31. Tsutomu Momose, Hiroshi Oya*, Yosuke Ohkura, and Masatake Iwasaki: Studies on Tetralin Derivatives. I. Bacteriostatic Activity *in vitro*.

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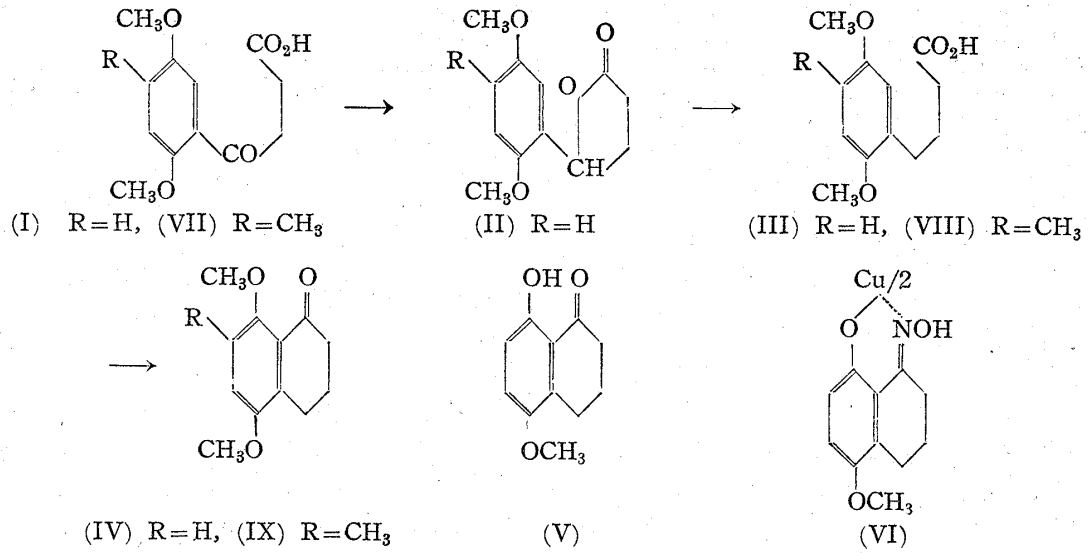
As there is no report on the bacteriostatic activities of tetralin derivatives, the authors prepared some hydroxytetralins, hydroxytetralones, and their derivatives, and tested their antibacterial activities *in vitro* to compare with those of naphthalene derivatives.

ar-1-Hydroxytetralin[1], *ar*-2-hydroxytetralin[2], *ar*-1,4-dihydroxytetralin[3], 5-hydroxytetralone-(1)[4], 6-hydroxytetetralone-(1)[5], 7-hydroxytetralone-(1)[6], and tetrahydronaphthoquinone[7] were prepared according to the literature references.

6,7-Dihydroxytetralone-(1) was prepared by the demethylation of its methyl ether[8], and *ar*-2,3-dihydroxytetralin was obtained similarly from the Clemmensen reduction product of the methyl ether.

5,8-Dihydroxytetralone-(1) and 7-methyl-5,8-dihydroxytetralone-(1) were prepared by the following scheme:



The Friedel-Crafts condensation of hydroquinone dimethyl ether with succinic anhydride in carbon disulfide gave a poor yield, but in nitrobenzene the yield was 87%. The product (I) can be reduced by the Clemmensen method, but it is better to reduce electrolytically to the lactone (II) with mercury cathode in alkaline solution and then to the acid (III) catalytically over palladium-carbon. The ring closure of the chloride to the ketone (IV) is usually done by stannic chloride. On the other hand, elimination of one methyl group occurs by aluminum chloride. The demethylated position is assumed as 8 by the fact that its oxime is precipitated by cupric or nickel ion forming

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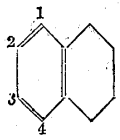
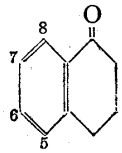
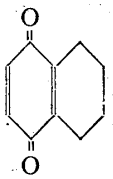
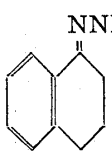
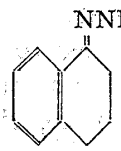
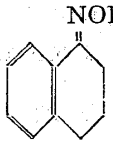
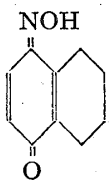
1) Bamberger, Althausse: Ber., 21, 1893(188).
2) Schröter: Ann., 426, 111(1922).
3) Russig: J. prakt. Chem., (2), 62, 32(1900).
4) Nakamura: J. Pharm. Soc. Japan, 61, 292(1941).
5) Papa, Schwenk: J. Org. Chem., 14, 366(1948).
6) Vesely, Strusa: Chem. Zentr., 1933, II, 398.
7) Bamberger, Lengfeld: Ber., 23, 1131(1890).
8) Campbell, Schrage, K. Campbell: J. Org. Chem., 15, 1135(1950).

the complex (VI) the same as that of salicylaldoxime. Further studies on this point will be published elsewhere.

The methyl homologs were prepared similarly with toluhydroquinone dimethyl ether and succinic anhydride, except that the ketoacid (VII) obtained is reduced in a good yield to (VIII) by the Clemmensen method. The cyclisation of the acid chloride was carried out by stannic chloride, and the ketone (IX) was demethylated to dihydroxytetetralone.

The thiosemicarbazones, hydrazones, and oximes of above ketones were obtained by the usual method.

	Substituent	*M. tuberculosis*	*St. aureus*	*E. coli*
	1-OH	16,000	16,000	8,000
	2-OH	8,000	8,000	4.000
	1,4-OH	32,000	128,000	64,000
	2,3-OH	128,000	512,000	128,000
	none	2,000	4,000	2,000
	5-OH	2,000	4,000	2,000
	6-OH	4,000	8,000	8,000
	7-OH	2,000	4,000	2,000
	5,8-OH	16,000	128,000	4,000
	6,7-OH	2,000	4,000	4,000
	$7\text{-}CH_3$-5,8-OH	64,000	128,000	16,000
		32,000	128,000	64,000
	none	32,000	64,000	>8,000
	7-OH	16,000	8,000	>2,000
	5-OH	4,000	4,000	4,000
	6-OH	8,000	64,000	16,000
	7-OH	4,000	4,000	4,000
	5,8-OH	16,000	128,000	32,000
	6,7-OH	>8,000	32,000	8,000
	5,8-OH	16,000	128,000	8,000
	$7\text{-}CH_3$-5,8-OH	64,000	128,000	16,000
		64,000	128,000	64,000

The bacteriostatic activity *in vitro* (in maximum dilution) is shown in the table. It is found that some tetralin derivatives have considerable activities against the bacteria used. Dihydroxytetralins are more active than dihydroxytetralones; monohydroxytetralins and monohydroxytetralones are less active, and their derivatives such as thiosemicarbazones, hydrazones, and oximes have only little biological meaning.

The authors are indebted to Mr. T. Hattori and Miss T. Kawano for the microanalyses.

Experimental*

2,5-Dimethoxybenzoylpropionic Acid (I)—To a solution of 180 g. of hydroquinone dimethyl ether, 150 g. of succinic anhydride, and 850 cc. of anhydrous nitrobenzene, was added 350 g. of anhydrous aluminum chloride in small portions with stirring at 0° to 5°, and stirred for 3 days at this temperature. The mixture was poured on ice, nitrobenzene was removed by steam distillation, and the residual solid was dissolved in aqueous sodium carbonate solution. On acidifying the filtrate there was obtained 270 g. of (I), m.p. 99~100°.

γ-Hydroxy-γ-(2,5-dimethoxyphenyl)-butyrolactone (II)—Cathodic solution was prepared by dissolving 100 g. of 2,5-dimethoxybenzoylpropionic acid in 400 cc. of 5% sodium hydroxide, and anodic solution was 5% sodium hydroxide. This was electrolysed at 5 A. with mercury cathode and platinum anode for 7 hours. The solution was acidified with hydrochloric acid and heated on a water bath, separating oily substance which solidified on cooling. This was extracted with benzene, washed with 5% sodium bicarbonate solution, and evaporated residue was recrystallized from alcohol, forming prisms of m.p. 93°. Yield, 95 g. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.55; H, 6.15.

γ-(2,5-Dimethoxyphenyl)-butyric Acid (III)—10 g. of the lactone dissolved in 50 cc. of glacial acetic acid absorbed ca. 1.1 L. of hydrogen over palladium-carbon catalyst. The solvent was evaporated *in vacuo*, and residual substance was distilled, $b.p_2$ 180~182°, which was recrystallized from benzene-petroleum ether, forming plates of m.p. 63~64°. Yield, 9.5 g. *Anal.* Calcd. for $C_{12}H_{16}O_4$: C, 64.27; H, 7.20. Found: C, 64.22; H, 7.43.

The acid could also be obtained by the Clemmensen reduction of 2,5-dimethoxybenzoylpropionic acid in 40% yield.

5,8-Dimethoxytetralone-(1) (IV)—To a solution of 60 g. of γ-(2,5-dimethoxyphenyl)-butyric acid in 150 cc. of anhydrous benzene was added 60 g. of phosphorus pentachloride at once, and refluxed for 15 minutes. The solution was cooled with ice, 140 g. of anhydrous stannic chloride was added, diluted with the same volume of benzene quickly, and stood overnight. The complex was decomposed with ice-coolded diluted hydrochloric acid, separated benzene layer was washed with aqueous sodium hydroxide solution, and evaporated. The residue was distilled *in vacuo*, $b.p_2$ 140~141°, and recrystallized from petroleum ether to plates of m.p. 60°. Yield, 35 g. *Anal.* Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.85. Found: C, 69.66; H, 6.67.

5-Methoxy-8-hydroxytetralone-(1) (V)—The acid chloride was prepared as above with 15 g. of butyric acid. The solution was poured into 13 g. of anhydrous aluminum chloride suspended in 50 cc. of anhydrous benzene below 10° and refluxed for 15 minutes. It was treated similarly, yielding pale yellow plates of m.p. 95° (from alcohol). *Anal.* Calcd. for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.60; H, 5.76.

The oxime was prepared in diluted alcohol with hydroxylamine hydrochloride and sodium acetate. The yielded plates were recrystallized from alcohol, m.p. 147°. *Anal.* Calcd. for $C_{11}H_{13}O_3N$: N, 6.76. Found: N, 6.52.

This oxime dissolved in diluted alcohol precipitated by cupric or nickel ion from their sodium acetate-buffer solution. *Anal.* Calcd. for $(C_{11}H_{12}O_3N)_2Cu$: Cu, 13.35. Found: Cu, 13.12. *Anal.* Calcd. for $(C_{11}H_{12}O_3N)_2Ni$: Ni, 12.46. Found: Ni, 11.96.

5,8-Dihydroxytetralone-(1)—10 g. of 5,8-dimethoxytetralone was refluxed with 40 g. of hydriodic acid (50%) for 20 minutes in carbon dioxide atmosphere. The mixture was diluted with water, separating yellow prisms which were recrystallized from alcohol, m.p. 181°. Yield, 7 g. *Anal.* Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66. Found: C, 67.28; H, 5.71.

The oxime, prepared by the usual method as colorless plates (from dilute alcohol), m.p. 138°. *Anal.* Calcd. for $C_{10}H_{11}O_3N$: N, 7.25. Found: N, 7.39.

The hydrazone was prepared in water with hydrazine hydrate and recrystallized from water, forming prisms of m.p. 112°. *Anal.* Calcd. for $C_{10}H_{12}O_2N_2$: N, 14.58. Found: N, 14.61.

4-Methyl-2,5-dimethoxybenzoylpropionic Acid (VII)—This acid was synthesized similarly as for (I) from 60 g. toluhydroquinone dimethyl ether, 58 g. of succinic anhydride, 110 g. of anhydrous aluminum chloride, and 300 cc. of nitrobenzene. It was recrystallized from alcohol, forming

* All the melting points are uncorrected.

pale yellow prisms of m.p. 179°. Yield, 78 g. *Anal.* Calcd. for $C_{13}H_{16}O_5$:C, 61.89; H, 6.39. Found: 61.45; H, 5.95.

γ-(4-Methyl-2,5-dimethoxyphenyl)-butyric Acid (VIII)—A mixture of 180 g. of amalgamated zinc, 80 g. of 4-methyl-2,5-dimethoxybenzoylpropionic acid, and 500 cc. of concentrated hydrochloric acid was refluxed for 8 hours. Then 200 cc. of concentrated hydrochloric acid was added and refluxing was continued for additional 4 hours. The solidified substance was dissolved in benzene, washed with water, and the solution was concentrated, separating prisms which were recrystallized from benzene, m.p. 101~102°. Yield, 50 g. *Anal.* Calcd. for $C_{13}H_{18}O_4$:C, 65.52;H, 7.61. Found: C, 65.13; H, 7.44.

7-Methyl-5,8-dimethoxytetralone-(1) (IX)—This ketone was prepared similarly as for (IV) from 45 g. of γ-(4-methyl-2,5-dimethoxyphenyl)-butyric acid, 300 cc. of benzene, 45 g. of phosphorus pentachloride, and 105 g. of anhydrous stannic chloride. It was distilled *in vacuo*, $b.p_6$ 160°, and recrystallized from petroleum ether, forming needles of m.p. 45°. *Anal.* Calcd. for $C_{13}H_{16}O_3$:C, 70.89; H, 7.32. Found:C, 71.11; H, 7.00.

7-Methyl-5,8-dihydroxytetralone-(1)—30 g. of the above methyl ether was demethylated with 120 g. of hydriodic acid (50%). The phenol was recrystallized from alcohol, forming yellow prisms of m.p. 182°. *Anal.* Calcd. for $C_{11}H_{12}O_3$:C, 68.74; H, 6.29. Found:C, 68.37; H, 6.23.

The oxime was recrystallized from alcohol, forming colorless plates, m.p. 227°. *Anal.* Calcd. for $C_{11}H_{13}O_3N$:N, 6.76. Found:N, 6.79.

6,7-Dihydroxytetralone-(1)—3 g. of 6,7-dimethoxytetralone, prepared according to the literature, was demethylated with 10 g. of hydriodic acid (50%). The phenol was recrystallized from water to colorless needles, m.p. 195°. *Anal.* Calcd. for $C_{10}H_{10}O_3$:C, 67.40; H, 5.66. Found:C, 66.91; H, 5.37.

The hydrazone was recrystallized from water, forming needles of m.p. 188° *Anal.* Calcd. for $C_{10}H_{12}O_2N_2$:N, 14.58. Found:N, 14.78.

***ar*-2,3-Dimethoxytetralin**—3 g. of 6,7-dimethoxytetralone was reduced by the Clemmensen method to 6,7-dimethoxytetralin, which was recrystallized from petroleum ether to needles of m.p. 57°. Yield, 1.5 g. *Anal.* Calcd. for $C_{12}H_{16}O_2$:C, 74.57; H, 8.38. Found: C, 75.18; H, 7.92.

***ar*-2,3-Dihydroxytetralin**—The above methyl ether was demethylated with hydriodic acid (50%) and recrystallized from water, forming needles of m.p. 127~128°. *Anal.* Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.24; H, 7.07.

The thiosemicarbazones were prepared with the ketone and thiosemicarbazide in water, refluxing several hours, and were recrystallized from water. Tetralone thiosemicarbazone, m.p. 199°. *Anal.* Calcd. for $C_{11}H_{13}N_3S$:N, 19.16. Found: N, 19.30. 7-Hydroxytetralone thiosemicarbazone, m.p. 209° (decomp.). *Anal.* Calcd. for $C_{11}H_{13}ON_3S$:N, 17.86. Found: N, 17.80.

Other hydrazones were prepared in the usual manner and recrystallized from water. 5-Hydroxytetralone hydrazone, m.p. 188~189°. *Anal.* Calcd. for $C_{10}H_{12}ON_2$:N, 15.90. Found:N, 15.89. 6-Hydroxytetralone hydrazone, m.p. 195°. *Anal.* Calcd. for $C_{11}H_{12}ON_2$:N, 15.90. Found: N, 15.81. 7-Hydroxytetralone hydrazone, m.p. 182°. *Anal.* Calcd. for $C_{10}H_{12}ON_2$:N, 15.90. Found:N, 15.85.

Tetrahydronaphthoquinone oxime, m.p 159°. *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 67.78; H, 6.26. Found: C, 67.70; H, 5.98.

Bacteriological Procedure—*Mycobacterium tuberculosis* H_{37} strain was cultured in Kirchner's medium, supplemented with horse serum to 10% concn. The compounds were dissolved in the medium to make 1:1,000 in concentration and diluted multiplyingly with the same medium. Each test tube containing 5 cc. of solution was inoculated with 0.05 mg. of the bacterium cultured for 3 weeks at 37° in Oka-Katakura's medium. The results were observed after 3 weeks' cultivation at 37°. *Staphylococcus aureus*, Terashima strain, was cultured in semisynthetic medium added with casein hydrolysate in 0.4%, and *Escherichia coli communis* in ammonium medium, with the preparation of solutions carried out as described above. The inoculum was 0.1 cc. of 1:10,000 in dilution of both strains cultured for 24 hours at 37° in broth. The results were observed after 24 hours' cultivation at 37°. These data are given in the accompanying table.

Summary

Some hydroxytetralins, hydroxytetralones, and their derivatives, some of which were newly synthesized, were examined as to their bacteriostatic activities *in vitro* against *Mycobacterium tuberculosis* H_{37}, *Staphylococcus aureus* Terashima, and *Escherichia coli communis*. It was found that *ar*-2,3-dihydroxytetralin, *ar*-1,4-dihydroxytetralin, and its derivatives have some activities.

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