[Chem. Pharm. Bull. 21(5)1080—1089(1973)]

UDC 547.831.5'233.057 : 615.28.015.11

Studies on Chemotherapeutic Agents. I. Syntheses of Quinoline and Naphthyridine Sulfonamide or Phosphonic Acid Derivatives

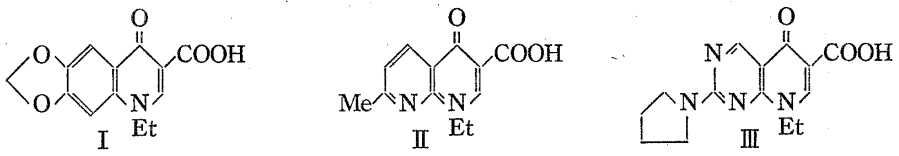
Hiroaki Yanagisawa, Hideo Nakao, and Akiko Ando

Central Research Laboratories, Sankyo Co., Ltd.[1]

(Received November 11, 1972)

Sulfonamide or phosphonic acid analogs of oxolinic acid (I) and nalidixic acid (II), in which the carboxyl groups of I and II were replaced by sulfamoyl and phosphono groups, were synthesized conveniently by the modification of the Camps'es quinoline synthesis. They were evaluated for antimicrobial activity but no significant activity was noted.

Recently it was found that some compounds having the 3-carboxy-4-pyridone moiety, *i.e.* oxolinic acid (I),[2] nalidixic acid (II)[3] and piromidic acid (III)[4] possess antimicrobial activity, especially against gram-negative microorganisms.

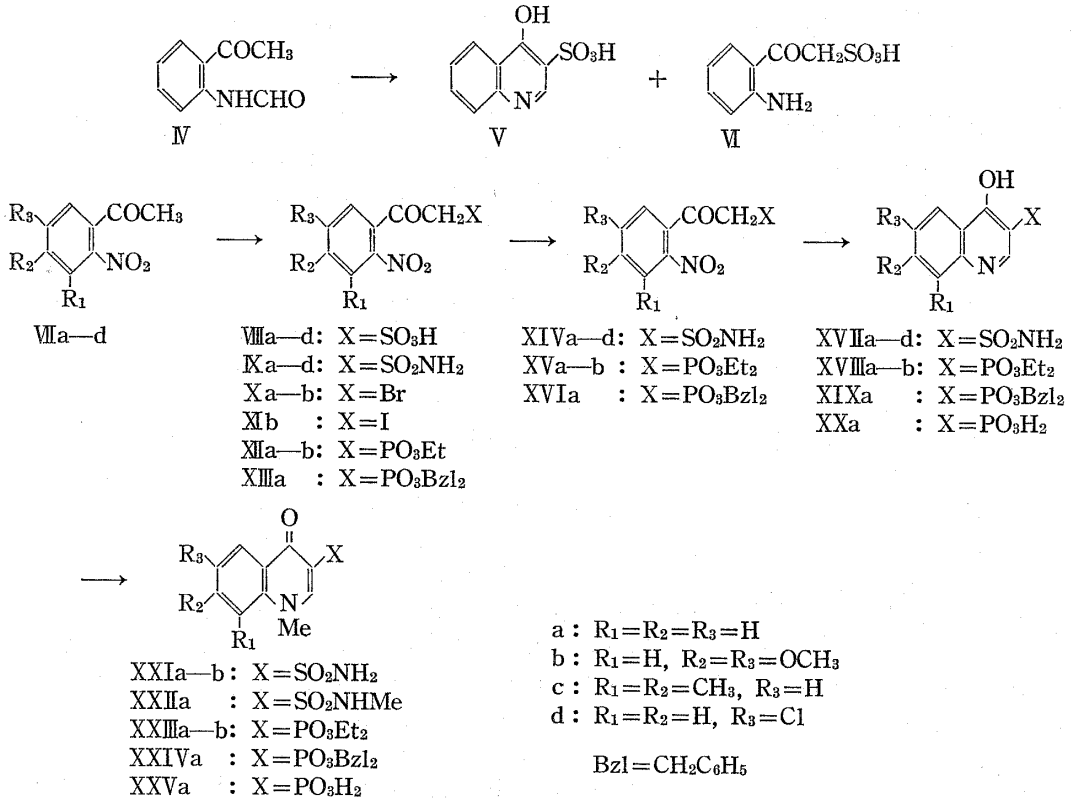


On the other hand, as shown in *p*-aminobenzoic acid *v.s.* sulfanilamide it seems to be of interest to replace a carboxyl group in biologically active molecules by an analogous group such as a sulfamoyl or a phosphono group. Thus we were interested in the syntheses of compounds such that a carboxyl group in I or II was replaced by a sulfamoyl or phosphono group in order to obtain useful antimicrobial agents. The present paper is concerned with the syntheses of the title compounds involving a new cyclization reaction which forms 4-hydroxyquinoline or 4-hydroxynaphthyridine rings.

The syntheses of 4-hydroxyquinolines are shown in Cahrt 1.

Application of Camps'es cyclization reaction,[5] in which 4-hydroxyquinoline is obtained from *o*-formamidoacetophenone (IV) with base seemed to be a suitable method for synthesizing the above-mentioned compounds. Therefore initially the synthesis of *o*-formamidoacetophenone-ω-sulfonamide was attempted. Sulfonation of IV with sulfur trioxide-dioxane[6] did not afford the expected compound, *o*-formamidoacetophenone-ω-sulfonic acid, but the mixture of 4-hydroxyquinoline-3-sulfonic acid (V) and *o*-aminoacetophenone-ω-sulfonic acid (VI), which were separated by fractional recrystallization. The structure of V was confirmed by elemental analysis, ultraviolet (UV) spectrum [λ_{max}^{MeOH} mμ (log ε): 236 (4.39), 292 (3.77), 313 (4.01), 326 (3.99): similar to 4-hydroxyquinoline] and nuclear magnetic resonance (NMR) spectrum [δ ppm (DMSO-d_6): 8.83 (1H, s, C_2-H), 7.6—8.2 (4H, m, benzene ring protons)].

1) Location: *Hiromachi, Shinagawa-ku, Tokyo, 140, Japan.*
2) D. Kaminsky and R.I. Meltzer, U.S. Patent, 3287458 (1966); D. Kaminsky and R.I. Meltzer, *J. Med. Chem.*, **11**, 160 (1968); F.J. Turner, S.M. Ringel, J.F. Martin, P.J. Storino, J.M. Daly, and B.S. Schwartz, *Antimicrobial Agents and Chemotherapy*, **1967**, 475.
3) G.Y. Lesher, E.J. Foelich, M.D. Gruett, J.H. Bailey, and R.P. Brundage, *J. Med. Chem.*, **5**, 1063 (1962).
4) S. Minami, T. Shono, and J. Matsumoto, *Chem. Pharm. Bull.* (Tokyo), **19**, 1482 (1971); S. Minami, T. Shono, and J. Matsumoto, *ibid.*, **19**, 1426 (1971).
5) R. Camps, *Chem. Ber.*, **34**, 2703 (1901).
6) W.E. Truce and C.C. Alfieri, *J. Am. Chem. Soc.*, **72**, 2740 (1950).



IV V VI

VIIa—d

VIIIa—d: X=SO_3H
IXa—d: X=SO_2NH_2
Xa—b: X=Br
XIb : X=I
XIIa—b: X=PO_3Et
XIIIa : X=PO_3Bzl_2

XIVa—d: X=SO_2NH_2
XVa—b : X=PO_3Et_2
XVIa : X=PO_3Bzl_2

XVIIa—d: X=SO_2NH_2
XVIIIa—b: X=PO_3Et_2
XIXa : X=PO_3Bzl_2
XXa : X=PO_3H_2

XXIa—b: X=SO_2NH_2
XXIIa : X=SO_2NHMe
XXIIIa—b: X=PO_3Et_2
XXIVa : X=PO_3Bzl_2
XXVa : X=PO_3H_2

Chart 1

The structure of VI was also assigned by elemental analysis, infrared (IR) spectrum [ν_{max}^{Nujol} cm^{-1}: 3400 (NH_2), 1665 (C=O)], UV spectrum [λ_{max}^{MeOH} mμ (log ε): 228 (4.27), 265 (3.85), 363 (3.68): similar to *o*-aminoacetophenone)] and NMR spectrum [δ ppm (DMSO-d_6): 8.13 (1H, d,d, J=1.9, 8.0 Hz, C_6-H), 6.7—7.6 (3H, m, C_3-H, C_4-H, C_5-H), 6.63 (4H, s, NH_2), 4.20 (2H, s, $COCH_2SO_2$)]. In this reaction *o*-formamidoacetophenone-ω-sulfonic acid initially may be formed, but a part undergoes rapidly cyclization to afford V since the methylene group of the sulfonic acid was activated by sulfo group and another undergoes hydrolysis to give VI because of the strong acidity of the sulfonic acid. Attempts to convert V to the corresponding sulfonamide (XVIIa) were unsuccessful because of the slight solubility of V in organic solvents and the facile reactivity of 4-hydroxy group in V. For these reasons *o*-nitroacetophenone (VIIa) was used as the starting compound in which the nitro group might be convertible to the formamido group after the introduction of a sulfamoyl group into the acetyl group of VIIa. Sulfonation of VIIa with sulfur trioxide-dioxane gave *o*-nitroacetophenone-ω-sulfonic acid (VIIIa) which was then treated with phosphoryl chloride-phosphorus pentachloride followed by ammonolysis to afford *o*-nitroacetophenone-ω-sulfonamide (IXa). This amide (IXa) was reduced with palladium-charcoal to afford *o*-aminoacetophenone-ω-sulfonamide (XIVa). The amine (XIVa) was allowed to react with triethyl orthoformate to give 4-hydroxyquinoline-3-sulfonamide (XVIIa) in an 84.3% yield. This cyclization reaction between an amino and a reactive methylene group with triethyl orthoformate is a new reaction for synthesizing the quinoline ring. Triethyl orthoformate may initially react with amino group of XIVa to form ethoxymethylenimino group[7] which may then react with reactive methylene group to afford XVIIa. On the other hand, treatment of *o*-aminoacetophenone with triethyl orthoformate did not afford 4-hydroxyquinoline, so that the reactive methylene group might be required for this reaction. The quinoline (XVIIa) was treated with methyl iodide-sodium

7) R.M. Roberts and P.J. Vogt, *J. Am. Chem. Soc.*, **78**, 4778 (1956).

methoxide or methyl iodide-silver oxide to afford 1-methyl-4-quinolone-3-sulfonamide (XXIa) and 1,N-dimethyl-4-quinolone-3-sulfonamide (XXIIa), respectively.

By a similar procedure 4-hydroxy-6,7-dimethoxyquinoline-3-sulfonamide (XVIIb), 4-hydroxy-7,8-dimethylquinoline-3-sulfonamide (XVIIc) and 6-chloro-4-hydroxyquinoline-3-sulfonamide (XVIId) were produced from 4,5-dimethoxy-2-nitroacetophenone (VIIb), 3,4-dimethyl-2-nitroacetophenone (VIIc) and 5-chloro-2-nitroacetophenone (VIId), respectively. Compound XVIIb was methylated with methyl iodide-sodium methoxide to give 6,7-dimethoxy-1-methyl-4-quinolone-3-sulfonamide (XXIb).

Next, the quinolines which possessed a 3-phosphono group, instead of 3-sulfamoyl group, were produced by a similar method. Treatment of *o*-nitrophenacyl bromide (Xa) with triethyl phosphite and tribenzyl phosphite gave diethyl *o*-nitrophenacylphosphonate (XIIa) and the dibenzyl ester (XIIIa), respectively. On the other hand reaction of 4,5-dimethoxy-2-nitrophenacyl bromide (Xb) with triethyl phosphite did not afford diethyl 4,5-dimethoxy-2-nitrophenacylphosphonate (XIIb), but reaction of the iodide (XIb) gave XIIb. Reduction of XIIa, XIIb and XIIIa with platinum oxide afforded the corresponding amino derivatives, XVa, XVb and XVIa, respectively, which were heated with triethyl orthoformate to give diethyl 4-hydroxy-3-quinolylphosphonate (XVIIIa), diethyl 4-hydroxy-6,7-dimethoxy-3-quinolylphosphonate (XVIIIb) and dibenzyl 4-hydroxy-3-quinolylphosphonate (XIXa), respectively. The quinolines, XVIIIa and XVIIIb, were methylated with methyl iodide-sodium ethoxide to afford diethyl 1,4-dihydro-1-methyl-4-oxo-3-quinolylphosphonate (XXIIIa) and diethyl 1,4-dihydro-6,7-dimethoxy-1-methyl-4-oxo-3-quinolylphosphonate (XXIIIb), respectively. The benzyl ester (XIXa) was methylated with methyl iodide-silver oxide to give dibenzyl 1,4-dihydro-1-methyl-4-oxo-3-quinolylphosphonate (XXIVa). Reaction of the esters, XVIIIa and XXIIIa, with 6N hydrochloric acid under reflux gave not the corresponding phosphonic acids but 4-hydroxyquinoline and 1-methyl-4-quinolone, respectively, while hydrogenolysis of the benzyl esters, XIXa and XXIVa, with palladium gave 4-hydroxy-3-quinolylphosphonic acid (XXa) and 1,4-dihydro-1-methyl-4-oxo-3-quinolylphosphonic acid (XXVa), respectively.

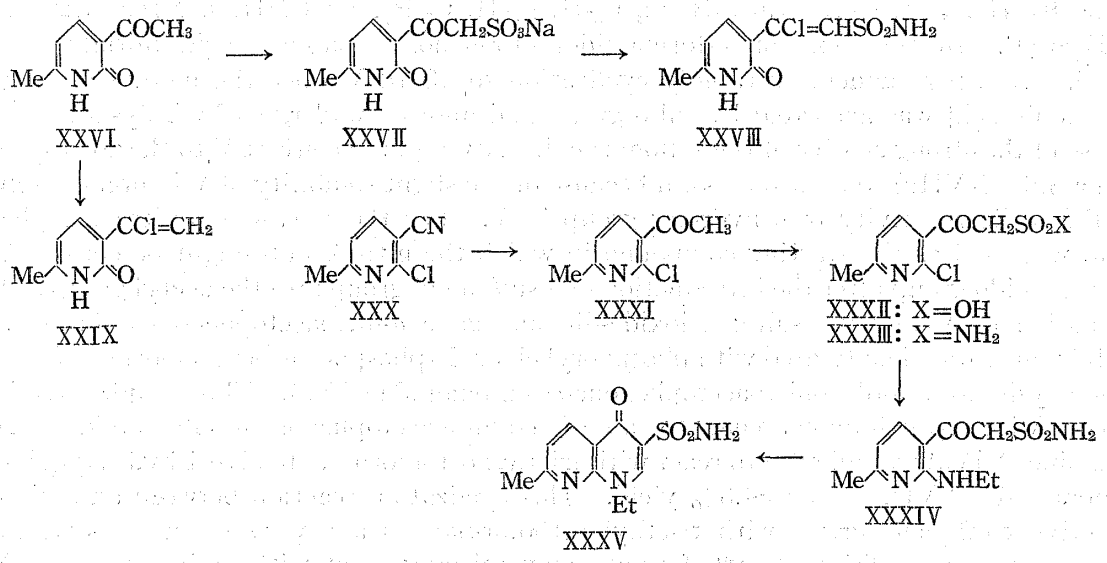


Chart 2

Next, 1-ethyl-7-methyl-1,8-naphthyridin-4-one-3-sulfonamide (XXXV) was synthesized (Chart 2). At first 3-acetyl-6-methyl-2-pyridone (XXVI) prepared from sodium formylacetone and acetoacetamide was considered to be a suitable starting compound because the 2-oxo function might be converted to an amino group via a chloro substituent. Sulfonation of the pyridone (XXVI) afforded (1,2-dihydro-6-methyl-2-oxo-nicotinoyl)methanesulfonic acid

Table I. *o*-Nitroacetophenone Derivatives

Compound	Yield (%)	Recrystallization solvent	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	S
IXa	52.7	*n*-PrOH	139.5—141	$C_8H_8O_5N_2S$	39.34 (39.48)	3.30 (3.22)	11.48 (11.65)	13.12 (13.10)
IXb	55.8	DMF–MeOH	214—216	$C_{10}H_{12}O_7N_2S$	39.47 (39.64)	3.98 (3.87)	9.21 (9.35)	10.53 (10.47)
IXc	51.3	*n*-PrOH	185—186 (decomp.)	$C_{10}H_{12}O_5N_2S$	44.10 (44.36)	4.44 (4.58)	10.29 (10.53)	11.76 (11.62)
IXd	28.6	*n*-PrOH	148—150	$C_8H_7O_5N_2ClS$	34.49 (34.50)	2.53 (2.58)	10.06 (10.13)	11.50 (11.26)
XIIa	53.7		syrup	$C_{12}H_{16}O_6NP$	47.84 (47.06)	5.36 (5.34)	4.65 (4.40)	
XIIb	20.7	IPE–*n*-Hexane	100—102	$C_{14}H_{20}O_8NP$	46.54 (46.84)	5.58 (5.48)	3.88 (3.88)	
XIIIa	30.3		syrup	$C_{22}H_{20}O_6NP$	62.11 (61.89)	4.74 (4.79)	3.30 (3.32)	

Table II. *o*-Aminoacetophenone Derivatives

Compound	Yield (%)	Recrystallization solvent	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	S
XIVa	93.4	EtOH	194—196 (decomp.)	$C_8H_{10}O_3N_2P$	44.86 (44.84)	4.70 (4.83)	13.08 (13.06)	14.96 (14.97)
XIVb	89.0	DMF–MeOH	231—233 (decomp.)	$C_{10}H_{14}O_5N_2S$	43.77 (44.01)	5.14 (5.05)	10.21 (10.22)	11.69 (11.35)
XIVc	65.8	*n*-PrOH	138—140 (decomp.)	$C_{10}H_{14}O_3N_2S$	49.57 (49.71)	5.82 (5.65)	11.56 (11.67)	13.23 (13.13)
XIVd	63.8	*n*-PrOH	135 (decomp.)	$C_8H_9O_3N_2ClS$	38.64 (38.63)	3.65 (3.66)	11.27 (11.08)	12.91 (12.75)

Table III. 4-Hydroxyquinoline Derivatives

Compound	Yield (%)	Recrystallization solvent	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	S
XVIIa	84.3	90% MeOH	303—305 (decomp.)	$C_9H_8O_3N_2S$	48.21 (48.56)	3.60 (3.45)	12.49 (12.12)	14.30 (14.13)
XVIIb	69.0	Pyr–MeOH	>280	$C_{11}H_{12}O_5N_2S$	46.46 (46.81)	4.25 (4.27)	9.85 (9.77)	11.27 (11.34)
XVIIc	83.1	DMF–MeOH	>280	$C_{11}H_{12}O_3N_2S$	52.36 (52.18)	4.79 (4.61)	11.10 (11.13)	12.71 (12.39)
XVIId	14.2	MeOH	>280	$C_9H_7O_3N_2ClS$	41.79 (42.23)	2.73 (2.89)	10.83 (10.82)	12.40 (12.44)
XVIIIa	92.4	EtOH–ether	155—157	$C_{13}H_{16}O_4NP$	55.52 (55.18)	5.74 (5.79)	4.98 (4.98)	
XVIIIb	53.1	EtOAc	202—204 (decomp.)	$C_{15}H_{20}O_6NP$	52.78 (52.44)	5.91 (5.84)	4.11 (4.24)	
XIXa	58.9	EtOH–ether	161—162	$C_{23}H_{20}O_4NP$	68.14 (68.16)	4.98 (4.83)	3.46 (3.70)	
XXa	75.8	DMF–MeOH	240—242 (decomp.)	$C_9H_8O_4NP \cdot \frac{1}{2}H_2O$	46.11 (46.16)	4.09 (3.87)	5.91 (5.98)	

(XXVII). Treatment of the sulfonic acid (XXVII) with phosphoryl chloride and phosphorus pentachloride followed by ammonolysis gave not the desired compound (XXXIII) or the 2-amino derivative of XXXIII but 2-chloro-2-(1,2-dihydro-6-methyl-2-oxo-3-pyridyl)ethenesulfonamide (XXVIII) wherein the structure was confirmed by elemental analysis, IR spectrum (no absorption of ketonic C=O group), UV spectrum [λ_{max}^{MeOH} mμ (log ε): 256 (3.92),

Table IV. 4-Quinolone Derivatives

Compound	Yield (%)	Recrystallization solvent	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N	S
XXIa	q.[a]	MeOH	244—246	$C_{10}H_{10}O_3N_2S$	50.40 (50.40)	4.23 (4.25)	11.76 (11.79)	13.45 (13.39)
XXIb	73.0	DMF–MeOH	220 (sintered) 257 (decomp.)	$C_{12}H_{14}O_5N_2S$	48.32 (48.40)	4.73 (4.66)	9.39 (9.69)	10.75 (10.53)
XXIIa	60.6	MeOH	254—261 (sintered)	$C_{11}H_{12}O_3N_2S$	52.37 (52.47)	4.80 (5.00)	11.08 (11.16)	12.71 (12.46)
XXIIIa	59.0	EtOH–ether	117—118	$C_{14}H_{18}O_4NP$	56.96 (56.08)	6.14 (6.20)	4.74 (4.80)	
XXIIIb	q.[a]	EtOAc	160—162	$C_{16}H_{22}O_6NP$	54.16 (54.08)	6.24 (6.24)	3.76 (3.95)	
XXIVa	86.4		syrup	$C_{24}H_{22}O_4NP$	68.73 (68.32)	5.29 (5.47)	3.34 (3.35)	
XXVa	54.3	DMF–MeOH	238—240 (decomp.)	$C_{10}H_{10}O_4NP \cdot 2H_2O$	44.11 (43.64)	5.35 (5.13)	5.04 (5.09)	

a) quantitative

Table V. Spectroscopic Data of Quinoline and Naphthyridine Derivatives

Compound	IR ν_{max}^{Nujol} cm^{-1}	UV λ_{max}^{MeOH} mμ (log ε)	NMR (δ) (in DMSO–d_6)
XVIIa	3250, 3100 1625, 1565	242 (4.27) 292 (3.83) 311 (3.95) 324 (3.93)	8.54 (1H, s, C_2-H) 6.79 (2H, s, SO_2NH_2)
XVIIIa	1625, 1585	242 (4.29) 292 (3.92) 311 (4.00) 323 (3.97)	8.35 (1H, d, J=13 Hz, C_2-H) 8.19 (1H, bd, J=9 Hz, C_8-H)
XXa	2800—2000 1650, 1620 1590	241 (4.24) 292 (3.85) 311 (3.96) 323 (3.93)	
XXIa	3300, 3100 3050, 1620 1570	244 (4.29) 293 (3.88) 317 (4.06) 328 (4.05)	8.64 (1H, s, C_2-H) 3.98 (3H, s, N_1-CH_3) 6.81 (2H, s, SO_2NH_2)
XXIIIa	1620, 1610 1585	242 (4.32) 293 (3.98) 316 (4.12) 328 (4.11)	8.38 (1H, d, J=13 Hz, C_2-H) 8.23 (1H, bd, J=8 Hz, C_8-H) 3.93 (3H, s, N_1-CH_3) 4.10 (2H, d,q, J=8, 7.2 Hz, ester CH_2) 1.23 (3H, t, J=7.2 Hz, ester CH_3)
XXVa	2800—2000 1630, 1590	238 (4.50) 294 (4.01) 320 (4.09) 330 (4.05)	
XXXV	3300, 3200 1625	253 (4.35) 322 (4.04) 332 (4.07)	8.81 (1H, s, C_2-H) 8.54 (1H, d, J=8.2 Hz, C_5-H or C_6-H) 7.50 (1H, d, J=8.2 Hz, C_5-H or C_6-H) 4.59 (2H, q, J=7.2 Hz, CH_2 in Ni-Et) 2.68 (3H, s, C_7-CH_3) 1.41 (3H, t, J=7.1 Hz, CH_3 in N_1-Et)

abbreviation s: singlet, d: doublet, t: triplet, q: quartet, bd: broad doublet

347 (4.36): similar to the pyridone XXVI] and NMR spectrum [one olefinic proton (5.66 ppm), singlet]. The pyridone (XXVI) was also converted to the olefinic compound, 3-(1-chlorovinyl)-6-methyl-2-pyridone (XXIX) by the same manner. From the above-mentioned results it was appeared that XXVI was unsuitable as a starting compound. Thus 2-chloro-3-cyano-6-methylpyridine (XXX) was selected as the starting compound. Grignard reaction of XXX gave 3-acetyl-2-chloro-6-methylpyridine (XXXI) which was converted to (2-chloro-6-methylnicotinoyl) methanesulfonamide (XXXIII). Treatment of XXXIII with ammonia-methanol did not give the corresponding 2-aminopyridine derivative, while aminolysis with ethylamine-ethanol afforded (2-ethylamino-6-methylnicotinoyl)methanesulfonamide (XXXIV) in a 48.2% yield. The product (XXXIV) was then reacted with triethyl orthoformate to afford 1-ethyl-7-methyl-1,8-naphthyridin-4-one-3-sulfonamide (XXXV).

The compounds prepared in this work were evaluated for their *in vitro* antibacterial activities against Eschrichia coli, Staphylococcus aureus, Sh. flexneri, Pseud. aeruginosa and Candida albicans. None of these compounds showed outstanding activity.

Experimental

4-Hydroxyquinoline-3-sulfonic Acid (V) and *o*-Aminoacetophenone-*ω*-sulfonic Acid (VI)——To a solution of sulfur trioxide (3.1 g) in dichloroethane (25 ml) was added dropwise dioxane (3.5 ml) at −20——−30° under stirring. After stirring the resulting mixture for 10 min at −10°, a solution of *o*-formamidoacetophenone[8] (IV; 6.2 g) in dichloroethane (40 ml) was added dropwise at −10°——−20°. After stirring for 1.5 hr in an ice bath, the reaction mixture was poured into ice–water (200 ml). The aqueous layer was separated and washed with dichloroethane (50 ml×3). Evaporation of the organic layer and washings gave the starting compound (IV): yield 2.04 g (33.0%). The aqueous layer was adjusted to pH 10 with 10% sodium hydroxide solution and the neutralyzed solution was evaporated. To the solid residue was added methanol (300 ml) and the mixture was refluxed for 1.5 hr. After removal of the insoluble materials with filtration and washing them with methanol, the filtrate and washings were evaporated to dryness to afford the mixture of sodium salts of V and VI. The sodium salts were dissolved in water (100 ml) and treated with Dowex 50 W×4 (H type). After removal of the resin by filtration, the filtrate was concentrated to 30 ml and the concentrate was allowed to stand in a refrigerator. Separated pale yellow needles of VI were collected by filtration: yield 3.28 g (37.0%). Recrystallization from 90% ethanol; mp 245° (color), 259—262° (foam). *Anal.* Calcd. for $C_8H_9O_4NS \cdot H_2O$: C, 41.19; H, 4.75; N, 6.00; S, 13.74. Found: C, 41.14; H, 4.23; N, 5.75; S, 13.80.

After concentration of the mother liquors, the crystalline residue was mixed with ethanol (20 ml) and allowed to stand in a refrigerator. Precipitates of V were collected by filtration: yield 1.74 g (20.4%). Recrystallization from 95% ethanol; mp 260—261° (decomp.). *Anal.* Calcd. for $C_9H_7O_4NS$: C, 47.99; H, 3.13; N, 6.22; S, 14.23. Found: C, 48.11; H, 3.01; N, 6.10; S, 14.52.

Benzylthiuronium Salt of V——To a solution of V (100 mg) in hot water (5 ml) was added a solution of benzylthiuronium chloride (200 mg) in water (5 ml) and the mixture was allowed to stand in a refrigerator. The deposited crystals were separated and recrystallized from water: quantitatively, mp 197° (decomp.). *Anal.* Calcd. for $C_{17}H_{17}O_4N_3S_2 \cdot 1/2H_2O$: C, 50.98; H, 4.53; N, 10.49; S, 16.01. Found: C, 50.74; H, 4.55; N, 10.25; S, 15.98.

o-Nitroacetophenone-*ω*-sulfonic Acids (VIIIa, VIIIb, VIIIc, VIIId)——(A typical example of the general procedure) *o*-Nitroacetophenone (VIIa; 24 g) was sulfonated by the same procedure as the preparation of V except the reaction condition (for 1.5 hr in an ice bath and then for 3.5 hr at room temperature). The title compound (VIIIa) was obtained as hygroscopic crystals: yield 18 g (50.6%).

The other sulfonic acids, VIIIb, VIIIc and VIIId were prepared from 4,5-dimethoxy-2-nitroacetophenone (VIIb),[9] 3,4-dimethyl-2-nitroacetophenone (VIIc)[10] and 5-chloro-2-nitroacetophenone (VIId)[11] by the similar procedure in 64.8, 70.5 and 69.6% yields, respectively.

Benzylthiuronium Salt of VIIIa——The sulfonic acid (VIIIa; 300 mg) was treated with benzylthiuronium chloride (800 mg) in the same manner as the preparation of the benzylthiuronium salt of V. The benzylthiuronium salt was recrystallized from water with charcoal: yield 170 mg (33.6%); mp 149—150° (de-

8) L.J. Dolby and D.L. Booth, *J. Am. Chem. Soc.*, **88**, 1049 (1966).
9) R.M. Lairdand and R.E. Porken, *J. Chem. Soc.*, **1963**, 6065.
10) A. Brändstrom and S.A.I. Carlsson, *Acta Chem. Scand.*, **21**, 983 (1967).
11) N.J. Leonard and S.N. Boyd, Jr., *J. Org. Chem.*, **11**, 405 (1946).

comp.). *Anal.* Calcd. for $C_{16}H_{18}O_6N_3S_2$: C, 46.59; H, 4.40; N, 10.19; S, 15.54. Found: C, 46.59; H, 4.21; N, 10.24; S, 15.68.

***o*-Nitroacetophenone-*ω*-sulfonamides (IXa, IXb, IXc, IXd)**——(A typical example of the general procedure) A mixture of VIIIa (8.0 g) and phosphoryl chloride (80 ml) was heated at 80° for 2 hr under stirring. To the obtained solution was added portionwise phosphorus pentachloride (10 g) and the mixture was further heated at 80° for 3 hr under stirring. After evaporation of phosphoryl chloride, diethyl ether (150 ml) was added to the residue and anhydrous ammonia was bubbled into the mixture under stirring in an ice bath for 1 hr. After additional stirring for 1 hr at room temperature, the reaction mixture was concentrated. The residue was dissolved in the mixture of ethyl acetate (200 ml) and water (100 ml). The organic layer was separated and the aqueous layer was washed with ethyl acetate (50 ml × 3). The organic layer and washings were combined and dried over sodium sulfate. Evaporation of ethyl acetate gave crystalline IXa.

The other sulfonamides, IXb, IXc and IXd were prepared from VIIIb, VIIIc and VIIId by the similar procedure, respectively. Their preparation were, however, carried out at 60—65° for 3 hr.

***o*-Aminoacetophenone-*ω*-sulfonamides (XIVa, XIVb, XIVc, XIVd)**——(A typical example of the general procedure) A mixture of IXa (1.36 g) and 10% palladium-charcoal (200 mg) in hot methanol (100 ml) was hydrogenated at an atmospheric pressure and room temperature for 1 hr. The catalyst was filtered off and the filtrate was evaporated to give XIVa as yellow crystals.

The other amino compounds, XIVb, XIVc and XIVd were prepared from IXb, IXc and IXd by the similar procedure, respectively. Reduction of IXb was carried out in dimethylformamide.

4-Hydroxyquinoline-3-sulfonamides (XVIIa, XVIIb, XVIIc, XVIId)——(A typical example of the general procedure) A mixture of XIVa (1.70 g) and triethyl orthoformate (30 ml) was heated for 2 hr at 100—110° under stirring. The reaction mixture was concentrated and hot methanol (50 ml) was added to the crystalline residue. Crystals of XVIIa were collected by filtration.

The other hydroxyquinolines, XVIIb, XVIIc and XVIId were prepared by the similar procedure. The reaction conditions of their preparation are as follows: XVIIb and XVIId, 60°, 4 hr, in dimethylformamide; XVIIc, 80°, 2 hr, in dimethylformamide.

1-Methyl-4-quinolone-3-sulfonamides (XXIa, XXIb)——Methylation by methyl iodide and sodium methoxide. (A typical example of the general procedure) A mixture of XVIIa (300 mg), methyl iodide (1 ml) and 0.425N sodium methoxide (3.6 ml) was refluxed for 3.5 hr under stirring. The reaction mixture was concentrated to 1 ml and the separated crystals of XXIa were collected by filtration.

The other quinolone XXIb was prepared by the similar procedure.

1,N-Dimethyl-4-quinolone-3-sulfonamide (XXIIa)——Methylation by methyl iodide and silver oxide. A mixture of XVIIa (300 mg), methyl iodide (600 mg) and silver oxide (300 mg) in dimethylformamide (4 ml) was stirred for 4 hr at room temperature. Precipitates were filtered off and the filtrate was concentrated. The products were extracted with hot methanol (20 ml × 4) and the extracts were concentrated. The residue was placed on a silica gel column (20 g, 1.6 × 18.5 cm) and eluted with chloroform and chloroform–ethanol (20: 1 and 5: 1), successively. The eluates containing XXIIa were evaporated to give crystals: yield 205 mg (60.6%). After elution of XXIIa, XXIa was eluted: yield 95 mg (29.8%).

***o*-Nitrophenacyl Bromides (Xa, Xb)**——(A typical example of the general procedure) To a solution of VIIa (5.0 g) in dichloroethane (60 ml) was added dropwise bromine (5.0 g) at 50° under stirring and the mixture was further stirred for 30 min at 50°. The reaction mixture was washed with water (20 ml) and aqueous sodium bicarbonate. The organic layer was dried over magnesium sulfate and evaporated to give Xa as syrup quantitatively which was used in the next reaction without further purification.

The other bromide Xb was produced by the similar procedure from VIIb.[9]

4,5-Dimethoxy-2-nitrophenacyl Iodide (XIb)——A mixture of Xb (14.0 g) and potassium iodide (28 g) in acetone (300 ml) was stirred for 15 hr at room temperature and the precipitates were filtered off. The filtrate was evaporated and the residue was chromatographed on a dry column[12] of silica gel with chloroform. The title compound (XIb) was obtained as crystals: yield 11.7 g (72.3%). Recrystallization from ethanol, mp 138—141° (decomp.). This compound was difficult to purify for elemental analysis, but the structure was confirmed by spectral data. IR ν_{max}^{Nujol} cm^{-1}: 1710 (C=O), 1520 (NO_2). NMR δ ppm ($CDCl_3$): 7.70 (1H, s, C_3–H), 6.98 (1H, s, C_6–H), 4.23 (2H, s, $COCH_2I$), 4.02 (6H, s, OCH_3).

Dialkyl *o*-Nitrophenacylphosphonates (XIIa, XIIb, XIIIa)——(A typical example of the general procedure) To triethyl phosphite (17.8 g) was added dropwise Xa (17.8 g) at 160° under stirring and an atmosphere of nitrogen. The mixture was further stirred for 2—3 min at 160° and the reaction products were purified by a dry column chromatography of silica gel with diethyl ether. Compound XIIa (*Rf* 0.19) was obtained as syrup (11.8 g, 53.7%) and the structural isomer (*Rf* 0.45), diethyl α-(*o*-nitrostyryl) phosphate, was also obtained as syrup (9.7 g, 44.2%).

12) B. Loev and M.M. Goodman, *Chem. Ind.* (London), **1965**, 15; **1967**, 2026.

The other phosphonate (XIIIa) was prepared by the similar procedure from Xa and tribenzyl phosphite. The reaction was carried out at 145—150° for 1.5 hr and the product was purified by a dry column chromatography of silica gel with diethyl ether–chloroform (1: 1).

The phosphonate (XIIb) was prepared by the similar procedure from the iodide (XIb) and triethyl phosphite. The reaction was carried out at 100° for 2 hr and the product was purified by a dry column chromatography of silica gel with diethyl ether–ethyl acetate (2: 1).

Dialkyl *o*-Aminophenacylphosphonates (XVa, XVb, XVIa)——(A typical example of the general procedure) A solution of XIIa (9.8 g) in methanol (50 ml) was hydrogenated with platinum oxide (200 mg) at an atmospheric pressure and room temperature for 1 hr. The catalyst was removed by filtration and the filtrate was evaporated to afford XVa as a yellow syrup (8.2 g, 93.0%).

The other amines, XVb and XVIa were prepared by the similar procedure.

Dialkyl 4-Hydroxy-3-quinolylphosphonates (XVIIIa, XVIIIb, XIXa)——(A typical example of the general procedure) A mixture of XVa (360 mg) and triethyl orthoformate (1 ml) was heated at 100° for 75 min under stirring. The reaction mixture was purified by preparative layer chromatography (PLC) (20×20×0.2 cm, 2 sheets) on silica gel with chloroform–ethanol (6: 1).

The other quinolines, XVIIIb and XIXa were respectively obtained from XVb and XVIa by the similar procedure. The reaction of their preparation was conducted at 100° for 3 hr and the products separated from the reaction mixture as crystals were collected by filtration.

Dialkyl 1,4-Dihydro-1-methyl-4-oxo-3-quinolylphosphonates (XXIIIa, XXIIIb)——(A typical example of the general procedure) A solution of XVIIIa (1.15 g) and methyl iodide in 0.0915N sodium ethoxide (45 ml) was heated at 70° for 1 hr under stirring. The reaction mixture was concentrated and the residue was dissolved in the mixture of water (50 ml) and ethyl acetate (50 ml). The aqueous layer was washed with ethyl acetate (20 ml×3). The filtrate and washings were combined, dried over magnesium sulfate and evaporated. The residual syrup was chromatographed on a silica gel column (25 g, 2×21.5 cm) with chloroform–ethyl acetate (10: 1 and 5: 1) and the eluates containing XXIIIa was evaporated.

The other quinoline (XXIIIb) was obtained from XVIIIb by the similar procedure. The product was purified by PLC (chloroform–ethanol 20: 1) on silica gel.

Dibenzyl 1,4-Dihydro-1-methyl-4-oxo-3-quinolylphosphonate (XXIVa)——A mixture of XIXa (430 mg), methyl iodide (0.3 ml) and silver oxide (430 mg) in dimethylformamide (43 ml) was treated in the same manner as the preparation of XXIIa. The product (XXIVa) was purified by PLC (chloroform: ethanol= 20: 1) on silica gel.

Acid Hydrolysis of XVIIIa——A mixture of XVIIIa (150 mg) and 6N hydrochloric acid (7 ml) was refluxed for 8 hr under stirring. After evaporation of the solvent, the syrupy residue was dissolved in methanol and neutralized with ammonia–methanol. The solvent was again evaporated and the residue was dissolved in water (5 ml) and ethyl acetate (40 ml). The aqueou layer was separated and washed with ethyl acetate (10 ml×8). The organic layer and washings were combined, dried over magnesium sulfate and evaporated to give crystalline 4-hydroxyquinoline, which was recrystallized from *n*-propanol–diethyl ether: yield 53 mg (83.3%); mp 205—207°.

Acid Hydrolysis of XXIIIa——Compound XXIIIa (320 mg) was hydrolyzed by the same procedure as described in hydrolysis of XVIIIa. The product was extracted with ethyl acetate by a continuous liquid–liquid extractor. 1-Methyl-4-quinolone was obtained as crystals which were recrystallized from ethanol–diethyl ether: yield 148 mg (86.1%); mp 148—150°.

4-Hydroxy-3-quinolylphosphonic Acid (XXa)——A mixture of palladium chloride (400 mg) and methanol (7 ml) was shaken under an atmosphere of hydrogen for 10 min. To this mixture was added a solution of XIXa (400 mg) in methanol (13 ml) and the mixture was shaken under an atmosphere of hydrogen for 10 min. The catalyst was removed off by filtration and the filtrate was evaporated. The glassy residue was dissolved in methanol (4 ml) and the solution was allowed to stand in a refrigerator. The separated crystals of XXa were collected by filtration.

1,4-Dihydro-1-methyl-4-oxo-3-quinolylphosphonic Acid (XXVa)——Compound (XXIVa; 345 mg) was hydrogenated with palladium (150 mg) by the same procedure as described for the preparation of XXa. Some of the product (XXVa) deposited in the reaction mixture. The catalyst and deposited XXVa were removed by filtration and deposited XXVa was extracted with dimethylformamide. The filtrate and extracts were combined and concentrated. Methanol was added to the concentrate and the precipitated XXVa was separated by filtration.

3-Acetyl-6-methyl-2-pyridone (XXVI)——To a solution of sodium formylacetone[13] (51 g) and acetoacetamide (49 g) in water (250 ml) was added piperidine acetate (28.5 ml) and the mixture was refluxed for 4 hr. To the reaction mixture was added water (200 ml) and the solution was adjusted to pH 6 with acetic acid. The separated yellow crystals of 2,4-cresotamide were collected by filtration and washed with water: yield of 2,4-cresotamide 9.64 g (13.6%); recrystallization from methanol; mp 180—181°. *Anal.* Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.41; H, 6.13; N, 9.44. NMR δ ppm (DMSO-d_6): 12.98

13) L.A. Perez-Medina, R.P. Mariella, and S.M. McElvain, *J. Am. Chem. Soc.*, **69**, 2574 (1947).

(1H, s, phenol OH), 8.0 (2H, broad s, $CONH_2$), 7.77 (1H, d, J=8.5 Hz, C_6–H), 6.6—6.8 (2H, m, C_3–H and C_5–H), 2.27 (3H, s, CH_3).

The filtrate separated from crystals of 2,4-cresotamide was concentrated to dryness and XXVI was extracted with acetone (200 ml×5). The extracts were evaporated and the residue was chromatographed on a dry column of silica gel with acetone–chloroform (1: 2). The title compound (XXVI) was obtained as crystals: yield 7.36 g (10.4%); recrystallization from isopropanol; mp 208—210° (decomp.). *Anal.* Calcd. for $C_8H_9O_2N$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.41; H, 6.13; N, 9.44. NMR δ ppm (DMSO-d_6): 8.00 (1H, d, J=7.3 Hz, C_4–H), 6.20 (1H, d, J=7.3 Hz, C_5–H). 2.55 (3H, s, $COCH_3$), 2.30 (3H, s, C_6–CH_3).

Sodium (1,2-Dihydro-6-methyl-2-oxo-nicotynoyl)methanesulfonate (XXVII)——Compound (XXVI) was sulfonated by the same procedure as the synthesis of V. Finely ground XXVI (1.5 g) was added to sulfur trioxide (1.9 g)–dioxane (2.1 ml) in dichloroethane (20 ml) at −20——30° and the reaction was carried out at room temperature for 5 hr under stirring. The reaction mixture was poured into ice-water (30 ml) and the aqueous layer was adjusted to pH 9 with 10% sodium hydroxide solution. The aqueous layer was separated, washed with chloroform (30 ml) and evaporated to dryness. Sodium salt (XXVII) was extracted with hot methanol (50 ml×2, 30 ml×2 and 20 ml×4) from the powdered residue: crystals: yield 1.15 g (50%). The product was used in the next reaction without further purification.

2-Chloro-2-(1,2-dihydro-6-methyl-2-oxo-3-pyridyl)ethenesulfonamide (XXVIII)——Compound (XXVII) (1.15 g) was treated with phosphoryl chloride and phosphorus pentachloride according to the procedure as described in the synthesis of IXa. The reaction product was purified by a column chromatography (silica gel 40 g, 2.5×21.5 cm) with chloroform–ethyl acetate (1: 1), ethyl acetate and ethyl acetate–ethanol (10: 1). The eluates containing XXVIII were evaporated to give crystals: yield 170 mg (13.7%). Recrystallization from methanol; mp 238—240° (decomp.). *Anal.* Calcd. for $C_8H_9O_3N_2ClS$: C, 38.64; H, 3.65; N, 11.27; Cl, 14.25; S, 12.89. Found: C, 39.12; H, 3.56; N, 10.93; Cl, 14.04; S, 12.40.

3-(1-Chlorovinyl)-6-methyl-2-pyridone (XXIX)——Compound (XXVI) (2.0 g) was treated with phosphoryl chloride and phosphorus pentachloride according to the procedure as described in the synthesis of IXa. The reaction mixture was poured into ice–water (100 ml) and neutralized with sodium bicarbonate. The precipitates of XXIX were collected by filtration: yield 1.74 g (77.3%). Recrystallization from diisopropyl ether; mp 160—162°. *Anal.* Calcd. for C_8H_8ONCl: C, 56.65; H, 4.75; N, 8.26; Cl, 20.91. Found: C, 56.12; H, 4.53; N, 8.29; Cl, 21.53.

3-Acetyl-2-chloro-6-methylpyridine (XXXI)——To Grignard reagent prepared from magnesium (2.82 g) and methyl iodide (8 ml) in diethyl ether (110 ml) was added dropwise a solution of XXX[13] (8.0 g) in diethyl ether (200 ml) under stirring at room temperature. The mixture was further stirred at 60° for 7 hr and then for 15 hr at room temperature. 3N Hydrochloric acid (70 ml) was added to the reaction mixture. After evaporation of diethyl ether, the residue was stirred for 2 hr at room temperature and methylene chloride (80 ml) was added. The aqueous layer was neutralized with 10% sodium hydroxide solution. The organic layer was separated and the aqueous layer was washed with methylene chloride. The organic layer and washings were dried over magnesium sulfate and concentrated to give a brown syrup which was purified by distillation: bp 95° (1 mmHg); yield 5.2 g (58.3%). *Anal.* Calcd. for C_8H_8ONCl: C, 56.65; H, 4.75; N, 8.26; Cl, 20.91. Found: C, 56.61; H, 4.89; N, 7.94; Cl, 20.76.

(2-Chloro-6-methylnicotinoyl)methanesulfonamide (XXXIII)——Compound (XXXI) (7.57 g) was sulfonated with sulfur trioxide (9.2 g)–dioxane (10.3 ml) by the same procedure as the synthesis of V. The reaction was carried out for 20 hr at room temperature. The sodium salt of XXXII, obtained quantitatively as crystals from XXXI, and phosphorus pentachloride was successively added to phosphoryl chloride (60 ml) in an ice bath under stirring and the mixture was heated at 60° for 2 hr. After evaporation of phosphoryl chloride, the residue was suspended in diethyl ether (200 ml) and anhydrous ammonia was bubbled into the suspension for 1.5 hr in an ice-salt bath. The mixture was allowed to stand at room temperature over a night and evaporated to dryness. The residue was dissolved in ethyl acetate (200 ml) and water (100 ml). The organic layer was separated and the aqueous layer was washed with ethyl acetate (50 ml×4). The organic layer and washings were combined and evaporated. The residue was chromatographed on a dry column of silica gel with ethyl acetate–chloroform (1: 1). The title compound (XXXIII) was obtained as crystals: yield 8.13 g (70.7%). Recrystallization from ethanol–benzene; mp 168—170°. *Anal.* Calcd. for $C_8H_9O_3N_2ClS$: C, 38.64; H, 3.65; N, 11.27; S, 12.89; Cl, 14.25. Found: C, 38.67; H, 3.54; N, 11.27; S, 12.74; Cl, 14.25.

(2-Ethylamino-6-methylnicotinoyl)methanesulfonamide (XXXIV)——A solution of XXXIII (2.13 g) in 35% ethylamine–methanol (30 ml) was heated at 50—60° for 25 hr in an autoclave. The solvent was removed by evaporation and the crystalline residue was recrystallized from ethanol: yield 1.06 g (48.2%); mp 203—205°. *Anal.* Calcd. for $C_{10}H_{15}O_3N_3S$: C, 46.67; H, 5.87; N, 16.33; S, 12.46. Found: C, 46.67; H, 5.90; N, 16.31; S, 12.57.

1-Ethyl-7-methyl-1,8-naphthyridin-4-one-3-sulfonamide (XXXV)——A mixture of XXXIV (548 mg) and triethyl orthoformate (15 ml) was stirred at 100° for 2 hr and then at 120° for 2 hr. The reaction mixture was evaporated and the residue was purified by PLC (20×20×0.2 cm, 2 sheets) with ethyl acetate–

methanol (1 : 2) on silica gel. The title compound XXXV (*Rf* 0.32) was obtained as crystals which were recrystallized from ethanol: yield 250 mg (44.0%); mp 228° (decomp.). *Anal.* Calcd. for $C_{11}H_{13}O_3N_3S$: C, 49.42; H, 4.90; N, 15.72; S, 12.00. Found: C, 49.49; H 5.02; N, 15.50; S, 12.00.

Acknowledgement The authors express their deep gratitudes to Dr. G. Sunagawa, director of this laboratories for his kind encouragement.