Catalytic Property of Penicillamine-Mo Complexes

Table III presents the results of the reduction of acetylene with the penicillamine–Mo complexes and sodium borohydride system. Indeed, these Mo complexes catalyze the reduction of the substrate to ethylene and ethane, and the reaction was absolutely dependent upon the addition of the complex, the substrate, and borohydride. The reaction of the complex (II) system was enhanced 1.5 fold by ATP. The low activity of the complex (IV) is attributed to less readiness of conversion to catalytically active monomeric form. Unfortunately, the catalytic activity of the complex (I) was low against expectation, nevertheless the high population of paramagnetic species. It is presumed that the low activity of the complex (I) is due to lack of efficient residual coordination sites of Mo for the substrate.

[Chem. Pharm. Bull. 25(2) 349—352 (1977)]

UDC 547.834.2.04.04.09 : 615.31'7.076.7

Synthetic Antibacterials. VII.[1] N-(1,8-Naphthyridin-7-yl)-methylenamine Derivatives

Sadao Nishigaki, Noriko Mizushima, and Keitaro Senga

Pharmaceutical Institute, School of Medicine, Keio University[2]

(Received May 19, 1976)

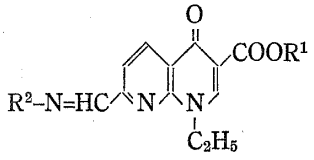
Treatment of ethyl 1,4-dihydro-1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate (**1**) with selenium dioxide afforded a mixture of ethyl 1,4-dihydro-1-ethyl-7-formyl-4-oxo-1,8-naphthyridine-3-carboxylate (**2**) and 1,4-dihydro-1-ethyl-7-formyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (**3**). Condensation of **2** or **3** with respective amines provided the corresponding N-(1,4-dihydro-3-ethoxycarbonyl-1-ethyl-4-oxo-1,8-naphthyridin-7-yl)methylenamine (**4**—**15**) and N-(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-1,8-naphthyridin-7-yl)methylenamine (**16**—**27**), respectively. These compounds were tested for *in vitro* antibacterial activity.

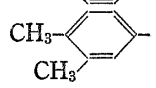
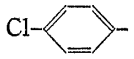
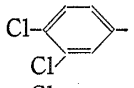
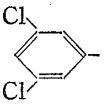
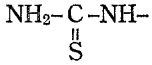
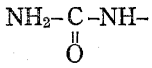
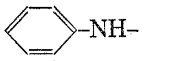
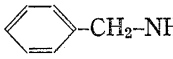
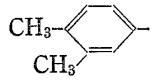
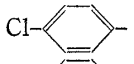
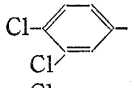
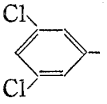
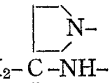
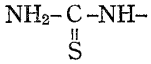
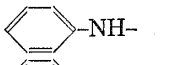
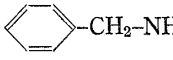
Keywords——N-(1,8-naphthyridin-7-yl)methylenamines; *in vitro* antibacterial activity; selenium dioxide oxidation; ethyl 1,4-dihydro-1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate; ethyl 1,4-dihydro-1-ethyl-7-formyl-4-oxo-1,8-naphthyridine-3-carboxylate; 1,4-dihydro-1-ethyl-7-formyl-4-oxo-1,8-naphthyridine-3-carboxylic acid

In the previous papers[1,3a–c] of this series, we have synthesized a number of 1,8-naphthyridine and pyrido[2,3-*d*]pyrimidine derivatives carrying a vinylene group and found that certain compounds exhibit potent *in vitro* activity against various microorganisms. In connection with these findings, it became desirable to synthesize a series of 1,8-naphthyridine derivatives having an azomethine group at the position 7 to pursue their antibacterial activity since the trivalent nitrogen atom (–N=) and the –CH= group have successfully been interchanged in many bioisosteric systems.[4]

1) Part VI: S. Nishigaki, N. Mizushima, and K. Senga, *Chem. Pharm. Bull.* (Tokyo), 24, 1658 (1976).
2) Location: *35, Shinanomachi, Shinjuku-ku, Tokyo 160, Japan.*
3) *a*) S. Nishigaki, F. Yoneda, K. Ogiwara, T. Naito, R. Dohmori, S. Kadoya, Y. Tanaka, and I. Takamura, *Chem. Pharm. Bull.* (Tokyo), **17**, 1827 (1969); *b*) S. Nishigaki, N. Mizushima, F. Yoneda, and H. Takahashi, *J. Med. Chem.*, **14**, 638 (1971); *c*) S. Nishigaki, K. Ogiwara, S. Fukazawa, M. Ichiba, N. Mizushima, and F. Yoneda, *J. Med. Chem.*, **15**, 731 (1972).
4) A. Burger, "Medicinal Chemistry," Part I, ed. by A. Burger, Wiley-Interscience, New York, 1970, p. 64, and references cited therein.

TABLE I. N-(1,8-Naphthyridin-7-yl)methylenamine Derivatives



Compd. No.	R^1	R^2	mp (°C)	Yield (%)	Recrystn. solvent	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
4	C_2H_5	OH	222—224	28	EtOH	$C_{14}H_{15}O_4N_3$	58.12	5.23	14.53	58.41	5.09	14.73
5	C_2H_5	CH_3	177—178	52	EtOH	$C_{15}H_{17}O_3N_3$	62.70	5.96	14.63	62.43	6.11	14.38
6	C_2H_5		169—170	34	ether	$C_{20}H_{19}O_3N_3$	68.75	5.48	12.03	69.02	5.27	11.89
7	C_2H_5		203—205	27	EtOH	$C_{22}H_{23}O_3N_3$	70.01	6.14	11.13	70.26	5.96	11.11
8	C_2H_5		230—231	26	EtOH	$C_{20}H_{18}O_3N_3Cl$	62.58	4.73	10.95	62.35	4.54	11.06
9	C_2H_5		260—261	36	EtOH	$C_{20}H_{17}O_3N_3Cl_2$	57.43	4.10	10.04	57.70	3.88	10.02
10	C_2H_5		220—222	29	EtOH	$C_{20}H_{17}O_3N_3Cl_2$	57.43	4.10	10.04	57.37	4.12	9.78
11	C_2H_5		183—185	23	ether	$C_{19}H_{24}O_3N_4$	64.02	6.79	15.72	64.08	6.84	15.83
12	C_2H_5		264—266	72	DMF	$C_{15}H_{17}O_3N_5S$	51.86	4.93	20.16	51.62	5.17	20.02
13	C_2H_5		273—275	51	DMF	$C_{15}H_{17}O_4N_5$	54.37	5.17	21.14	54.08	4.89	20.88
14	C_2H_5		283—285	41	EtOH	$C_{20}H_{20}O_3N_4$	65.92	5.53	15.38	65.76	5.24	15.67
15	C_2H_5		224—226	53	EtOH	$C_{21}H_{22}O_3N_4$	66.65	5.86	14.81	66.68	5.91	14.90
16	H	OH	246—248	46	EtOH	$C_{12}H_{11}O_4N_3$	55.17	4.24	16.09	55.17	4.43	15.81
17	H	CH_3	223—225	50	EtOH	$C_{13}H_{13}O_3N_3$	60.22	5.05	16.21	60.27	5.19	16.23
18	H		>300	62	DMF	$C_{18}H_{15}O_3N_3$	67.28	4.71	13.08	67.51	4.68	12.81
19	H		>300	46	DMF	$C_{20}H_{19}O_3N_3$	68.75	5.48	12.03	69.02	5.18	12.09
20	H		275—277	56	DMF	$C_{18}H_{14}O_3N_3Cl$	60.77	3.97	11.81	60.60	3.97	11.70
21	H		289—291	38	DMF	$C_{18}H_{13}O_3N_3Cl_2$	55.40	3.36	10.77	55.38	3.43	10.54
22	H		>300	26	DMF	$C_{18}H_{13}O_3N_3Cl_2$	55.40	3.36	10.77	55.52	3.21	10.96
23	H		279—280	82	DMF	$C_{17}H_{20}O_3N_4$	62.18	6.14	17.06	62.08	6.00	17.32
24	H		290—291	61	DMF	$C_{16}H_{18}O_3N_4$	61.13	5.77	17.83	61.12	5.94	17.74
25	H		276—278	47	DMF	$C_{13}H_{13}O_3N_5S$	48.90	4.10	21.93	49.11	3.95	22.23
26	H		285—287	68	DMF	$C_{18}H_{16}O_3N_4$	64.27	4.80	16.66	64.23	4.88	16.90
27	H		258—259	34	DMF	$C_{19}H_{18}O_3N_4$	65.13	5.18	15.99	65.05	5.02	16.27

Fusion of ethyl 1,4-dihydro-1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate(**1**)[5] with selenium dioxide at 140—150° afforded a mixture of ethyl 1,4-dihydro-1-ethyl-7-formyl-4-oxo-1,8-naphthyridine-3-carboxylate (**2**) and 1,4-dihydro-1-ethyl-7-formyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (**3**)[6] in 36 and 10% yield, respectively. The hydrolysis of **2** with hydrochloric acid also gave **3**. The condensation of **2** or **3** with respective amines provided the corresponding N-(1,4-dihydro-3-ethoxycarbonyl-1-ethyl-4-oxo-1,8-naphthyridin-7-yl)methylenamine (**4**—**15**) and N-(3-carboxy-1,4-dihydro-1-ethyl-4-oxo-1,8-naphthyridin-7-yl)methylenamine (**16**—**27**), respectively. These 1,8-naphthyridine derivatives prepared are listed in Table I.

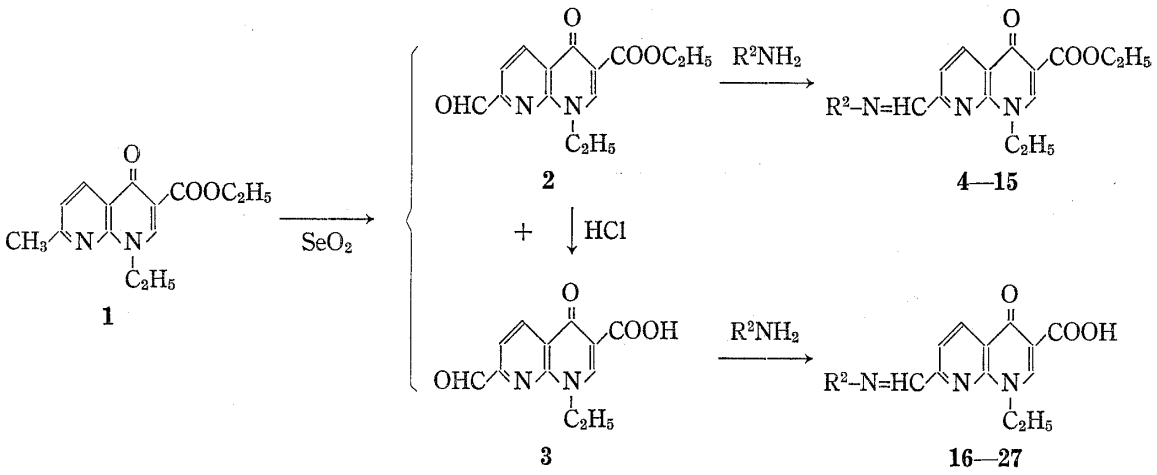


Chart 1

Screening Results[7]

A series of N-(1,8-naphthyridin-7-yl)methylenamines (**4**—**27**) prepared were tested for *in vitro* antibacterial activity against a number of microorganisms. Among them, **11** and **16** exhibited the activity against *S. sonnei* at 25 μg/ml, and the latter also showed the activity against *E. coli* NIH at the same concentration. Furthermore, **26** possessed the activity at 25 μg/ml against *Bord. bronchiseptica*. None of other compounds exhibited sufficient activity against tested microorganisms.

Experimental[8]

Reaction of Ethyl 1,4-Dihydro-1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate (1) with Selenium Dioxide——SeO_2 (3.33 g, 0.03 mole) was added to the melted (at 150°) ethyl 1,4-dihydro-1-ethyl-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate (**1**)[5] (7.8 g, 0.03 mole) and the mixture was fused at 140—150° for 30 min. The reaction mixture was extracted with boiling benzene (500 ml). After cooling the extract, the precipitated solid was filtered and recrystallized from EtOAc to give 0.75 g (10%) of 1,4-dihydro-1-ethyl-7-formyl-4-oxo-1,8-naphthyridine-3-carboxylic acid (**3**), mp 266—268° (Lit.[6] mp 259.4—261.4°). *Anal.* Calcd. for $C_{12}H_{10}O_4N_2$: C, 58.53; H, 4.09; N, 11.38. Found: C, 58.32; H, 4.12; N, 11.34.

The benzene filtrate which removed **3** was dried (Na_2SO_4) and evaporated to dryness *in vacuo*. The residue was triturated with ether and the solid was recrystallized from ether to give 2.95 g (36%) of ethyl 1,4-dihydro-1-ethyl-7-formyl-4-oxo-1,8-naphthyridine-3-carboxylate (**2**), mp 158—159°. *Anal.* Calcd. for $C_{14}H_{14}O_4N_2$: C, 61.31; H, 5.15; N, 10.21, Found: C, 61.37; H, 5.25; N, 10.32.

Heating of **2** (1.8 g, 0.0066 mole) in 60 ml of 1 N HCl at 120—130° for 10 min afforded 0.85 g (53%) of **3**.

5) G.Y. Lesher, E.J. Froelich, M.D. Gruett, J.H. Bailey, and R.P. Brundage, *J. Med. Pharm. Chem.*, **5**, 1063 (1962).
6) This compound has been claimed in the patent, U. S. Patent 3590036 (1971).
7) The values of inhibitory concentration represent minimum inhibitory concentration (MIC). The MIC is the lowest concentration of the compound that prevents visible growth after 18 hr of incubation at 37°.
8) Melting points were taken on a Yanagimoto melting point apparatus and are uncorrected.

N-(1,4-Dihydro-3-ethoxycarbonyl-1-ethyl-4-oxo-1,8-naphthyridine-7-yl)methylenamines (4—15)——General Procedure: A mixture of **2** (0.001 mole) and respective amines (0.001 mole) in EtOH (10 ml) was heated at the reflux for 1—3 hr. The precipitated solid was filtered and recrystallized from proper solvent listed in Table I to give the corresponding product. When the product did not precipitated out from the cooled reaction mixture, the solution was evaporated to dryness *in vacuo* and the residue was covered with ether to separate the product.

In the case of **4**, **12**, **13**, and **15**, the corresponding amine–HCl was used. In these cases, the amine–HCl was dissolved in H_2O (0.5 ml) and heated with **2** in EtOH.

N-(3-Carboxy-1,4-dihydro-1-ethyl-4-oxo-1,8-naphthyridin-7-yl)methylenamines (16—27)——General Procedure: A mixture of **3** (0.001 mole) and respective amines (0.001 mole) in EtOH (10 ml) was heated at the reflux for 1—3 hr. The precipitated solid was filtered, and recrystallized from proper solvent listed in Table I to give the corresponding product.

In the case of **16**, **24**, **25**, and **27**, the corresponding amine-HCl was used. In these cases, the amine-HCl was dissolved in H_2O (0.5 ml) and heated with **3** in EtOH.

[Chem. Pharm. Bull. 25(2) 352—354 (1977)]

UDC 577.152.04 : 546.185.211.04.09

Inhibition of Alkaline Phosphatase from Human Placenta and Intestine by Inorganic Phosphate[1]

Mamoru Sugiura, Kazuyuki Hirano,[2a] Shiro Iino, Hiroshi Suzuki, and Toshitsugu Oda[2b]

Department of Pharmacy, Tokyo College of Pharmacy,[2a] and 1st Department of Medicine, Faculty of Medicine, University of Tokyo[2b]

(Received May 22, 1976)

The degree of the inhibition of alkaline phosphatases from human placenta and intestine by inorganic phosphate was examined and its results showed an additional difference in alkaline phosphatases between human placenta and intestine in the inhibition by inorganic phosphate.

Keywords——human alkaline phosphatases; serum alkaline phosphatase; placenta; intestine; inhibition by inorganic phosphate

It is known that alkaline phosphatase (E. C. 3.1.3.1) is inhibited by inorganic phosphate. This fact shows that a serine residue of alkaline phosphatase is phosphorylated and its dephosphorylation process is the rate-determining step, and the phosphorylated enzyme is stable in an acidic region.[3] For this reason, the relationship between alkaline phosphatase and inorganic phosphate seems very important.

In a previous paper,[4] we reported the comparison of properties of the purified alkaline phosphatase from human placenta and intestine, and there was a difference in their sensitivity to inorganic phosphate.

In the present work, the degree of inhibition of purified alkaline phosphatases from human placenta and intestine, and human serum alkaline phosphatase by inorganic phosphate were examined.

---

1) This paper forms part CXI of a series entitled "Studies on Enzymes" by M. Sugiura.
2) Location: *a) Horinouchi 1432–1, Hachioji, Tokyo, 192–03, Japan; b) Hongo 7–3–1, Bunkyo-ku, Tokyo, 113, Japan.*
3) M. Fosset, D. Chappelet-Torde, and M. Lazdunski, *Biochemistry*, **13**, 1783 (1974).
4) M. Sugiura, M. Isobe, K. Hirano, S. Iino, H. Suzuki, and T. Oda, *Chem. Pharm. Bull.* (Tokyo), **23**, 1542 (1975).