

REVISED STRUCTURE FOR THE NAPHTHALENECARBOXYLIC ACID FROM CARZINOPHILIN*

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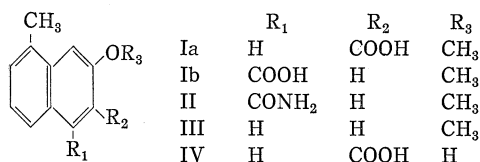
A naphthalenecarboxylic acid was obtained by alkaline hydrolysis of carzinophilin¹⁾ isolated from the fermentation broth of *Str. sahachiroi*, and it was reported that the structure of this acid is 1-methyl-7-methoxynaphthalene-6-carboxylic acid (Ia) based on comparisons of infrared and ultraviolet absorption spectra from the isolated material and related synthetic compounds^{2,3)}.

Recently, we obtained the same naphthalenecarboxylic acid during the structural reinvestigation of carzinophilin and found that some spectroscopic features such as the nuclear magnetic resonance (NMR), mass, and infrared spectra** of this acid were not sufficient evidence for the structure of Ia. In this communication we wish to report the revised structure (Ib) for this acid.

Hydrolysis of carzinophilin with 5% ammonium hydroxide solution afforded a neutral component (II), m. p. 178°C, mass spectrum M^+m/e 215.096 (Calcd. for $C_{13}H_{13}O_2N$: 215.095); and an acid component (Ib), m. p. 180°C, mass spectrum M^+m/e 216.079 (Calcd. for $C_{13}H_{12}O_3$: 216.096).

Since the infrared spectrum of II reveals an amide absorption (ν_{NH} 3200~3400 cm^{-1} , $\nu_{C=O}$ 1640 cm^{-1}), the mass spectrum of II shows a molecular peak at m/e 215, and alkaline hydrolysis of II affords an acid (Ib), we can conclude that II is a primary amide of Ib.

Chart 1.



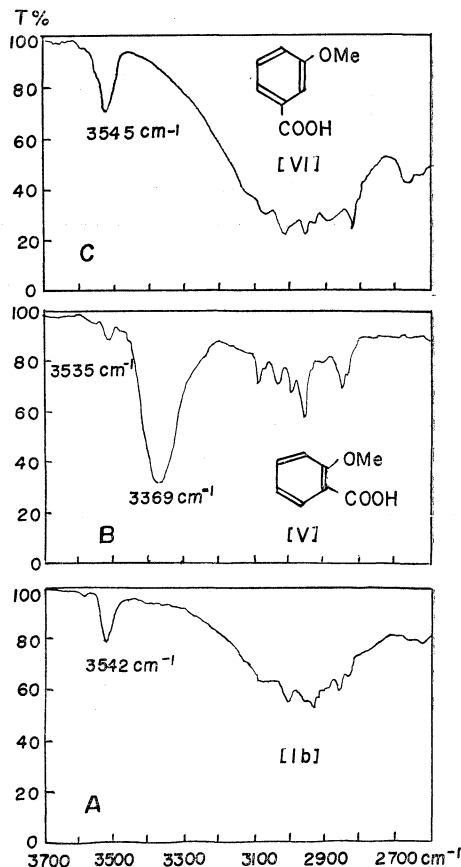
The acid (Ib) was identical with the naphthalenecarboxylic acid obtained by TANAKA *et al.*, from the comparison of NMR spectra and mixed melting point.

Decarboxylation of Ib in the presence of basic copper carbonate in quinoline afforded the naphthalene derivative identified with the authentic 1-methyl-7-methoxynaphthalene³⁾.

Based on an intramolecular hydrogen bonding between hydroxyl and carboxyl groups, TANAKA *et al.* reported that the demethyl derivative of Ia had the structure in which the carboxyl group was located in the position *ortho* to the hydroxyl group as shown by formula (IV). However this conclusion is somewhat questionable, because the estimation of hydrogen bonding was carried out in a crystal state in Nujol.

IR spectrum (Fig. 1) of a dilute solution

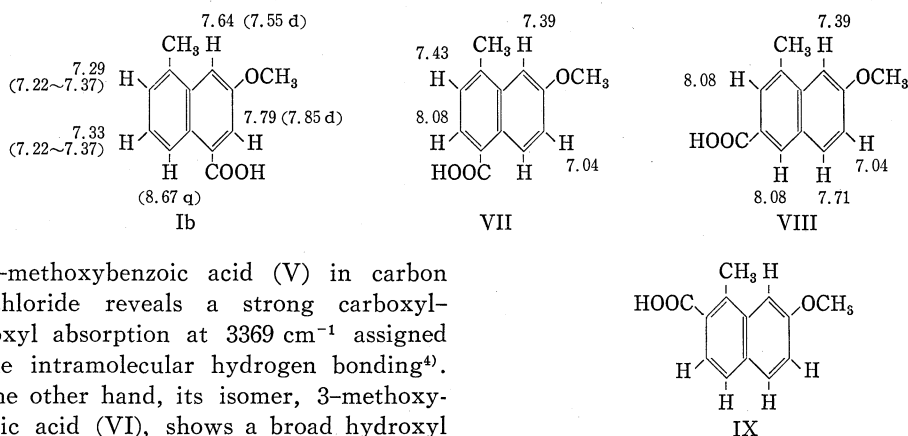
Fig. 1. IR spectra of 1-methyl-7-methoxynaphthalene-5-carboxylic acid (Ib), 2-methoxybenzoic acid (V), and 3-methoxybenzoic acid (VI) (4/1,000 M, in CCl_4)



* Structure of carzinophilin, Part 1.

** IR spectra were measured with Jasco-DS-4039 spectrometer using a 1-cm cell and NMR spectra were measured with Varian HA-100 spectrometer. Mass spectra were measured with Japan Electro Optics JMS-OIS spectrometer.

Chart 2. Calculated chemical shifts (ppm) of the aromatic protons of possible compounds. (The figure in parentheses shows chemical shift observed)

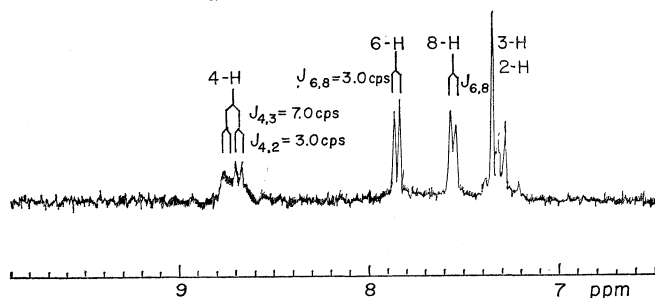


of 2-methoxybenzoic acid (V) in carbon tetrachloride reveals a strong carboxyl-hydroxyl absorption at 3369 cm^{-1} assigned to the intramolecular hydrogen bonding⁴. On the other hand, its isomer, 3-methoxybenzoic acid (VI), shows a broad hydroxyl absorption of an intermolecular hydrogen bonding in the C-H stretching or lower wave number region. Comparison of the IR spectra of Ib and the above-described model compounds shows that the spectrum of Ib is very similar to that of VI. In the mass spectrum, the fragment peak $[M-H_2O]^+$ appears commonly for compounds in which the methoxyl group is located in the position *ortho* to the carboxyl group⁵ such as compound V, but the spectrum of Ib lacks this peak. Therefore, it is apparent that the structure Ia in which the carboxyl group is located *ortho* to the methoxyl group is inconsistent with this spectrum.

From the consideration of the IR and mass spectra of Ib and from the structure of the compound (III) obtained by the decarboxylation of Ib, there are still three possible structures (VII, VIII and IX) in addition to Ib for naphthalenecarboxylic acid in question.

First, the structure IX is excluded from

Fig. 2. NMR spectrum of aromatic protons of 1-methyl-7-methoxy-naphthalene-5-carboxylic acid (Ib) (100 Mc in $CD_3-CO-CD_3$)



the possible structures because the authentic compound melts at 202°C and because its NMR spectrum differs from that of Ib.

From the consideration of the effect of a substituent ($-\text{OCH}_3$, $-\text{CH}_3$ and $-\text{COOH}$) on the chemical shift of aromatic protons^{6,7} and the difference in chemical shift between α - and β -protons of naphthalene ($\alpha\text{H } 7.81\text{ ppm}$, $\beta\text{H } 7.46\text{ ppm}$ in CCl_4)⁷, chemical shifts of aromatic protons in the three possible structures (Ib, VII and VIII) were calculated as shown in Chart 2.

As shown in Fig. 2, the NMR spectrum of Ib shows characteristic peaks in the aromatic region. The double doublet centered at $\delta 8.67\text{ ppm}$, $J(\text{ortho})=7.0$ and $J(\text{meta})=3.0\text{ cps}$, is attributed to the *ortho*-proton of the carboxyl group or especially the *peri*-proton of naphthalene-1-carboxylic acid because it appears at the lowest field and also this peak can be attributed to the H_x of the ABX system of 1,2,3-trisubstituted benzene from the coupling constants. The peaks appearing at $\delta 7.35\text{ ppm}$ doublet, $J(\text{meta})=3.0\text{ cps}$ and $\delta 7.27\text{ ppm}$ doublet, $J(\text{meta})=3.0\text{ cps}$, can be attributed to the two aromatic protons of 1,2,3,5-tetrasubstituted benzene. Consequently, VII and VIII can be excluded from the possible structures. The remaining structure (Ib) is consistent with the above

characterization. As shown in Fig. 2, the peaks are reasonably assigned to each of the aromatic protons and the chemical shifts approximate the calculated values.

In view of the above facts, we can conclude that the structure of naphthalene-carboxylic acid (Ib) is 1-methyl-7-methoxy-naphthalene-5-carboxylic acid.

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MASAYUKI ONDA

YAEKO KONDA

* ATSUKO NOGUCHI

School of Pharmacy, Kitasato
University, Minato-ku, Tokyo

* Department of Chemistry,
Sophia University,
Chiyoda-ku, Tokyo

SATOSHI ŌMURA

TŌJU HATA

Kitasato Institute,
Minato-ku, Tokyo

References

- 1) HATA, T.; F. KOGA, Y. SANO, K. KANAMORI, A. MATSUMAE, R. SUGAWARA, T. HOSHI, T. SHMIA, S. ITO & S. TOMIZAWA: Carzinophilin, a new tumor inhibitory substance produced by *Streptomyces*. I. J. Antibiotics, Ser. A 7 : 107~112, 1954
- 2) TANAKA, M.; T. KISHI & Y. MARUTA: Carzinophilin. I. The structure of methanolysis product. I. J. Antibiotics, Ser. B 12 : 361~364, 1959
- 3) TANAKA, M.; T. KISHI & Y. MARUTA: Carzinophilin. II. The structure of methanolysis product. II. J. Antibiotics, Ser. B 13 : 177~181, 1960
- 4) ŌKI, M. & J. HIROTA: Intramolecular hydrogen bonds of carboxylic acids. (in Japanese) J. Chem. Soc. Japan, Pure Chem. Sect. 86 : 115~130, 1965
- 5) AZEL, T. & H. E. LUMPKIN: Correlation of mass spectra with structure in aromatic oxygenated compound, methyl-substituted aromatic acid and aldehyde. Anal. Chem. 33 : 386~389, 1961
- 6) SPIESECKE, H. & W. G. SCHNEIDER: Substituent effect on the C¹³ and H¹ chemical shifts in monosubstituted benzenes. J. Chem. Phys. 35 : 731~759, 1961
- 7) EVANS, H. B., Jr.; A. R. JARPLEY & J. H. GOLDSTEIN: Nuclear magnetic resonance spectra of mono- and di-substituted benzenes containing OH, SH, NH₂, and COOH. J. Phys. Chem. 72 : 2552~2556, 1968

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