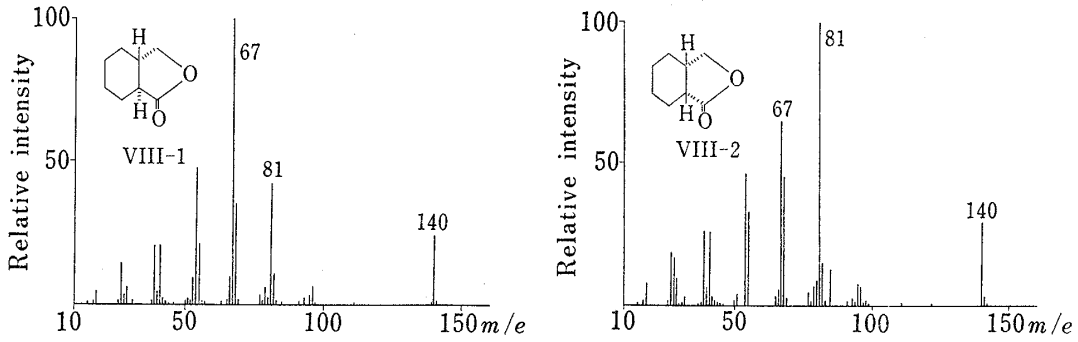


Fig. 3. Mass Spectra of *cis*- and *trans*-Hexahydrophthalides (VIII-2 and VIII-1)

cyclohexene.[13a] The similarities are also observed in the mass spectra of IVa, IVb, IVc and IVd.

12) The peak at *ca.* 2.7 (δ) in IVc disappeared on treatment with alkaline D_2O.

13) *a*) H. Budzikiewicz, C. Djerassi, and D.H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, 1967, p. 205; *b*) N. Wasada, T. Tsuchiya, E. Yoshii, and E. Watanabe, *Tetrahedron*, **23**, 4624 (1967); *c*) P.H. Chen, W.F. Kuhn, F. Will III, and R.M. Ikeda, *Org. Mass Spectr.*, **3**, 199 (1970); *d*) E. Honkanen, T. Moisio, and P. Karvonen, *Acta Chem. Scand.*, **23**, 531 (1969); *e*) L. Friedman and F.A. Long, *J. Am. Chem. Soc.*, **75**, 2832 (1953).

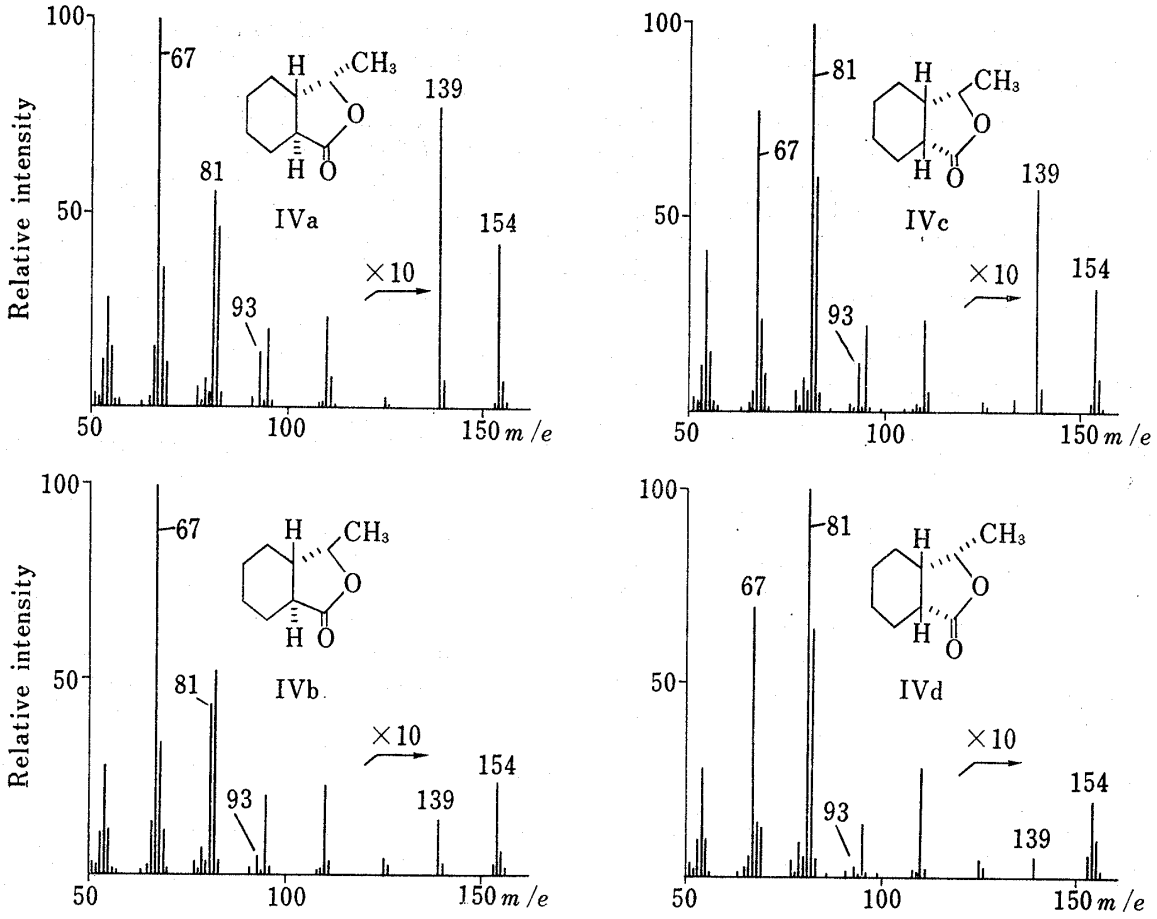


Fig. 4. Mass Spectra of 3-Methylhexahydrophthalides (IVa, IVb, IVc, and IVd)

ii) The base peaks are observed at *m/e* 67 for the *trans* ring-fused lactones VIII-1, IVa and IVb, while at *m/e* 81 for the *cis* ring-fused lactones VIII-2, IVc and IVd. Therefore these characteristics can be employed to differentiate the mode of ring junction.

iii) Meyerson and Weitkanp[14] paid a particular attention to the ratio of the relative intensity of the ions [M-15$^+$] and [M$^+$] in the mass spectra of isomeric methyl-*trans*-decalines and they found that the [M-15$^+$]/[M$^+$] values of compounds having an equatorial methyl group were several times larger than those of compounds having an axial one. On the other hand, Nakata[15] found the reverse relationship between the conformations of methyl groups and the [M-15$^+$]/[M$^+$] values in the case of isomeric 1-methyl-*trans*-quinolizidines and he ascribed the difference to an unshared electron pair of the nitrogen atom. In the present study, as shown in Table III, the [M-15$^+$]/[M$^+$] value of the *trans* ring-fused lactone (IVa) possessing an axial-like α-methyl group is about 3 times larger than that of IVb having an equatorial-like β-methyl group and likewise, the [M-15$^+$]/[M$^+$] value of the *cis* ring-fused lactone (IVc) is about 6 times larger than that of IVd. These findings are in parallel with those observed by Nakata and appear to be in no conflict with the above mentioned stereochemical analysis of these lactones undertaken by PMR spectrometry.

14) H. Meyerson and A.W. Weitkanp, *Org. Mass Spectr.*, **2**, 603 (1969).
15) H. Nakata, Summaries on the 7th Symposium of Mass Spectrometry for Organic Compounds, (Oct. 1972, at Kobe), p. 69.

Experimental[16]

Methyl *trans*-2-Acetylcyclohexanecarboxylate (II-1)——A mixture of methyl *trans*-2-chloroacetylcyclohexanecarboxylate (I-1) (1.5 g), Na_2CO_3 (360 mg) and MeOH (60 ml) was catalytically hydrogenated over 10% Pd-C for 2 hr at room temperature and under atmospheric pressure. An amount of H_2 uptake was 136 ml. After filtration, the filtrate was concentrated *in vacuo* and the residue was dissolved in ether, washed with water, and dried over Na_2SO_4. Evaporation of the solvent, followed by distillation *in vacuo* gave a colorless liquid, bp 99—100°/4 mmHg. Yield, 1.15 g (91%), IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1740 (ester CO), 1715 (ketone CO). PMR δ: 2.18 (3H, s, $-COC\underline{H}_3$), 3.65 (3H, s, $-OC\underline{H}_3$). The ester (II-1) was hydrolyzed in a usual manner with NaOH–EtOH to give the corresponding carboxylic acid (III), which was recrystallized from ether. Colorless prisms, mp 133—134.5°. *Anal.* Calcd. for $C_9H_{14}O_3$: C, 63.51; H, 8.15. Found: C, 63.39; H, 8.29. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3200—2400, 1700 (COOH). PMR δ: 2.19 (3H, s, $-COC\underline{H}_3$), 9.33 (1H, broad, $-COO\underline{H}$). The acid was esterified in a usual manner with CH_2N_2 to revert to II-1 quantitatively.

Reduction of II-1 to 3-Methyl-*trans*-hexahydrophthalides (IVa and IVb)——i) A solution of II-1 (2.2 g) in anhyd. EtOH (60 ml) was catalytically hydrogenated over PtO_2 (900 mg) and the resulting solution was treated in a usual manner to afford a colorless oil (mixture of IVa and IVb, 2.05 g), which was heated with hydrazine hydrate (1.5 g) in anhyd. EtOH under reflux to give *trans*-2-(1′-hydroxyethyl)cyclohexanecarbohydrazide (Vb) as colorless needles (recrystallized from EtOH), mp 195—196°. *Anal.* Calcd. for $C_9H_{18}O_2N_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.46; H, 10.03; N, 15.25. IR ν_{max}^{KBr} cm^{-1}: 3300 (OH, NH), 1640 (amide I CO), 1530 (amide II CO). After removal of the crystals, the mother liquor was concentrated to give another hydrazide (Va) as colorless needles (recrystallized from anhyd. EtOH–ether), mp 132—133°. *Anal.* Calcd. for $C_9H_{18}O_2N_2$: C, 58.03; H, 9.74; N, 15.04. Found: C, 58.11; H, 9.73; N, 15.10. The hydrazides Va and Vb were hydrolized with KOH–EtOH or hydrochloric acid to revert quantitatively to the corresponding lactones IVa and IVb, respectively. IVa: Colorless prisms, mp 43—44° (recrystallized from petroleum ether). *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.69; H, 9.34. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760 (lactone CO). IVb: Colorless liquid, bp 92°/3.5 mmHg. *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.30; H, 9.50. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1767 (lactone CO). The composition of the crude lactone mixture (IVa and IVb) initially obtained by the above mentioned catalytical hydrogenation was in the ratio 1: 5. GC retention time: IVa, 8.7 min; IVb, 6.6 min.

ii) To a solution of $NaBH_4$ (20 mg) in MeOH (0.5 ml) was added a solution of II-1 (50 mg) in MeOH (1 ml) and the resulting solution was allowed to stand at room temperature for 30 min, acidified with 10% HCl and concentrated. The residual oil was extracted with ether, washed with water, and dried over Na_2SO_4. Concentration of the solvent gave a colorless liquid (40 mg), the composition of which was IVa: IVb=2: 3 by GC.

Methyl *cis*-2-Chloroacetylcyclohexanecarboxylate (I-2)——Starting from *cis*-2-methoxycarbonylcyclohexanecarboxylic acid, was prepared the corresponding acid chloride according to the literature.[8] To a solution of the acid chloride in a small amount of anhyd. ether was added excess of CH_2N_2 in ether and the solution was kept standing at room temperature overnight and saturated with dry HCl gas. After removal of an insoluble material by filtration, the mother liquor was washed with water, and dried over Na_2SO_4, concentrated and distilled *in vacuo*. Colorless viscous liquid, bp 115—117°/4 mmHg. Yield, 79.2%. *Anal.* Calcd. for $C_{10}H_{15}O_3Cl$: C, 54.93; H, 6.91. Found: C, 55.00; H, 7.00. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1735 (ester CO), 1724 (ketone CO). PMR δ: 4.27 (2H, s, $-COC\underline{H}_2Cl$), 3.65 (3H, s, $-OC\underline{H}_3$).

Methyl *cis*-2-Acetylcyclohexanecarboxylate (II-2)——The foregoing I-2 was catalytically hydrogenated in the similar manner as in the case of II-1 to give a colorless liquid, bp 98—99°/4 mmHg. Yield, 89.1%. *Anal.* Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.77; H, 9.06. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 (ester CO), 1710 (ketone CO). PMR δ: 2.07 (3H, s, $-COC\underline{H}_3$), 3.65 (3H, s, $-OC\underline{H}_3$).

Reduction of II-2 to 3-Methyl-*cis*-hexahydrophthalides (IVc and IVd)——i) Reduction of II-2 with $NaBH_4$ in the similar manner as in the case of II-1 gave a mixture of IVc and IVd quantitatively, which was shaken in a few minutes with a 1.5% aqueous solution containing 0.8 molar equivalent of NaOH. The residual oil was extracted with ether and the aqueous layer was acidified to separate out another oil, which was extracted with ether. Of two oils obtained from these extracts after evaporation of the solvent, the former oil contained IVd in a rich amount and the latter, IVc in a rich amount. By repetition of this procedure, the separation of IVd and IVc having more than 95% purity was effected. IVc: Colorless liquid, bp 86°/4 mmHg. *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.50; H, 9.00. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1770 (lactone). IVd: Colorless liquid, bp 93°/3 mmHg. *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.10; H, 9.20. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1764 (lactone CO). The composition of the crude lactone mixture (IVc and IVd) obtained after reduction was in the ratio 3: 2. GC retention time: IVc 6.6 min; IVd 7.8 min.

16) All melting points were uncorrected. PMR spectra were determined in deuteriochloroform with Varian A-60A Analytical Spectrometer using tetramethylsilane as an internal reference unless specified otherwise. Condition of gas chromatograph (GC): Column, Carbowax 20M 0.3 × 100 cm; Column temperature, 200°; Carrier gas, N_2.

ii) A solution of 3-methylphthalide (VI) (6.0 g) in acetic acid (60 ml) was catalytically hydrogenated over PtO_2 (600 mg) at room temperature under atmospheric pressure for 7 hr. An amount of H_2 uptake was 3470 ml. After removal of the catalyst by filtration, the mother liquor was concentrated *in vacuo* and the residue was shaken with a mixture of ether and 10% Na_2CO_3 solution. The ethereal solution was washed with water, dried over Na_2SO_4, and evaporated and the residue was distilled to give a colorless liquid, bp 129—132°/9.5 mmHg (a mixture of IVc and IVd in the ratio 1: 13). Yield, 3.5 g.

Isomerization of I-2 to I-1——A mixture of I-2 (50 mg), Na_2CO_3 (12 mg) and MeOH (5 ml) was kept standing at room temperature for 3.5 hr. Aftet removal of the solvent by evaporation *in vacuo* below 30°, the residue was extracted with ether and the ethereal solution was washed with water, dried over Na_2SO_4 and evaporated to give crystals, mp 62—63°. Yield, 40 mg (80%). The product was identified with I-1 by the mixed fusion, IR and PMR.

Isomerization of II-2 to II-1——A solution of II-2 (100 mg), 10% HCl (0.5 ml) and EtOH (0.5 ml) was heated under reflux for 35 min, and evaporated *in vacuo*. The residual mass was treated with cold ether to afford crystals (20 mg, 21.6%), mp 132.5—134.5°, undepressed on admixture with III. The composition of the oil obtained from the ethereal solution after removal of the crystals was II-1: II-2=9: 1 by GC. GC retention time: II-1, 4.4 min; II-2, 5.3 min. Moreover, II-2 was hydrolized with 10% NaOH in EtOH under reflux for 1.4 hr to afford III in an 82% yield.

Isomerization of IVc and IVd to IVb and IVa——i) A mixture of IVc(120 mg) and 10% NaOH (1.5 ml) was heated under reflux for 7 hr, acidified with HCl and extracted with ether. The ethereal solution was washed with water, dried over Na_2SO_4, evaporated and distilled *in vacuo* to afford a colorless oil (80 mg, 67%), bp 92°/3.5 mmHg, which was identified with IVb by IR and PMR. Heating of IVc with hydrazine hydrate in EtOH for a long time furnished Vb in a 74% yield.

ii) A mixture of IVd (2.0 g) and 10% NaOH (100 ml) was heated under reflux for 60 hr. The reaction mixture treated as above gave colorless prisms (1.45 g, 72.5%), mp 42—44°, undepressed on admixture with IVa.

***cis*-Hexahydrophthalide (VIII-2)**——i) A solution of phthalide (VII) (2.0 g) in AcOH (35 ml) was catalytically hydrogenated over PtO_2 (500 mg) at room temperature and under atmospheric pressure for 3 hr. An amount of H_2 uptake was 1490 ml. When treated in a usual manner, was obtained a colorless liquid (VIII-2) (1.1 g, 52.5%), bp 121—122.5°/12 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1775 (CO). This compound was heated with hydrazine hydrate in anhyd. EtOH to convert to *cis*-2-hydroxymethylcyclohexanecarbohydrazide, mp 106.5—107.5° (lit.[9], mp 106°), which on heating with 10% KOH–EtOH for 1 hr was reverted to the original VIII-2 (identified by IR). Hydrolysis of VIII-2 with 10% NaOH under reflux for 60 hr gave *trans*-2-hydroxymethylcyclohexanecarboxylic acid (IX) as colorless needles, mp 106—109° (recrystallized from ether–petroleum ether). *Anal.* Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 61.14; H, 8.60. IR ν_{max}^{KBr} cm^{-1}: 3460 (OH), 3200—2400, 1715 (COOH).

ii) A solution of VII (5 g) in EtOH (100 ml) was catalytically hydrogenated over Raney Ni (5 g) with an initial pressure of 87 kg/cm^2 and at 150° for 3 hr and the resulting mixture was treated in a usual manner to afford a colorless liquid (3.2 g, 61%), bp 121—123°/10 mmHg, which was identified to be VIII-2 by IR.

***trans*-Hexahydrophthalide (VIII-1)**——The foregoing acid (IX) (200 mg) was heated at 125—135° for 30 min and distilled *in vacuo* to give a colorless liquid (100 mg, 56.4%), bp 120—121°/12 mmHg. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765 (CO). Treatment of the product with hydrazine hydrate furnished the corresponding hydrazide, mp 176—177° (lit.,[9] mp 176°).

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