Organic Chemistry Research Laboratory,
Tanabe Seiyaku Co., Ltd.
Toda, Saitama

Yasuhiko Sato
Hideo Nakai
Tomishige Mizoguchi
Masazumi Kawanishi

Faculty of Pharmaceutical Sciences,
Hokkaido University
Kita-12-jo, Nishi-6-chome, Sapporo

Yuichi Kanaoka

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Stereochemistry of 3-Methylhexahydrophthalide

Four stereoisomers (IIa, IIb, IIc and IId) of 3-methylhexahydrophthalide were synthesized according to the scheme illustrated in Chart 1 and configurations of these lactones were clarified from isomerization, reactivity with hydrazine, and from spectrometric data of proton magnetic resonance (PMR) and mass spectra.

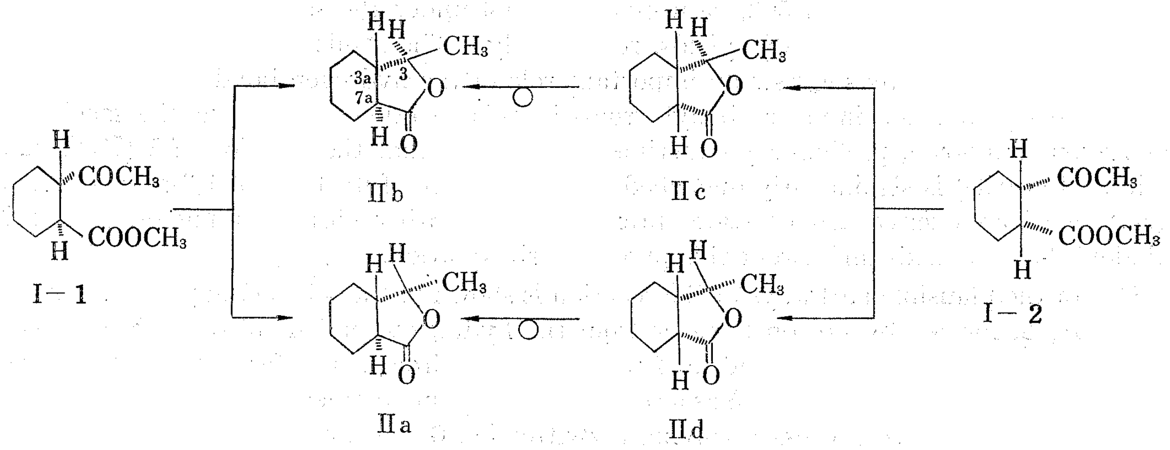

Chart 1

Starting from *trans*-2-methoxycarbonylcyclohexanecaroxylic acid *via* acid chloride and diazoketone, the corresponding ω-chloroketone[1] (mp 62°) was prepared and by dechlorination over Pd-charcoal catalyst, converted to methyl *trans*-2-acetylcyclohexanecarboxylate (I-1, bp 99—100°/4 mmHg). Reduction of the ester (I-1) with sodium borohydride in methanol gave two isomers (IIa and IIb) of 3-methyl-*trans*-hexahydrophthalide in a ratio of IIa: IIb=2: 3. Separation of IIb (bp 92°/3.5 mmHg) from IIa (mp 43°) utilized the difference in the rate of lactone-ring opening. The mixture of IIa and IIb was treated with hydrazine hydrate at a room temperature and the precipitated hydrazide (mp 196°) was collected by filtration, and another hydrazide (mp 133°) of IIa was obtained by heating the mother liquor with an additional amount of hydrazine hydrate. The original lactones were reproduced on hydrolysis of the above hydrazides with concentrated hydrochloric acid. In a similar

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[1] S. Kimoto, M. Okamoto, M. Uneo, S. Ohta, M. Nakamura, and T. Niiya, *Chem. Pharm. Bull.* (Tokyo), **18**, 2141 (1970).

manner as above, two stereoisomers (IIc and IId) of 3-methyl-*cis*-hexahydrophthalide were prepared from methyl *cis*-2-acetylcyclohexanecarboxylate[2] (I-2, bp 98—99°/4 mmHg). The method using hydrazine hydrate is difficult to separate IIc and IId, but the lactone-ring opening of IId by diluted sodium hydroxide solution was slower than that of IIc. The mixture of IIc and IId was added to 1.5% aqueous solution containing 0.8 molar equivalent of sodium hydroxide, the resulting mixture was stirred for a few minutes and devided into an oily layer (containing IId in larger quantities) and an aqueous layer, which on acidification gave another oil (containing IIc in larger quantities). The foregoing oily layer and the oil obtained by acidifying the aqueous solution were each treated again with diluted alkaline solution. After repetition of this operation, IId (bp 94°/3 mmHg) and IIc (bp 86°/4 mmHg) were isolated in almost pure state. Of these four lactones, IIa is obtained in a pure state as crystals, but the others are oily substances. Purity of the latter was checked by gas chromatography (column 0.3×100 cm of Carbowax 20 M; column temperature: 200°; carrier gas: N_2). As the retention time of IIc was almost equal to that of IIb, there remains a question of its purity. When boiled with 10% sodium hydroxide solution, the *cis*-lactones (IIc and IId) converted to the corresponding *trans*-lactones (IIb and IIa) with inversion of the configuration at C-7a. From these evidences, mutual relationship of configuration among these four stereoisomers was clarified.

The PMR spectra listed in Table I show that the coupling constants, J H(3)—H(3a), of *trans*-lactones (IIa and IIb) are 6.7 and 9.7 Hz. Therefore, it is obvious that IIa and IIb possess α- and β-methyl groups respectively from the well-known Karplus rule.[3] On the other hand, the J values of *cis*-lactones (IIc and IId) are 4.2 and 3.6 Hz and difference between them is not large enough to assign either to IIc and IId. However, as mentioned above, transformation of IId to IIa and IIc to IIb is only due to inversion of C-7a configuration and, therefore, it is obvious that IId and IIc should possess α-methyl and β-methyl, respectively.

In order to obtain more informations, PMR spectra of *cis*- and *trans*-hexahydrophthalide (III-2 and III-1), prepared according to the literature[4,5] were taken in the presence of Eu$(DPM)_3$, but conclusive evidence was not obtained.

In mass spectra, base peaks of *trans*-ring-fused IIa, IIb and III-1 were found at m/e 67 and, in contrast, those of *cis*-ringfused IIc, IId and III-2 were found at m/e 81.

TABLE I. Proton Magnetic Resonance Data[a] of the Four Stereoisomers of 3-Methylhexahydrophthalide (IIa, IIb, IIc, and IId)

	Chemical shifts (δ)		Coupling constants (Hz)	
	CH_3	H(3)	J CH_3-H(3)	J H(3)-H(3a)
IIa	1.34	4.65	6.7	6.7
IIb	1.28	4.14	6.1	9.7
IIc	1.31	4.30	6.4	4.2
IId	1.34	4.44	6.5	3.6

a) Deuteriochloroform solutions of 0.5—0.7 mole concentration are used.

Kyoto College of Pharmacy,
Yamashina-Misasagi
Higashiyama-ku, Kyoto, 607, Japan

YASUHIRO FUJIWARA
SHOSHICHIRO KIMOTO
MASAO OKAMOTO

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[3] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
[4] P. Kolsaker, *Acta Chem. Scand.*, **16**, 1056 (1962).
[5] H. Christol, A. Donche, and F. Plenat, *Bull. Soc. Chim. France*, **1966**, 2535.