Antibacterial Activity of 3-Methylcyclopentanone Derivatives in Relation to Methylenomycins

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Abstract : 3-Methylcyclopentanone derivatives were synthesized for examination of antibacterial activity, and it was evaluated by molecular orbital calculation.

This parameter at minimum inhibitory concentration(MIC) was found closely correlated with absolute electronegativity(χ) derived from the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital(LUMO). The values of ΔN and ΔE calculated from χ and absolute hardness(η) of 3-methylcyclopentanones and amino acids also showed good correlation with MIC. In relation to methylenomycins, cyclopentanone antibiotics, antibacterial activity was investigated by comparing the χ , ΔN and ΔE .

2,3-Epoxy-3-methyl-5-methylenecyclopentanone 4 whose antibacterial activity was the strongest, may possibly have potential as a cyclopentanone antibiotic based on χ , ΔN and ΔE data.

Key words : antibacterial activity, 3-methylcyclopentanones, methylenomycins, absolute electronegativity(χ), quantity of electron transfer(ΔN), stabilization energy(ΔE)

1 Introduction

Methylenomycin A and B were firstly isolated from a strain of *Streptomyces violaceruber* and claimed the structure for 4-carboxy-2,3-dimethyl-2,3-epoxy-5-methylenecyclopentanone and 2,3-dimethyl-5-methylene-2-cyclopentenone, respectively¹⁾⁻³⁾. Those compounds known as methylenomycins were medicinally important cyclopentanone antibiotics and much attention was devoted on the synthesis of those²⁾⁻⁷⁾.

We were interested in the compounds of 3-methyl-5-methylene-2-cyclopentenone 3 and 2,3-epoxy-3-methyl-5-methylenecyclopentanone 4 which are structurally similar to methylenomycin A and B and simplicity in structures prompted us to synthesize both as well as their related compounds. And the evaluation of antibacterial activities of those was a focus of interest.

Synthetic works for 3-methyl-2-cyclopentenone 1, 2,3-epoxy-3-methylcyclopentanone 2 as well as

3 and 4 were carried out starting from 2,5-hexanedione(acetyl acetone). The epoxydation of 1 and exomethylenation of 1 and 2 were conducted by usual manner as shown in Fig. 2. On the reaction with chloride ion, both 2 and 4 were easily converted to 2-chloro-3-methyl-2-cyclopentenone 5 and 2-chloro-3-methyl-5-methylene-2-cyclopentenone 6, respectively.

For the evaluation of biological activity, absolute hardness(η : originated from the principle of hard and soft acids and bases) and absolute electronegativity(χ) which calculated from HOMO, LUMO⁸⁾ of 3-methylcyclopentanones were discussed with a consideration of a lipophilic character of these. It is generally understood that the biological activity (or antibacterial activity) has been proposed to involve binding of the substrate with amino acid residue in enzyme or protein. Especially, the amino acid residues in active center in enzyme are generally composed of -SH, -OH or -NH₂(=NH) groups which originate from cysteine, serine or lysine(histidine), respectively⁹⁾. Binding these amino acid

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Fig. 1 Methyleneomycin (A & B) and Related Compounds.

Fig. 2 Synthetic Routes for 3-Methylcyclopentanones.

residues with substrate means an inactivation of enzyme and this develops to the antibacterial activity. Studying the reaction of these amino acids with 3-methylcyclopentanones seemed an important aspect for the discussion of the antibacterial activity. Amino acids like these have electron donating groups of $-\text{SH}$, $-\text{OH}$ or $-\text{NH}_2(=\text{NH})$, while 3-methylcyclopentanones containing the enone or epoxy functional groups in the molecule would serve as electron accepting groups. Under these compounds of both, the reaction of Michael type would be expected to occur as seen in the literature¹⁰⁾.

For further discussion of antibacterial activity, a molecular interpretation of binding affinity of amino acid and 3-methylcyclopentanones was incorporated with the considerations of the quantity of electron transfer (ΔN) from amino acid to 3-methylcyclopentanones and the stabilization energy (ΔE) for binding both⁹⁾. The χ , ΔN and ΔE of methylenomycins were also compared with those of the compounds (1~6), and the relationship between the structure and antibacterial activity of those related compounds was discussed.

2 Experimental

2.1 Synthesis

GC-MS spectra were taken on a Hewlett Packard 5890 Q-pole spectrometer at 70 eV and major peaks were indicated as m/z . (methylsilicone gum 10 m, 80-150°C/5°C rating, flow rate He 45 ml/min.) NMR spectra were recorded on a JEOL JNM-MY 60 and IR spectra were obtained on a Shimadzu IR 400 spectrometer, respectively.

3-Methyl-2-cyclopentenone(1)

This compound was easily prepared from the treatment of acetylacetone in dilute alkaline solution¹¹⁾. Also, this was supplied by Tokyo Kasei Kogyo Co., Ltd. bp. 90 ~ 95°C/17 mm MS m/z (rel.int.): 96(M^+ , 100), 81(M-15, 36), 67(39), 53(26) IR $\nu_{\text{max}}(\text{film})\text{cm}^{-1}$: 3450, 2850, 1670, 1590, 1400, 1250, 1150, 930, 805 $^1\text{H-NMR}$ (CCl_4) δ : 2.08 (3 H, s, CH_3), 2.27-2.57 (4 H, m, $2\times\text{CH}_2$), 5.75 (H, s, $\text{C}=\text{CH}$).

2,3-Epoxy-3-methylcyclopentanone(2)

9.6 g of 1 in 60 mL of MeOH was converted to 2 with 15 mL of 30% H_2O_2 in usual manner¹²⁾. bp. 65 ~ 70°C/15 mm MS m/z (rel.int.): 112 (M^+ , 100), 97 (M-15, 8.6), 83(12.9), 69(39.8), 55(57) IR ν_{max}

(film) cm^{-1} : 3450, 2950, 1740, 1410, 1260, 1220, 1060, 840, 800 $^1\text{H-NMR}(\text{CCl}_4)$ δ : 1.51 (3H, s, CH_3), 2.0-2.14 (4H, m, $2\times\text{CH}_2$), 2.96 (H, s, epoxy-H).

3-Methyl-5-methylene-2-cyclopentenone(3)

To a stirred solution of NaOEt (0.04 mol) in 30 mL of EtOH was added 2.9 g of 1 and 5.8 g of ethyl oxalate and the mixture was stirred for 1 hr at room temperature. The resulted sodioderivative of (1)-oxalate was poured onto THF and treated with 9 mL of 37% formalin. After extraction with ether, extracts was washed with 10% KHCO_3 and dried over Na_2SO_4 . Usual work up gave 2.8 g of 3 as a light brown oil. MS m/z (rel.int.): 108 (M^+ , 100), 93 (M-15, 2.2), 79 (76), 65 (8.6), 53 (5.4) IR $\nu_{\text{max}}(\text{film})\text{cm}^{-1}$: 3400, 2900, 1740, 1680, 1640, 1600, 1410, 1380, 1260, 1180, 1100, 1000, 920, 850 $^1\text{H-NMR}(\text{CCl}_4)$ δ : 2.1 (3 H, s, CH_3), 3.16 (2 H, m, CH_2), 5.80 (H, s, =CH at s-trans C=O), 5.9 (H, s, =CH at s-cis C=O), 6.05 (H, s, =CH at s-cis C=O)

2,3-Epoxy-3-methyl-5-methylenecyclopentanone(4)

To a stirred suspension of NaH (1.7 g) in 30 mL of ether was added 4.5 g of 2 and 7.3 g of ethyl oxalate, and then a few drops of EtOH was added to initiate the reaction. After stirring for 3 hrs at room temperature, the resulted brown colored mixture was poured into water and the sodioderivative of (2)-oxalate was extracted with water for several times. To the water extracts was added 12 mL of 37% formalin and the mixture was stirred for 1 hr at room temperature. After extraction with ether, extracts was concentrated *in vacuo* and subjected to a silicagel column chromatography (ether : hexane = 1 : 1) for purification. 300 mg of 4 was isolated as a colorless oil. MS m/z (rel.int.): 124 (M^+ , 18), 95 (100), 82 (11), 67 (84), 54 (23) IR $\nu_{\text{max}}(\text{film})\text{cm}^{-1}$: 3300, 2905, 2915, 1760, 1730, 1690, 1640, 1440, 1420, 1400, 1370, 1180, 1160, 1100, 1030, 810 $^1\text{H-NMR}(\text{CCl}_4)$ δ : 1.59 (3 H, s, CH_3), 2.68-2.84 (2 H, m, CH_2), 3.31 (H, s, epoxy-H), 5.35 (H, s, =CH at s-cis C=O), 6.05 (H, s, =CH at s-cis C=O)

2-Chloro-3-methyl-2-cyclopentenone(5)

30 mg of 2 in 1 mL of acetone was mixed with 5 mL of 1% saline at room temperature and left overnight. Extraction with ether gave 5 as a colorless oil. MS m/z (rel.int.): 132 (M^+ + 2, 32.6), 130 (M^+ , 100), 117 (4.3), 115 (15.2), 104 (9.8), 102

(30.4), 95 (19.6), 89 (3.2), 87 (10.8), 67 (63), 65 (16.3) IR $\nu_{\text{max}}(\text{film})\text{cm}^{-1}$: 3460, 2900, 1650, 1580, 1410, 1240, 1140, 940, 810 $^1\text{H-NMR}(\text{CCl}_4)$ δ : 2.12 (3 H, s, CH_3), 2.30-2.60 (4 H, m, $2\times\text{CH}_2$)

2-Chloro-3-methyl-5-methylene-2-cyclopentenone(6)

20 mg of 4 in 1 mL of acetone solution was mixed with 5 mL of 1% saline as above and the same treatment afforded 6 as a colorless oil.

MS m/z (rel.int.): 144 (M^+ + 2, 33.0), 142 (M^+ , 100), 129 (1.0), 127 (3.2), 116 (9.6), 114 (34.4), 107 (22.6), 101 (2.2), 99 (9.7), 79 (90.3), 77 (60.2), 75 (6.5), 73 (8.6) IR $\nu_{\text{max}}(\text{film})\text{cm}^{-1}$: 3350, 2920, 1720, 1650, 1630, 1590, 1400, 1370, 1230, 1160, 1080, 950, 900, 860 $^1\text{H-NMR}(\text{CCl}_4)$ δ : 2.15 (3 H, s, CH_3), 3.22 (2 H, m, CH_2), 5.30 (H, s, =CH at s-cis C=O), 6.0 (H, s, =CH at s-cis C=O)

2.2 Measurements of Antibacterial Activity

Paper disk method was conveniently used for the comparison of the tested compounds and a measurment of MIC of those was performed by the previous method¹³⁾. The result was shown in Table 1.

2.3 Metabolite Study of the Compounds

To learn a metabolite of the tested compounds, GC-MS study was incorporated. To an each 3 mL of *Bacillus subtilis* IFO 3009 suspended in isotonic sodium chloride solution and the same volume of without bacteria solution, was added the 100 μL of 3-methylcyclopentanones in 1% acetone solution and 2 μL of ethylbenzene as an internal standard, and whole was incubated at 36°C for each incubation hour. After each incubation hour, 2 mL of ether was added for the extraction of the tested compounds and the metabolites, and the extracts were concentrated *in vacuo*. To the residue was added a 50 μL of acetone and 5 μL of which was injected for GC-MS analysis.

2.4 Computer Calculation Method

Throughout this paper, semiempirical quantum chemical calculation has been performed by using MOPAC 97 in winMOPAC(v.2) program package released by Fujitsu Co., Ltd.¹⁴⁾. All the structures in 3-methylcyclopentanones and lysine, cysteine, serine and histidine were optimized with AM1 Hamiltonian. The orbital energies of HOMO and LUMO, absolute hardness(η) and absolute electronegativity(χ) of 3-methylcyclopentanones and amino acids were calculated from following equations and the results were listed in Table 2.

Table 1 Antibacterial Activities of 3-Methylcyclopentanone Derivatives.

		Inhibition zones*		MIC** ($\mu\text{g/mL}$)	
		<i>B. subtilis</i> IF03009	<i>E. coli</i> IF03301	<i>B. subtilis</i> IF03009	<i>E. coli</i> IF03301
3-Methyl-2-cyclopentenone	(1)	+	+	410	420
2,3-Epoxy-3-methylcyclopentanone	(2)	$\pm$	+	520	500
3-Methyl-5-methylene-2-cyclopentenone	(3)	++	++	200	180
2,3-Epoxy-3-methyl-5-methylenecyclopentanone	(4)	+++	+++	70	40
2-Chloro-3-methyl-2-cyclopentenone	(5)	$\pm$	+	420	420
2-Chloro-3-methyl-5-methylene-2-cyclopentenone	(6)	+	+	340	400
Sorbic acid		$\pm$	+	500	500

* 30 μL of 1% acetone solution of the tested compounds were absorbed in paper discs (8mm). After drying briefly, these were subjected for the test. zone size: +++ 30-40mm, ++ 20-29mm, + 10-19mm, $\pm$ 8-9mm

** 10 $\mu\text{g/mL}$ gradations in concentrations were used. Figures showed distinct no growth concentrations.

Table 2 Calculated Absolute Hardness (η), Electronegativity (χ) of 3-Methylcyclopentanones and Some Amino Acids (eV).

		HOMO	LUMO	χ	η
3-Methyl-2-cyclopentenone	(1)	- 10.071	- 0.047	5.059	5.012
2,3-Epoxy-3-methylcyclopentanone	(2)	- 10.449	0.484	4.983	5.467
3-Methyl-5-methylene-2-cyclopentenone	(3)	- 10.026	- 0.259	5.143	4.884
2,3-Epoxy-3-methyl-5-methylenecyclopentanone	(4)	- 10.460	- 0.194	5.327	5.133
2-Chloro-3-methyl-2-cyclopentenone	(5)	- 9.736	- 0.312	5.024	4.712
2-Chloro-3-methyl-5-methylene-2-cyclopentenone	(6)	- 9.720	- 0.487	5.104	4.617
Lysine		- 9.940	1.175	4.383	5.558
Cysteine		- 9.223	0.520	4.352	4.872
Serine		- 10.581	0.912	4.835	5.747
Histidine		- 9.191	0.556	4.318	4.874

* At the AM1 level

$$\eta = 1/2(\partial\mu/\partial N)_\nu = 1/2(\partial^2 E/\partial N^2)_\nu = 1/2(A-I)$$

$$\chi = -\mu = (\partial E/\partial N)_\nu = -1/2(I+A)$$

$$\eta = 1/2(\epsilon_{\text{LUMO}} - \epsilon_{\text{HOMO}}), \quad \chi = -1/2(\epsilon_{\text{HOMO}} + \epsilon_{\text{LUMO}})$$

where ν , E and μ are the external potential, the energy and the chemical potential of the ground state with N electrons. I and A are ionization energy and electron affinity in eV, respectively.

The quantity of electron transfer(ΔN) and stabilization energy(ΔE) for the reaction of 3-methylcyclopentanones with amino acids, were calculated using following equations⁸⁾.

$$\Delta N = (\chi_B - \chi_A)/2(\eta_A + \eta_B)$$

$$\Delta E = -(\chi_B - \chi_A)^2/4(\eta_A + \eta_B)$$

where A and B represent the χ and η of amino acids and 3-methylcyclopentanones, respectively.

3 Results and Discussion

GC-MS study revealed the metabolites of the 3-methylcyclopentanones. The peaks of the compounds (1 and 3) in GC showed no remarkable change at elapsed incubation times, but on the compounds (2 and 4), appeared new peaks at 1 hour elapsed incubation and gradually increased with a decrease of 2 and 4. These new peaks were identified as 2-chloro-3-methylcyclopentenones, i.e.(5 and 6). These compounds were non-enzymatically formed products, which were confirmed by the experiment without bacteria incubation and the reaction with saline and the compounds(2 and 4). No conversion was occurred without chloride ion on both compounds. There was a literature dealing non-enzymatical formation of chlorinated

products in biosynthesis of epoxydon and related compounds¹⁵⁾. Also, it was confirmed that the Cl^- and the C2 at epoxy ring of the compounds(2 and 4) were found to react by the reaction step method in computer calculation and graphically shown LUMO of C2 at epoxy ring of the compounds(2 and 4) were big enough to react with HOMO of Cl^- . Therefore, the Cl^- may attack the epoxy ring at C2 of the compounds and then ring opening, followed by dehydration affords the compounds (5 and 6), respectively.

To discuss the antibacterial activity of 3-methylcyclopentanones, the relationships between the values of χ and η as well as MIC of these were investigated, and found that the χ of 3-methylcyclopentanones correlated well with MIC in logarithm as shown in Fig. 3. ($r = -0.981$ for *B.subtilis* and -0.960 for *E.coli*) This means the compounds of higher χ show stronger antibacterial activity than those of lower. But the relationship between η of 3-methylcyclopentanones and MIC in logarithm did not show clear correlation. ($r = -0.034$ for *B.subtilis* and 0.065 for *E.coli*).

It is likely that the antibacterial activity of 3-methylcyclopentanones is controlled by absolute electronegativity more than absolute hardness.

The lipo-hydrophilic character of a molecule has been well stated and is useful method for the evaluation of biological activity^{16)~18)}.

Log P(logarithm of partition coefficient) of the compounds(1 ~ 6) and 3-methylcyclopentanone were calculated using the Tables of physicochemical constants in aliphatic compounds¹⁷⁾ and the substituent constants(π) of the compounds (1~6) were calculated from log P of each compound - log P of 3-methylcyclopentanone. Using the substit-

uent constants, regression analysis was made on the effect of substituents in antibacterial activity of 3-methylcyclopentanones on *B.subtilis* and *E.coli*.

However, the low correlation coefficient was found between the observed and the calculated MIC in molar concentration expressed as $\log(1/C)$. (i.e. $\log(1/C) = 2.481 + 0.0467 \pi^2 - 0.1427 \pi$, $r = 0.198$ for *B.subtilis* and $\log(1/C) = 2.488 - 0.0944 \pi^2 - 0.3658 \pi$, $r = 0.285$ for *E.coli*) It seems that the molecules having functional groups restricted within benzene ring, for instance, would afford a good correlation between the observed and the calculated biological activity¹⁶⁾. But in 3-methylcyclopentanones, variety in functional groups in cyclopentanone rings, it is hardly expect to have a good correlation. The correlation coefficient between the χ and logP also showed low value. ($r = -0.207$).

We incorporated ΔN and ΔE for further interpretation between 3-methylcyclopentanones and amino acids like lysine, cysteine, serine and histidine which would contribute to a formation of active center in enzyme. The ΔN value expresses the degree of polarization of charge in amino acid-3-methylcyclopentanones complexes. The positive value of ΔN indicates an electron will transfer from lower χ of amino acid to higher χ of 3-methylcyclopentanone. The ΔE value should be equal to the magnitude of binding affinity with amino acid and 3-methylcyclopentanones. The big value of ΔN or ΔE means the easiness of the reaction with these amino acids and 3-methylcyclopentanones, and would suggest the strength of antibacterial activity of 3-methylcyclopentanones. The correlation coefficient of ΔN vs $\log(\text{MIC})$ on *B.subtilis* was $-0.90 \sim -0.97$ and that of $-\Delta E$ vs $\log(\text{MIC})$ was -0.90

Fig. 3 Plot of Correlation between $\log(\text{MIC})$ on (a) *Bacillus subtilis* and (b) *Escherichia coli* vs. Absolute Electronegativity (χ) of 3-Methylcyclopentanones.

(1) 3-Methyl-2-cyclopentenone (2) 2,3-Epoxy-3-methylcyclopentanone (3) Methyl-5-methylene-2-cyclopentenone (4) 2,3-Epoxy-3-methyl-5-methylenecyclopentanone (5) 2-Chloro-3-methyl-2-cyclopentenone (6) 2-Chloro-3-methyl-5-methylene-2-cyclopentenone

~ -0.99 , respectively as shown in Fig. 4 and 5.

The values of ΔN and ΔE also indicate the good indexes for predicting the antibacterial activity of 3-methylcyclopentanones.

The χ , ΔN and ΔE values for binding affinities of methylenomycins with these amino acids were also investigated for the discussion of antibacterial activities of cyclopentanone antibiotics.

The compounds(11,12 and 13) are antibiotics

known as 4-carboxy-methylenomycin B, methylenomycin A and sarkomycin, respectively and possess the big values of χ as well as ΔN and ΔE compared with other related compounds. To predict the relationship between structure and antibacterial activity, the values of χ , for instance, on the compounds shown in Tables 2 and 3 were compared and the followings were found for the possession of big χ .

Fig. 4 Plot of Correlation between log(MIC) on *Bacillus subtilis* vs. Quantity of Electron Transfer (ΔN) from Amino acids to 3-Methylcyclopentanones.

(1) 3-Methyl-2-cyclopentenone (2) 2,3-Epoxy-3-methylcyclopentanone (3) 3-Methyl-5-methylene-2-cyclopentenone (4) 2,3-Epoxy-3-methyl-5-methylenecyclopentanone (5) 2-Chloro-3-methyl-2-cyclopentenone (6) 2-Chloro-3-methyl-5-methylene-2-cyclopentenone

Fig. 5 Plot of Correlation between log(MIC) on *Bacillus subtilis* vs. Stabilization Energy (ΔE) for Binding Amino acids to 3-Methylcyclopentanones.

(1) 3-Methyl-2-cyclopentenone (2) 2,3-Epoxy-3-methylcyclopentanone (3) 3-Methyl-5-methylene-2-cyclopentenone (4) 2,3-Epoxy-3-methyl-5-methylenecyclopentanone (5) 2-Chloro-3-methyl-2-cyclopentenone (6) 2-Chloro-3-methyl-5-methylene-2-cyclopentenone

Table 3 Values of B, HN and HE Calculated for the Reaction of 2,3-Dimethylcyclopentanones with Some Amino Acids.

	B	Lysine		Cysteine		Serine		Histidine	
		ΔN	$-\Delta E$	ΔN	$-\Delta E$	ΔN	$-\Delta E$	ΔN	$-\Delta E$ (eV)
2,3-Dimethyl-2-cyclopentenone (7)	4.812	0.02072	0.00445	0.02379	0.00548	—	0.00107	0.02554	0.00630
2,3-Dimethyl-2,3-epoxy-2-cyclopentanone (8)	4.890	0.0231	0.00586	0.02641	0.00704	0.00249	0.00007	0.02778	0.00795
2,3-Dimethyl-5-methylene-2-cyclopentenone (Methylenomycin B) (9)	4.917	0.02606	0.00696	0.02956	0.00835	0.00393	0.00016	0.03133	0.00938
2,3-Dimethyl-2,3-epoxy-5-methylene-cyclopentanone (10)	5.238	0.04021	0.01721	0.04454	0.01975	0.01865	0.00377	0.04624	0.02129
4-Carboxy-2,3-dimethyl-5-methylene-2-cyclopentenone (4-Carboxymethylenomycin B) (11)	5.347	0.04691	0.02262	0.05189	0.02582	0.02447	0.00627	0.05365	0.02761
4-Carboxy-2,3-dimethyl-2,3-epoxy-5-methylenecyclopentanone (Methylenomycin A) (12)	5.583	0.05616	0.03371	0.06157	0.03791	0.03441	0.01288	0.06325	0.04002
3-Carboxy-2-methylenecyclopentanone (Sarkomycin) (13)	5.464	0.05004	0.02705	0.05496	0.03057	0.02862	0.00901	0.05663	0.03246
4-Carboxy-2,3-dimethyl-2-cyclopentenone (14)	5.233	0.04121	0.01753	0.04575	0.02017	0.01896	0.00378	0.04750	0.02175
4-Carboxy-2,3-dimethyl-2,3-epoxycyclopentanone (15)	5.534	0.05199	0.02992	0.05692	0.03364	0.03105	0.01085	0.0586	0.03560
4-Carboxy-2,3-epoxy-3-methyl-5-methylene cyclopentanone (16)	5.824	0.06774	0.04882	0.07398	0.05447	0.04570	0.02261	0.0757	0.05700

1. Methyl group at 2 position in cyclopentanone ring is not needed because the χ of 1 is bigger than that of 7, similarly χ of 2 > that of 8, χ of 3 > that of 9 and χ of 4 > that of 10.
2. Carboxy group at 4 position affords big χ by comparison with 7 and 14 or 11 and 9 or 12 and 10.
3. Coexistence of epoxy and exomethylene groups in the molecule contributes bigger χ than single possession of these as seen in the series of 4, 3, 2 or 10, 9, 8 or 12, 15, 11.

Considering the above facts of 1,2 and 3, the structure of 2-demethyl-methylenomycin A 16 possesses a bigger χ than that of methylenomycin A and is expected to possess a strong antibacterial activity.

The data comparison of χ , ΔN and ΔE of methylenomycins with those of 4, which showed the strongest antibacterial activity among the tested compounds, revealed that the values of χ , ΔN and ΔE of 4 ranked between those of the compound(10 and 11), suggesting the 4 would expected to be a promising cyclopentanone antibiotics.

The absolute electronegativity(χ) and quantity of electron transfer(ΔN) or stabilization energy(ΔE) which calculated from χ and η of some amino acids and 3-methylcyclopentanones would suggest the good indexes for predicting the antibacterial activity of these related compounds.

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References

- 1) (a) T. Haneishi, N. Kitahara, Y. Takiguchi, M. Arai, *J. Antibio.*, **XXVII**(6) 386 (1974).
(b) T. Haneishi, A. Terahara, M. Arai, T. Hata, C. Tamura, *J. Antibio.*, **XXVII**(6) 393 (1974).
(c) T. Haneishi, A. Terahara, K. Hamano, M. Arai, *J. Antibio.*, **XXVII**(6) 400 (1974).
- 2) U. Horneman, D. Hopwood, *Tetrahedron Letters*, **33**, 2977 (1978).
- 3) K. Sakai, S. Amemiya, K. Inoue, K. Kojima, *Tetrahedron Letters*, **25**, 2365 (1979).
- 4) (a) J. Jernow, W. Tautz, P. Rosen, J. F. Blount, *J. Org. Chem.*, **44**, 4210 (1979).
(b) J. Jernow, W. Tautz, P. Rosen, T. H. Williams, *J. Org. Chem.*, **44**, 4212 (1979).
- 5) R.M. Jr. Scarborough, B.H. Toden, A.B. Smith III, *J. Am. Chem. Soc.*, **102**, 3904 (1980).
- 6) K. Tonari, K. Machiya, I. Ichimoto, H. Ueda, *Agric. Biol. Chem.*, **45**, 295 (1981).
- 7) (a) K. Toki, *Agric. Biol. Chem.*, **31**, 333 (1958).
(b) R.K. Hill, P.J. Jr. Foley, L.A. Gardella, *J. Org. Chem.*, **2330** (1967).
(c) J.N. Marx, G. Minaskanian, *Tetrahedron Letters*, **43**, 4175 (1979).
- 8) S. Kobayashi, K. Sameshima, Y. Ishii, K. Tanaka, *Chem. Pharm. Bull.*, **43**, 1780 (1995).
- 9) K. Watanabe, "Gendaiyuukikagaku" revised ed., Baifuukann Publication (1990) p.172.
- 10) C.R. Huchinson, *J. Org. Chem.*, **36**, 1854 (1974).
- 11) R.M. Achenson, Sir R. Robinson, *J. Chem. Soc.*, 1127 (1952).
- 12) H.O. House, R.L. Wasson, *J. Am. Chem. Soc.*, **79**, 1488 (1957).
- 13) K. Tonari, *Seikatu Eisei*, **42**, 187 (1998).
- 14) Computer calculation was performed by the configuration as follows. CPU : Intel Pentium III, BIOS RAM : 4MB and System RAM : 768MB.
- 15) K. Nabeta, A. Ichihara, S. Sakamura, *Agric. Biol. Chem.*, **39**, 409 (1975).
- 16) C. Hansch, T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
- 17) M.S. Tute, "Advan. Drug Res." **6**, (1971) p.35, p.63.
- 18) T. Fujita, *Nippon Nougeikagaku-kaisi*, **41**, (1967) R 41.

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[総説]

ステロールおよびトリテルペノイドの
抗発がんプロモーター活性安川 憲^{*1}・秋久俊博^{*2}^{*1} 日本大学薬学部薬学科(〒274-8555 千葉県船橋市習志野台7-7-1)^{*2} 日本大学理工学部物質応用化学科(〒101-8308 東京都千代田区神田駿河台1-8)

21世紀を目前とした今、がんの撲滅は人類に科せられた重要な課題である。我々は、これまでの食用植物や菌類、さらには生薬における発がん抑制物質の探索に関する研究で、種々のステロールやトリテルペンアルコール並びにこれらの誘導体が、抗発がんプロモーターの *in vivo* 一次スクリーニング試験法であるマウス耳殻でのTPA誘発炎症に対して抑制効果を持つ事を見出してきた。本稿では、ステロールやトリテルペノイド類のTPA誘発マウス耳殻炎症、DMBAとTPAによるマウス皮膚二段階発がん実験、TPA誘発Epstein-Barrウイルス活性化、及びTPA誘発HeLa細胞への燐の取り込みなど、種々の抗発がんプロモーター試験における抑制効果について述べた。これらステロールやトリテルペノイドは食用植物、茸、及び生薬類の常成分であることから、毒性は無いか極めて少ないと考えられる。従って、ステロールやトリテルペノイド類は発がん抑制物質として有望な化合物群の一つとして期待される。

(連絡者：安川 憲・秋久俊博) Vol.49, No.6, 571 (2000)

[報文]

メチレノマイシンに関連した
3-メチルシクロペンタノン類の抗菌性について登成 健之介^{*1}・鮫島 圭一郎^{*2}^{*1} 近畿職業能力開発大学校(〒596-0103 大阪府岸和田市稲葉町1778)^{*2} 富士通株式会社(〒261-8588 千葉県千葉市美浜区中瀬9-3)

3-メチルシクロペンタノン類の抗菌性について、分子軌道法のHOMO, LUMOから導かれる絶対的電気陰性度(χ)および絶対的ハードネス(η)について論じ、3-メチルシクロペンタノン類の最小阻止濃度(MIC)とよく相関するのは χ であった。また、これらの物質とタンパク、酵素との反応性が抗菌作用におよぼすと予測し、タンパク、酵素のシンプルなものとして数種のアミノ酸を選び、これらと3-メチルシクロペンタノン類の反応性指標と考えられる電荷移動量(ΔN)および電荷移動親和力(ΔE)を考察した。その結果、これらは3-メチルシクロペンタノン類のMICと強い相関があることが判明した。

五員環抗生物質として知られるメチレノマイシン関連物についても、 χ , η , ΔN および ΔE を比較した結果、抗生物質として知られるものはこれらの絶対値が大きいことが判明し、今回得た2,3-Epoxy-3-methyl-5-methylenecyclopentanone 4も五員環抗生物質として期待できることが予測された。

(連絡者：登成 健之介) Vol.49, No.6, 583 (2000)