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Reaction of Aminotropones with Diketene. IV.[1] Effects of the pK_a Values of Aminotropones and Basic Catalysts on the Reaction of Aminotropones with Diketene

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It has been reported by the present authors that the reaction of aminotropones with diketene afforded the different kinds of products according to the reactivity of the starting aminotropones: 5-aminotropolone (**1**) afforded 5-acetoacetamidotropolone (**2**) and a pyridone derivative (**3**),[3] 4-aminotropolone (**4**) afforded a pyridone derivative (**5**) and a pyrone derivative (**6**),[1] 2-aminotropone (**7**) afforded 2-acetoacetamidotropone (**8**) and a pyrone derivative (**9**),[1] respectively.

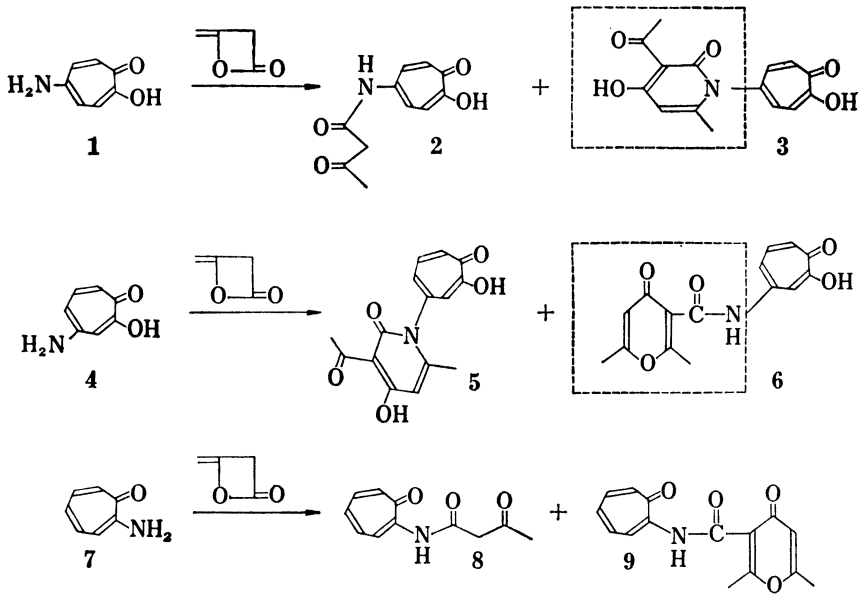
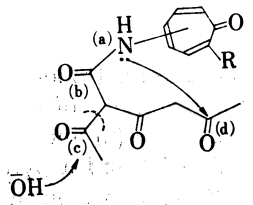


Chart 1

It is interesting to investigate the effective factors which control the formation of such a different kind of products. From this point of view, at first, effects of basic catalysts on the reaction of 5-aminotropolone (**1**) with diketene were investigated (Table I). The reaction of **1** with excess diketene at —4—0° afforded the monoacetoacetate (**2**) only in the presence of triethylamine, but gave **2** and the pyridone derivative (**3**) when potassium hydroxide was used as a catalyst. Moreover, treatment of the acetoacetate (**2**) with diketene in the presence of potassium hydroxide afforded the pyridone derivative (**3**) and a deacetylated compound (**10**)

1) Part III: H. Toda (née Sasaki), *Yakugaku Zasshi*, **87**, 1351 (1967).
2) Location *Katahira-2-chome 1-1, Sendai.*
3) S. Seto, H. Sasaki, and K. Ogura, *Bull. Chem. Soc. Japan*, **39**, 281 (1966).

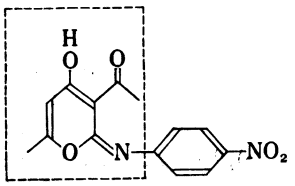
with a recovery of *ca.* 50% of **2**. The structure of **10** was confirmed by comparison of its infrared (IR) spectrum with that of the authentic sample[3] which was obtained by treatment of **3** with conc. sulfuric acid at 200°. Since the deacetylated compound (**10**) was not obtained by treatment of **3** with 85% potassium hydroxide solution, a mechanism of formation of **10** may be explained as follows; that is, in an intermediate (**11**), elimination of the acetyl group by action of alkali occurs before cyclization by attack of the NH group to the carbon atom of the CO group (d).



R=OH, H, OCH_3

11

Chart 2

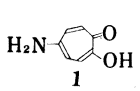
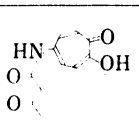
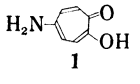
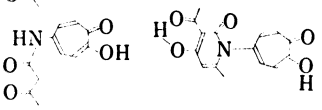
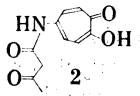
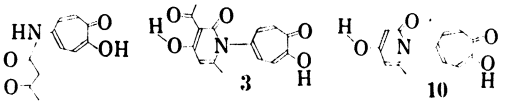


12

Chart 3

On the other hand, it has been found by Kubota that the reaction of the acetoacetyl derivative of *p*-nitroaniline with diketene afforded a corresponding pyrone derivative and / or a new pyrone–imine derivative (**12**) which was probably the third compound derived from the intermediate of **11**-type, according to kind and quantity of the catalyst used (Et_3N or KOH).[4] The present authors examined the reaction of 4-aminotropolone (**4**) with diketene in the similar manner to Kubota's, expecting a formation of a new pyrone–imine–type derivative. Treatment of **4** with diketene resulted in a recovery of a large amount of **4**, while formation of a trace of the pyridone derivative (**5**) was detected. From the results obtained above, it was found that in the case of the reaction of aminotropones with diketene, potassium hydroxide did not catalize the formation of a pyrone–imine–type derivative.

TABLE I. Reaction of 5-Aminotropolone with Diketene

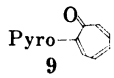
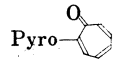
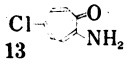
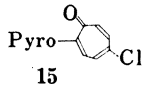
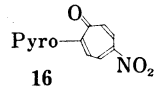
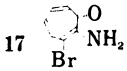
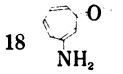
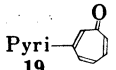
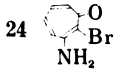
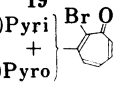
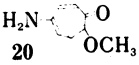
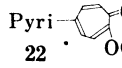
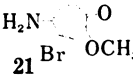
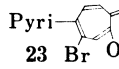
	Base	Solvent	D.K. mole	Products
 **1**	Et_3N	EtOH	5	
 **1**	KOH	EtOH	5	
 **2**	KOH	EtOH	5	 **3** **10**

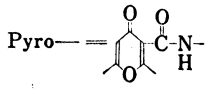
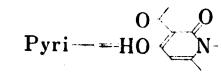
D.K. = diketene reaction temp. = −4—0°

Formation of pyridone, pyrone and pyrone–imine–type derivatives should be explained by such a mechanism that the intermediate (**11**) had three nucleophilic centres, the NH group (a) and two oxygen atoms of the CO groups (b) and (c), and the attacks of those nucleophilic

4) Y. Kubota, "D. Pharm. Thesis," Tohoku University, 1969.

TABLE II. Reaction of Aminotropones with Diketene

Starting materials	pK_a	Products	
		Et_3N, benzene refl.	Et_3N, room temp.
7 	2.24	Pyro—  9	Pyro— 
13 	1.26	Pyro—  15	
14 	<0.9	recovery	Pyro—  16
17 	≪0.9	recovery	
18 	3.33		Pyri—  19
24 	near 1		(25)Pyri + (26)Pyro 
20 	3.42		Pyri—  22
21 	2.07		Pyri—  23

Pyro—  Pyri— 

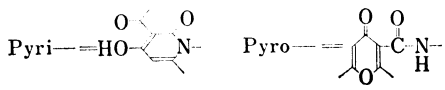
centers to the cationic center, the carbon atom of the CO group (d) afforded pyridone, pyrone-imine and pyrone derivatives, respectively. Therefore, electronegativities of a, b and c-positions may affect the kind of the products. Thus, the authors investigated the correlation of the basicities of aminotropones with the structures of the products (Table II). The structures of the products were elucidated by comparison of their IR and nuclear magnetic resonance (NMR) spectra with those of known pyridone and pyrone derivatives[1,3] (Table III). In the reaction of 2-aminotropone derivatives with diketene, 5-chloro[5] and 5-nitro[6] derivatives (**13** and **14**) of which pK_a values were lower than that of 2-aminotropone (**7**, pK_a 2.24[7]) afforded only pyrone derivatives (**15** and **16**), and 3-bromo derivative (**17**)[6,8] of which pK_a value was lower than 0.9 did not give any product.[3] Furthermore, 3-aminotropone[9] (**18**, pK_a 3.33[7]) afforded only a pyridone derivative (**19**), and 5-amino-2-methoxytropone[10] (**20**, pK_a 3.42[7]) and 5-amino-4-bromo-2-methoxytropone[10] (**21**, pK_a 2.07) also afforded only pyridone derivatives (**22** and **23**). 3-Amino-2-bromotropone (**24**)[9] which had the pK_a value of near 1 gave pyridone and pyrone derivatives (**25** and **26**). From these results, it is suggested that the products in

5) S. Kinumaki, Y. Ikegami, and K. Aita, *Bull. Chem. Res. Inst. Non-Aqueous Solutions, Tohoku Univ.*, **6**, 49 (1956).
6) T. Nozoe, S. Seto, H. Takeda, S. Morosawa, and K. Matsumoto, *Sci. Repts. Tohoku Univ.*, **1**, **36**, 126 (1952).
7) S. Seto, T. Hiratsuka, and H. Toda, *Yakugaku Zasshi*, **89**, 1673 (1969).
8) T. Sato, *Nippon Kagaku Zasshi*, **80**, 1171, 1340 (1959).
9) H. Toda, H. Sugiyama, and S. Seto, *Chem. Pharm. Bull.* (Tokyo), **17**, 2548 (1969).
10) S. Seto, K. Ogura, H. Toda, Y. Ikegami, and T. Ikenoue, *Bull. Chem. Soc., Japan*, **41**, 2696 (1968).

Table III. IR and NMR Data of Pyridone and Pyrone Derivatives

Pyridone Deriv.	IR bands (cm^{-1} KBr) $COCH_3$ ν_{CO}	IR bands (cm^{-1} KBr) α-Pyridone ν_{CO}	NMR signals (ppm) CH_3	$COCH_3$	$=\!\!<_H$	Pyridone OH	Solvent
Pyri(Br)(O)OCH$_3$	1650	1630	2.08	2.58	6.24	15.85	d_6-DMSO
Pyri(Br)(O)	1655	1615	2.10	2.55	6.16	15.58	d_6-DMSO
Pyri	1660	1610					

Pyrone Deriv.	IR bands (cm^{-1} KBr) Amide I	IR bands (cm^{-1} KBr) γ-Pyrone ν_{CO}	IR bands (cm^{-1} KBr) Amide II	NMR signals (ppm) CH_3 (6)	CH_3 (2)	$=\!\!<_H$	NH	Solvent
Pyro(O)Cl	1681	1655	1570					
Pyro(O)NO_2	1700	1642	1590					
Pyro(Br)(O)	1700	1659	1575	2.34	2.70	6.52	11.77	d_6-DMSO



the reaction of aminotropones with diketene are affected by basicities of the NH group of starting aminotropones; that is, the aminotropones which have relatively high pK_a values (2.07—3.42) tend to afford pyridone derivatives and decreasing of pK_a value increases a tendency of formation of pyrone derivatives. However, in our studies, any pyrone–imine-type derivative was not obtained.

Experimental[11]

Reaction of 5-Aminotropolone (1) with Diketene——a) In the Presence of Et_3N: Into a mixture of **1** (500 mg, 0.0036 mole), EtOH (18 ml) and Et_3N (300 mg, 0.0072 mole), diketene (1.5 g, 0.018 mole) was added with stirring at −4——3°. After stirring at −4—0° for 30 min and then at room temperature for 1.5 hr, the mixture was allowed to stand over night at room temperature. To the residue obtained by evaporation of the solvent, a small amount of water was added, and then the pH value of the solution was adjusted to *ca.* 3 with 1N HCl, and the solution was allowed to stand in a refrigerator for 2 days. Yellow prisms (**2**) which separated out were collected and washed with water, 467 mg.

b) In the Presence of KOH: Into a solution of **1** (500 mg) in an ethanolic KOH solution (KOH, 400 mg; EtOH, 18 ml), diketene (1.5 g) was added dropwise with stirring at −4—0° for 1 hr. Yellow powder which precipitated when the reaction mixture was allowed to stand at room temperature was collected by filtration, and dissolved in water, and then the pH value of the solution was adjusted to *ca.* 3 with 1 N HCl. Yellow cyrstals (**3**, 40 mg) which separated out were collected by filtration. The filtrate afforded yellow needles (**2**, 85 mg) by being allowed to stand in a refrigerator.

11) All melting points are uncorrected. The mesurements of the IR and nuclear magnetic resonance (NMR) spectra were carried out by using a Hitachi EPI model S-2 and EPI-G model 21 spectrophotometers and a Varian T-60 and a Japan Electron Optics C-60-HL spectrometers with tetramethylsilane as internal standard, respectively. The pK_a values were determined by spectroscopic method using a Cary model 14 spectrohpotometer and a Hitachi-Horiba model M-4 pH meter.

Reaction of 5-Acetoacetamidotropolone (2) with Diketone in the Presence of KOH——Into a suspension of **2** (500 mg, 0.0023 mole) in an ethanolic KOH solution (KOH, 258 mg; EtOH, 18 ml), diketene (**1** g, 0.012 mole) was added dropwise with stirring at −4—0° for **1** hr. Yellow crystals (K-salt of **3**) which separated out by being allowed to stand at room temperature for 1 hr were collected by filtration and dissolved in water, and then the pH value of the solution was adjusted to *ca.* 3 with 1N HCl to give pale yellow crystals (**3**, 56 mg). The filtrate obtaind above afforded yellow crystals (K-salt of **2**) by being allowed to stand in a refrigerator over night. Acidification of the aqueous solution of the crystals gave yellow crystals (**2**, 117 mg). The filtrate obtained by filtration of **2** was concentrated to give a yellow residue.

The aqueous solution of the residue was acidified with HCl and the resulting solution was allowed to stand in a refrigerator to give yellow crystals (**10**, 80 mg).

Treatment of 3 with KOH Solution ——A mixture of **3** (56 mg), KOH (258 mg) and water (9 ml) was allowed to stand at room temperature for 24 hr. The residue obtained by concentration of the above mixture was dissolved in water and then acidified with HCl to give pale yellow precipitate (recovery of **3**).

Reaction of 4-Aminotropolone (4) with Diketene in the Presence of KOH——Into a solution of **4** (500 mg) in an ethanolic KOH solution (KOH, 400 mg; EtOH, 18 ml), diketene (1.5 g) was added with stirring at room temperature. After stirring at room tempeature for 1 hr, the solvent was removed from the reaction mixture. A small amount of water was added to the residue and the resulting solution was acidified (pH 2) with 1N HCl. An oily substance obtained by acidification was separated from water layer, dissolved in EtOH and then allowed to stand in a refrigerator. Pale brown powder which precipitated was collected by filtration and recrystallized from EtOH to give a trace of the pyridone derivative (**5**) The starting materials (**4**, 110 mg) were recovered from th filtrate as pale yellow crystals.

Reaction of 2-Aminotropone (7) with Diketene in the Presence of Et_3N——To an ice-cooled mixture of **7** (100 mg) and diketene (2 ml), Et_3N (1 drop) was added with stirring. After stirring at room temperature for 40 min, pale yellow crystals (**9**) which separated out were collected by filtration.

Reaction of 2-Amino-5-chlorotropone (14) with Diketone in the Presence of Et_3N——To a mixture of **14** (30 mg), benzene (2 ml) and Et_3N (1 drop), diketene (0.1 ml) in benzene (2 ml) was added, and the mixture was heated at 80—85° for 1.5 hr. A crystalline substance obtained by removal of the solvent from the reaction mixture was washed well with benzene. Benzene-insoluble substance was collected and recrystallized from MeOH to give the pyrone derivative (**16**), 10 mg, mp 210° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}O_4NCl$: C, 58.94; H, 3.96; N, 4.58. Found: C, 59.29; H, 4.11; N, 4.59.

Reaction of 2-Amino-5-nitrotropone (15) with Diketene in the Presence of Et_3N——a) A solution of diketene (0.1 ml) in benzene (2 ml) was added dropwise to a mixture of **15** (30 mg), benzene (2 ml) and Et_3N (1 drop), and the mixture was heated at 80—85° for 3 hr. Reddish yellow powder (recovery of **15**, 20 mg) obtained by being allowed to stand at room temperature over night was collected and washed with benzene.

b) To an ice-cooled mixture of **15** (20 mg) and diketene (0.4 ml), Et_3N (1 drop) was added with stirring. After stirring below 0° for 15 min, the mixture allowed to stand at room temperature afforded a reddish crystalline substance. And then the obtained crystalline substance was washed with benzene. Pale brown powder which was insoluble in benzene was collected and recrystallized from MeOH–benzene to give orange fine prisms (**17**), 13 mg, mp 257—258° (decomp.). *Anal.* Calcd. for $C_{15}H_{12}O_6N_2 \cdot H_2O$: C, 53.89; H, 4.22; N, 8.38. Found: C, 55.50; H, 4.47; N, 8.26.

Reaction of 3-Aminotropone (18) with Diketene in the Presence of Et_3N——To an ice-cooled mixture of **18** (100 mg) and diketene (2 ml), Et_3N (1 drop) was added with stirring. Stirring was further continued for 2.5 hr at room temperature and then for 30 min at 30°. Pale orange substance which separated out was collected and recrystallized from MeOH to give colorless needles (**19**), 98 mg, mp 267—268° (decomp.). *Anal.* Calcd. for $C_{15}H_{13}O_4N$: C, 66.41; H, 4.83; N, 5.16. Found: C, 66.12; H, 4.71; N, 5.13.

Reaction of 5-Amino-2-methoxytropone (20) with Diketene in the Presence of Et_3N——A mixture of diketene (1 ml), Et_3N (1 drop) and **20** (yellow oil) which was prepared by methylation of 5-aminotropolone (**1**, 100 mg) with CH_2N_2, was stirred at room temperature for 5 min and then at 40—50° for 50 min. A small amount of benzene was added to the reaction mixture, and benzene-insoluble substance was collected and washed with MeOH to give colorless powder (**22**, 160 mg).

Reaction of 5-Amino-4-bromo-2-methoxytropone (21) with Diketene in the Presence of Et_3N——To an ice-cooled mixture of **21** (100 mg) and diketene (2 ml), Et_3N (1 drop) was added with stirring. After further stirring for 2.5 hr under the above condition, a small amount of benzene was added to a pale yellow residue obtained by evaporation of the solvent from the reaction mixture. Then, benzene-insoluble substance was collected and recrystallized from MeOH to give colorless crystals (**23**), 110 mg, mp 219—220° (decomp.). *Anal.* Calcd. for $C_{16}H_{13}O_5NBr$: C, 50.68; H, 3.46; N, 3.69. Found: C, 50.71; H, 3.77; N, 3.40.

Reaction of 3-Amino-2-bromotropone (24) with Diketene in the Presence of Et_3N——To an ice-cooled mixture of **24** (120 mg) and diketene (2 ml), Et_3N (1 drop) was added with stirring. Stirring was continued for 4 hr at room temperature. A small amount of benzene was added to the residue which was obtained by removal of excess diketene and benzene-insoluble pale orange crystals (**26**) were collected by filtration, 25 mg, mp 165° (decomp.). To the residue obtained by evaporation of benzene from the filtrate, MeOH was added and MeOH-insoluble substance (diketene polymer) was removed off by filtration. The filtrate

(MeOH–soluble part) was allowed to stand at room temperature and colorless crystals (**25**) which separated out were collected, 11 mg, mp 175° (decomp.). **25**: *Anal.* Calcd. for $C_{15}H_{12}O_4NBr$: C, 51.45; H, 3.45; N, 4.00. Found: C, 51.23; H, 3.53; N, 3.89. **26**: *Anal.* Calcd. for $C_{15}H_{12}O_4NBr$: C, 51.45; H, 3.45; N, 4.00. Found: C, 52.16; H, 3.40; N, 3.60.

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Pyrido[2,3-*d*]pyrimidine Antibacterial Agents. I. 8-Alkyl-5,8-dihydro-5-oxopyrido[2,3-*d*]-pyrimidine-6-carboxylic Acids and Related Compounds

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Since nalidixic acid (1-ethyl-1,4-dihydro-7-methyl-4-oxo-1,8-napthyridine-3-carboxylic acid)[2] was developed as an useful antibacterial agent for gram-negative microorganisms, attention has been focussed on the compounds consisting of pyrido[2,3-*d*]pyrimidine skeleton which has one more nitrogen atom than 1,8-naphthyridine ring system in nalidixic acid. Thus Lesher[3] has reported that 8-ethyl-2-methyl- and 2,4,8-trimethyl-5,8-dihydro-5-oxopyrido-[2,3-*d*]pyrimidine-6-carboxylic acids exhibit *in vivo* activity against *Klebsiella pneumoniae* and *Salmonella typhimurium* in mice on oral administration. In the similar interest Nishigaki, *et al.*[4] also have described on the synthesis of 2-methyl-4-substituted-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acids.

We have studied at the almost same time as Lehser on 8-alkyl-2-substituted- and -2,4-di-substituted-5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acids (VI)[5] and the related compounds. This paper deals with the synthesis and structure–antibacterial activity relationship of these compounds.

Condensation of 4-aminopyrimidines (I) with diethyl ethoxymethylenemalonate gave readily diethyl N-(4-pyrimidinyl)aminomethylenemalonates (II). Then II was subjected to thermal cyclization in refluxing diphenyl ether to afford ethyl 5,8-dihydro-5-oxopyrido[2,3-*d*]-pyrimidine-6-carboxylates (III). Hydrolysis and ethylation of III gave easily 5,8-dihydro-5-oxopyrido[2,3-*d*]pyrimidine-6-carboxylic acids (IV) and ethyl 8-ethyl-5,8-dihydro-5-oxopyrido-[2,3-*d*]pyrimidine-6-carboxylates (V), respectively.

The structure of V was supported by their infrared spectra in the dilute chloroform solution which showed the absorption bands at 1729 and 1690 cm^{-1} for Va, and at 1720 and 1680 cm^{-1} for Vc, indicative of the presence of β-ketoester function.

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