REACTION OF ETHYL β-ALKYLAMINOCROTONATES IN THE PRESENCE OF ORGANIC ACID

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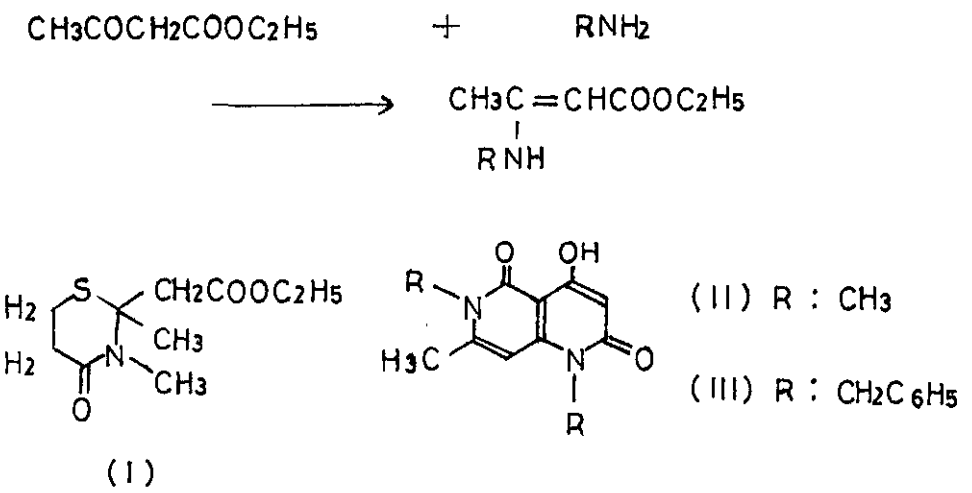
Abstract —— Condensation of ethyl β-alkylaminocrotonates, obtained from ethyl acetoacetate and amines, in the presence of 3-mercaptopropionic acid gave 1,6-naphthyridine-2,5-dione derivatives. The structures of these compounds were determined on the basis of several informations of chemical reactivities and spectral data.

A mixture of 3-mercaptopropionic acid and ethyl β-methylaminocrotonate, obtained from ethyl acetoacetate (24.5g, 188 mmol) and 40 % methanolic methylamine (50 ml), was heated at 160°C for 30 h to synthesize 2-ethoxycarbonylmethyl-2,3-dimethyl-3,4,5,6-tetrahydro-2H-1,3-thiazin-4-one (I)[1]. Although the attempt was unsuccessful, the reaction gave 1,4-dimethyl-6-(N-methylcarbamoylmethyl)-pyridin-2-one [2] (20.1 %), 3-acetyl-1,6-dimethyl-4-hydroxypyridin-2-one [3] (10.5 %) and a new compound, 4-hydroxy-1,6,7-trimethyl-1H,6H-1,6-naphthyridine-2,5-dione (II) in 4.8 % yield, mp 191-192°C (from EtOH) [IR ν_{max}^{KBr} cm^{-1} : 1695, 1650, 1600 ; ^{1}H-NMR ($CDCl_3$) ppm : 2.33 (3H, s, CH_3), 3.38 (3H, s, NCH_3), 3.43 (3H, s, NCH_3), 6.42 (1H, s, =CH-), 6.57 (1H, s, =CH-), 11.95 (1H, s, OH); ^{13}C-NMR ($CDCl_3$) ppm : 21.56 (q), 26.59 (q), 29.84 (q), 103.34 (d), 110.52 (d), 140.25 (s), 147.59 (s), 150.10 (s), 152.16 (s), 161.21 (s), 165.76 (s); MS m/e : 220 (M^+)]. The reaction of ethyl β-benzylaminocrotonate under the similar conditions for ethyl β-methylaminocrotonate to give II afforded 3-acetyl-1-benzyl-4-hydroxy-6-methylpyridin-2-one [3] (20.0 %) and 1,6-dibenzyl-4-hydroxy-7-methyl-1H,6H-1,6-naphthyridine-2,5-dione (III) in 2 % yield,

mp 165-166°C (from acetone) [IR ν_{max}^{nujol} cm^{-1} : 1690, 1650, 1610 ; ^{1}H-NMR ($CDCl_3$) ppm : 2.28 (3H, s, CH_3), 5.30 (4H, s, N-CH_2-x 2), 6.35 (1H, s, =CH-), 6.50 (1H, s, =CH-), 7.35 (10H, s, C_6H_5 x 2), 12.18 (1H, s, OH); ^{13}C-NMR ($CDCl_3$) ppm : 21.70 (q), 45.05 (t), 48.31 (t), 106.06 (d), 112.49 (d), 136.76 (s), 137.70 (s), 141.44 (s), 149.47 (s), 152.10 (s), 163.15 (s), 167.24 (s), 167.31 (s); MS m/e : 372 (M^+)].



(I)

The structures of II and III were elucidated as follows. Acetylation of II gave 4-acetoxy-1,6,7-trimethyl-1H,6H-1,6-naphthyridine-2,5-dione (IV) in 80.5 % yield, mp 208-210°C (from MeOH) [IR ν_{max}^{nujol} cm^{-1} : 1760, 1700, 1660, 1610; ^{1}H-NMR (DMSO-d_6) ppm : 2.33 (3H, s, CH_3), 2.49 (3H, s, $COCH_3$), 3.32 (3H, s, NCH_3), 3.61 (3H, s, NCH_3), 6.90 (1H, s, =CH-), 7.30 (1H, s, =CH-); MS m/e : 262 (M^+)]. The Fries rearrangement of IV in the presence of aluminum chloride gave 3-acetyl-4-hydroxy-1,6,7-trimethyl-1H,6H-1,6-naphthyridine-2,5-dione (V) in 47.1 % yield, mp 147-148°C (from EtOH) [IR ν_{max}^{nujol} cm^{-1} : 1695; ^{1}H-NMR ($CDCl_3$) ppm : 2.40 (3H, s, CH_3), 2.58 (3H, s, $COCH_3$), 3.43 (3H, s, NCH_3), 3.54 (3H, s, NCH_3), 6.45 (1H, s, =CH-), 12.68 (1H, s, OH); MS m/e : 262 (M^+)]. Reduction of III with diborane in THF gave 1,6-dibenzyl-4-hydroxy-7-methyl-5,6-dihydro-1H-1,6-naphthyridin-2-one (VI) in 79.2 % yield, mp 247-248°C (dec. from MeOH) [^{1}H-NMR (DMSO-d_6) ppm : 2.07 (3H, s, CH_3),

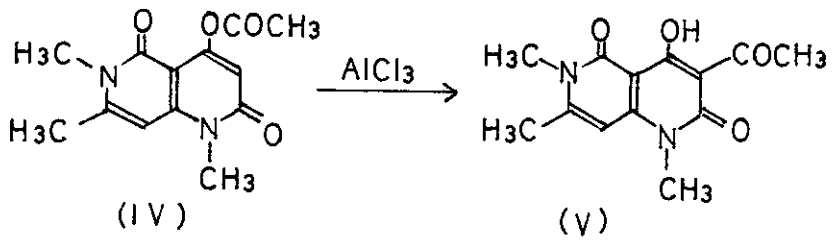
4.30 (2H, s, $-CH_2-$), 4.71 (2H, s, NCH_2-), 5.14 (2H, s, NCH_2-), 6.18 (1H, s, =CH-), 6.36 (1H, s, =CH-), 7.36 (5H, s, C_6H_5), 7.43 (5H, s, C_6H_5), 9.65 (1H, s, OH); MS m/e : 358 (M^+)] . Heating of VI with methyl iodide and potassium carbonate in DMF afforded 1,6-dibenzyl-4-methoxy-7-methyl-5,6-dihydro-1H-1,6-naphthyridin-2-one (VII) in 68.8 % yield, mp 149-150°C (from MeOH) [^{1}H-NMR ($CDCl_3$) ppm : 2.21 (3H, s, CH_3), 3.74 (3H, s, OCH_3), 4.37 (2H, s, $-CH_2-$), 4.75 (2H, s, NCH_2-), 5.17 (2H, s, NCH_2-), 6.22 (1H, s, =CH-), 6.30 (1H, s, =CH-), 7.33 (5H, s, C_6H_5), 7.40 (5H, s, C_6H_5) ; MS m/e : 372 (M^+)] . Hydrogenolysis of VII on 10 % palladium-carbon in ethanol at 60°C afforded 4-methoxy-7-methyl-5,6-dihydro-1H-1,6-naphthyridin-2-one (VIII) in 68.3 % yield, mp 253-254°C (from MeOH) [IR ν_{max}^{KBr} cm^{-1} : 3250, 1685, 1610 ; ^{1}H-NMR (DMSO-d_6) ppm : 2.19 (3H, s, CH_3), 3.71 (3H, s, OCH_3), 4.16 (2H, s, $-CH_2-$), 6.20 (1H, s, =CH-), 6.33 (1H, s, =CH-), 6.65 (1H, s, -NH-), 8.80 (1H, s, -NH-) ; MS m/e : 192 (M^+)] . Heating of a mixture of VIII and phosphorus pentachloride with a few drops of phosphorus oxychloride at 150°C afforded 2,3-dichloro-4-methoxy-7-methyl-1,6-naphthyridine (IX) in 31.7 % yield, mp 181°C (from CCl_4) [IR ν_{max}^{KBr} cm^{-1} : 1610 ; ^{1}H-NMR ($CDCl_3$) ppm : 2.64 (3H, s, CH_3), 4.09 (3H, s, OCH_3), 6.84 (1H, s, =CH-), 9.59 (1H, s, =CH-) ; MS m/e : 244 (M^+ + 2), 242 (M^+)] . In the ^{1}H-NMR spectrum of IX, the signal of 4.16 ppm due to the protons of methylene group of VIII disappeared and a new singlet signal at 9.59 ppm assigned to the α-position of the pyridine ring appeared. Paudler et al.[4] reported that the signals due to the C_2-position of 1,6-naphthyridine and 4-methoxy-1,6-naphthyridine appeared at 9.28 and 9.55 ppm, respectively. Moreover, they reported that the 4-bromo and 3,4,8-tribromo derivatives of 1,6-naphthyridine were obtained by heating of 4-hydroxy-1,6-naphthyridine with phosphorus pentabromide. In hydrogenolysis of IX on 10 % palladium-carbon, displacement of chlorine by hydrogen and reduction of N=C double bond took place, simultaneously, and 3-chloro-4-methoxy-7-methyl-5,6-dihydro-1,6-naphthyridine (X) was obtained in 80.6 % yield, mp 240-243°C (from MeOH) [^{1}H-NMR (DMSO-d_6) ppm : 2.32 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 4.55 (2H, s, $-CH_2-$), 6.96 (1H, s, =CH-), 8.17 (1H, s, =CH-) ; MS m/e : 212 (M^+ + 2), 210 (M^+)] . Reflux of

X with 5 % palladium-carbon in p-cymene [5] afforded the 3-chloro-4-methoxy-7-methyl-1,6-naphthyridine (XI) in 52.1 % yield, mp 158-159°C (from MeOH or Et_2O) [IR ν_{max}^{KBr} cm^{-1} : 1615 ; ^{1}H-NMR ($CDCl_3$) ppm : 2.66 (3H, s, CH_3), 4.04 (3H, s, OCH_3), 6.83 (1H, s, =CH-), 9.41 (1H, s, =CH-), 9.69 (1H, s, =CH-) ; ^{13}C-NMR ($CDCl_3$) ppm : 21.88 (q), 56.00 (q), 108.61 (d), 117.01 (s), 122.23 (s), 143.31 (s), 147.04 (s), 153.85 (s), 155.60 (d), 156.32 (d) ; MS m/e : 210 (M^+ + 2), 208 (M^+)]. Chemical shifts of the ^{1}H-NMR and ^{13}C-NMR spectra of XI were similar to those of 1,6-naphthyridine [5,6]. In addition, the ^{1}H- [7] and ^{13}C-NMR spectra of 1,6-dibenzyl-4,7-dimethyl-1H,6H-1,6-naphthyridine-2,5-dione (XII) prepeared by the Kato's method [7] were compared with those of III. The signals in ^{13}C-NMR spectrum of XII appeared at 21.52 (q), 23.88 (q), 46.15 (t), 46.99 (t), 97.15 (d), 118.76 (d), 129.32 (s), 136.41 (s), 147 93 (s), 152.43 (s), 161.80 (s), (in $CDCl_3$, ppm). These signals due to the corresponding carbons of individual position of two compounds appeared in moderately good agreement. The basis of these facts are consistent with the structure of II and III.

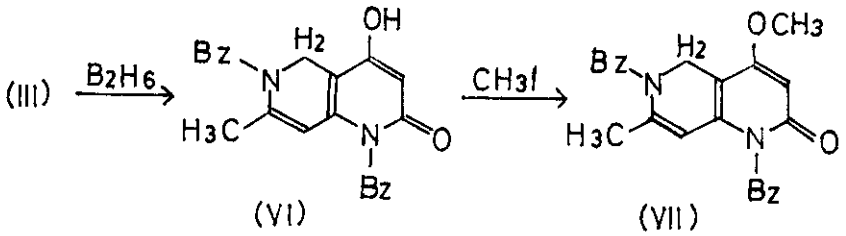
The details of the experiments and some discussions of the reaction mechanism will be reported in the coming paper.

Elemental analysis of the compounds

No	Molecular formula	Calcd. (%)			Found (%)		
		C	H	N	C	H	N
II	$C_{11}H_{12}N_2O_3$	59.99	5.49	12.72	59.90	5.45	12.75
III	$C_{23}H_{20}N_2O_3$	74.17	5.41	7.52	74.31	5.48	7.49
IV	$C_{13}H_{14}N_2O_4$	59.53	5.38	10.68	59.39	5.51	10.55
V	$C_{13}H_{14}N_2O_4$	59.53	5.38	10.68	59.45	5.29	10.72
VI	$C_{23}H_{22}N_2O_2$	77.07	6.19	7.82	77.29	6.19	7.60
VII	$C_{24}H_{24}N_2O_2$	77.39	6.50	7.52	77.10	6.32	7.20
VIII	$C_{10}H_{12}N_2O_2$	62.48	6.29	14.58	62.15	6.10	14.52
IX	$C_{10}H_8Cl_2N_2O$	49.40	3.32	11.52	49.46	3.35	11.52
X	$C_{10}H_{11}ClN_2O$	57.01	5.26	13.30	57.16	5.12	13.17
XI	$C_{10}H_9ClN_2O$	57.56	4.35	13.43	57.61	4.23	13.33



(IV) (V)



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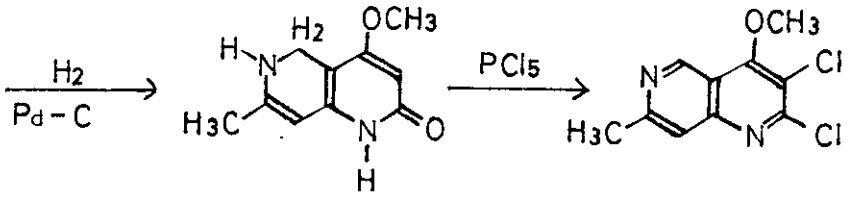
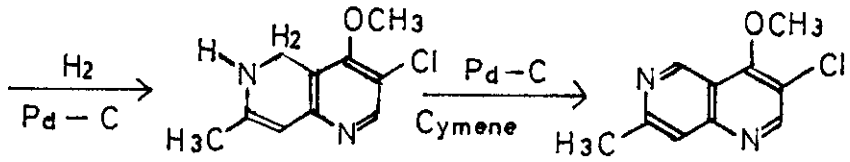
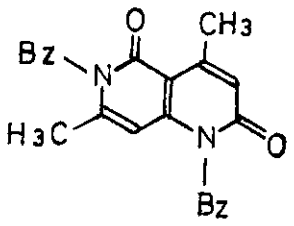


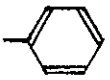
(VIII) (IX)



(X) (XI)



(XII)

Bz : 

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