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Reaction of 1,3-Oxazinium Salt with Active Methylene Compounds

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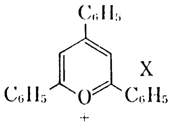
2,4,6-Triphenyl-1,3-oxazinium perchlorate reacts with active methylene compounds to give several butadiene derivatives and various pyridine derivatives. The reactions seem to proceed as follows: The carbanion from an active methylene compound attacks the 6-position of the oxazinium ring, and opens the ring to form a butadiene as an intermediate, which is then recyclized to a pyridine derivative according to a characteristic mode. The mode of recyclization differs with the constituent of each active methylene. There are five modes characteristic of cyano-, ester-, amido- and benzoyl constituents and nitromethane. A compound containing two different constituents usually follows either of the two possible modes.

Pyrylium, 1,3-oxazinium, and 1,3,5-oxadiazinium salts constitute a homologous series with respect to the number of nitrogen atoms in their rings. It was found that 1,3-oxazinium[1,2] and 1,3,5-oxadiazinium salts,[2-5] as well as pyrylium salt, are 6π-cation compounds. The high reactivity of the salts toward many kinds of nucleophiles is known, in particular that of pyrylium salt.[6-9] Active methylene compounds are nucleophiles which introduce a carbon atom with one or two nucleophilic substituents. Dimroth and Neubauer showed that active methylene compounds react with 2,4,6-triphenylpyrylium salt (**1**) to produce various benzenes.[10,11] Schmidt *et al.* reported that 2,4,6-triphenyl-1,3-oxazinium perchlorate (**2**) gives 2-benzoylamino-3-cyano-4,6-diphenylpyridine (**4**) on reaction with malononitrile.[12,13] We showed that 2,4,6-triphenyl-1,3,5-oxadiazinium salt (**3**) reacts with several active methylenes to give pyrimidine derivatives.[14,15] It was found that an active methylene does not always behave in the same manner in reacting with **1** and **3**; for example, benzoylacetonitrile reacts with **1** to give 2,4,6-triphenylbenzonitrile, and with **3** to give 5-cyano-2,4,6-triphenylpyrimidine and 5-benzoyl-4-benzoylamino-2,6-diphenylpyrimidine; methyl cyanoacetate reacts with **1** to give 2,4,6-triphenylbenzonitrile and with **3** to give 4-benzoylamino-5-methoxycarbonyl-2,6-diphenylpyrimidine. In order to clarify the behavior of active methylenes reacting with **1**, **2**, and **3**, the reactions of **2** with these methylene were studied. The results are discussed together with those dealing with **1** and **3**.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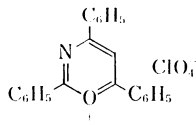
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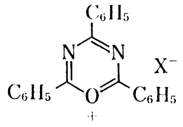
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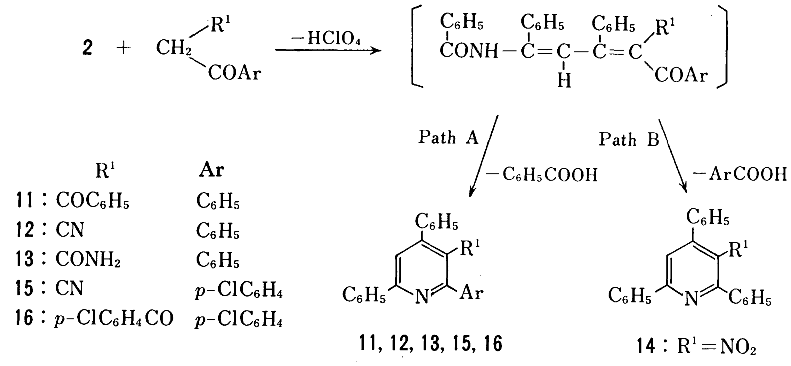
Results and Discussion

Methyl Cyanoacetate. Since methyl cyanoacetate reacts with **1** and **3** in different ways,[10,14] its reaction with **2** was examined. **5** was obtained in a good yield on refluxing this compound and **2** in dioxane in the presence of a 1.5 molar amount of triethylamine. The molecular weight of **5** was determined by mass spectroscopy to be 376. **5** has a cyano group (2205 cm^{-1}) and an ester group (1756, 1229 cm^{-1}). On the other hand, when 2-chloro-3-cyano-4,6-diphenylpyridine[13,16] was treated with benzoic acid in pyridine, the product was the same as **5**. Thus, **5** was identified to be 2-benzoyloxy-3-cyano-4,6-diphenylpyridine. It was found that this compound reacts with **1**, **2**, and **3** in different ways.

Diethyl Malonate. Diethyl malonate did not react on refluxing with **2**, but after treatment at room temperature it produced **6** which was determined to be an adduct of the oxazinium cation and the carbanion from this compound. Schmidt reported that **2** reacting with some active methylenes gives some adducts with butadiene structures.[13] It is assumed that **6** is a butadiene derivative. When **6** was heated above its melting point, **7** was derived. The molecular weight of **7** was determined to be 423. Its IR spectrum resembles that of **5** very closely, and shows the presence of two kinds of ester groups (1757, 1720, 1265, 1232 cm^{-1}). This and the results of elemental analysis indicate that **7** is 2-benzoyloxy-3-ethoxycarbonyl-4,6-diphenylpyridine. The type of reaction which gives **7** is thought to be the same as that for **5**. For **3**, this compound gives 4-benzoyloxy-5-ethoxycarbonyl-2,6-diphenylpyrimidine with the liberation of ethanol followed by benzoyl migration.[15] Therefore, this compound is regarded to react in the same way with **2** and **3** to give benzoyl-pyridine and -pyrimidine, respectively.

Cyanoacetamide and Ethyl Carbamoylacetate. When **2** was refluxed with cyanoacetamide in dioxane, **8** was obtained. Its IR spectrum coincided with that of 2-hydroxy-3-cyano-4,6-diphenylpyridine which was derived from dibenzoylmethane and this compound.[13] However, ethyl carbamoylacetate reacting with **2** gave **9** when left to stand at room temperature. This product is regarded as a butadiene derivative from its IR and NMR spectra. When heated above its melting point, **9** was converted into **10**. **10** is weakly acidic. Its IR spectrum has no absorption assigned to an amide group, but closely resembles that of **8**. Thus, **10** was determined to be 2-hydroxy-3-ethoxycarbonyl-4,6-diphenylpyridine. Since these two compounds possessing a carbamoyl group produce 2-hydroxypyridines, it may be certain that cyanoacetamide forms a butadiene derivative as an intermediate.

Dibenzoylmethane, Benzoylacetonitrile, Benzoylacetamide, Nitromethane, p-*Chlorobenzoylacetonitrile, and Bis(*p-*chlorobenzoyl)methane.* **11**, **12**, and **14** were obtained, respectively when dibenzoylmethane, benzoylaceto-



	R^1	Ar
11	COC_6H_5	C_6H_5
12	CN	C_6H_5
13	$CONH_2$	C_6H_5
15	CN	p-ClC_6H_4
16	p-ClC_6H_4CO	p-ClC_6H_4

Scheme 1.

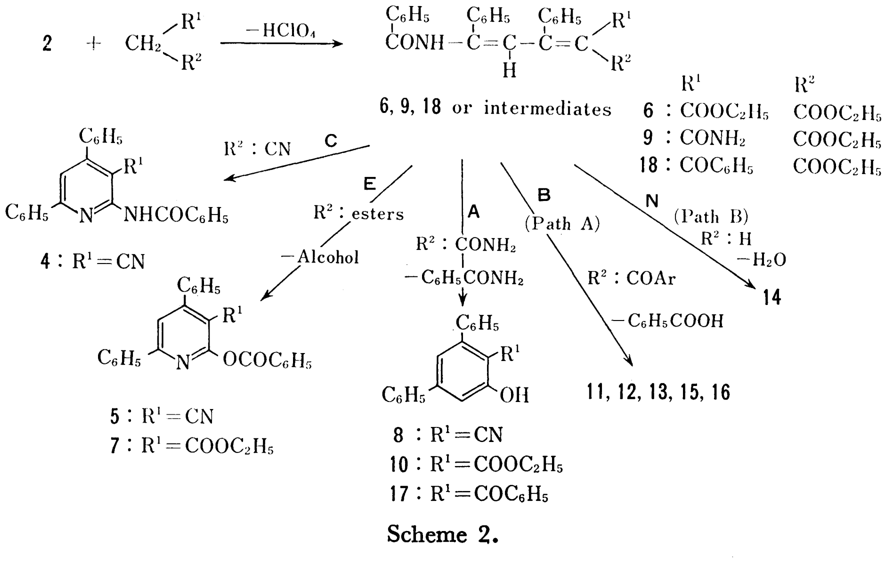
nitrile and nitromethane were refluxed with **2**, whereas treatment of **2** with benzoylacetamide at room temperature gave **13**. Their molecular weights were determined to be 411, 332, 350, and 352, respectively, the values being equal to the sums of the mass of the 2,4,6-triphenylpyridyl group (306) and that of each constituent, *i.e.*, the benzoyl (105), cyano (26), carbamoyl (44), and nitro groups (46), respectively. Their IR spectra were regarded as essentially the same except for the absorptions assigned to each group described above. On the other hand, **11** is identified to be 3-benzoyl-2,4,6-triphenylpyridine[17] with an authentic sample. Thus, **12**, **13**, and **14** were confirmed to be 3-cyano-, 3-carbamoyl-, and 3-nitro-2,4,6-triphenylpyridines. Two cyclization schemes can be assumed for the formation of **11**, **12**, or **13** as Scheme 1.

In order to determine which path is correct, the reaction of *p*-chlorobenzoylacetonitrile and bis(*p*-chlorobenzoyl)methane with **2** were examined. The resulting pyridines, **15** and **16**, respectively, have a *p*-chlorophenyl group in the 2-position. It is thus evident that these compounds possessing a benzoyl as well as a *p*-chlorobenzoyl group produce pyridines *via* path A. However, nitromethane gives **14** *via* path B. For benzoylacetamide, another product, **17**, was obtained together with **13** upon refluxing. **17** was confirmed to be 2-hydroxy-3-benzoyl-4,6-diphenylpyridine, since the IR spectrum of **17** closely resembles those of **8** and **10**.

Ethyl Benzoylacetate. This gave an adduct, **18**, upon treatment with **2** at room temperature. **18** was confirmed to be a butadiene similar to **6** and **9**. **18** was expected to give 3-ethoxycarbonyl-2,4,6-triphenylpyridine or 2-benzoyloxy-3-benzoyl-4,6-diphenylpyridine or both. However, heating of **18** above its melting point resulted in the recovery of **18**. This may be caused by the fact that bulky constituents such as benzoyl and ethoxycarbonyl groups sterically hinder the cyclization of **18**.

All the compounds employed in this investigation, except for ethyl benzoylacetate, gave various pyridines when treated with **2** as well as malononitrile. These reactions are thought to proceed as Scheme 2.

The carbanion from active methylene attacks the 6-position of the oxazinium ring, and opens the ring to form a butadiene as an intermediate, which then recyclizes to a pyridine derivative according to a characteristic mode. From the relation between the reagents employed and the constituents, which are parts of the pyridines produced, the cyclization processes can be classified into five modes. The first mode, **C**, is characteristic of the compound possessing a cyano group, and produces 2-benzoylaminopyridine with the migration of a benzoyl group. Malononitrile is of this mode. The second, **E**, takes in an ester group, *i.e.*, diethyl malonate and methyl cyanoacetate, and is characterized by the formation of 2-benzoyloxypyridines with



Scheme 2.

the liberation of an alcohol followed by the benzoyl migration. The third, **A**, takes place in cyanoacetamide, ethyl carbamoylacetate, and benzoylacetamide, and these derive 2-hydroxypyridines with the liberation of benzamide. The fourth, **B**, occurs in dibenzoylmethane, benzoylacetonitrile, and benzoylacetamide. This mode is characteristic of path A with the liberation of benzoic acid. For these four modes, the phenyl group in the 2-position of **2** is mobile, that is, on the cyclization to pyridines it migrates as a benzoyl group (**C**, **E**) or escapes as a benzoic acid (**B**) or a benzamide (**A**). However, nitromethane is considered to follow the fifth mode (**N**), and the phenyl group is introduced into the 2-position of **14** as such.

The compounds possessing the same two constituents follow this mode characterized by their own constituents. However, the compounds possessing two different constituents have two possible modes, and in practice, with the exception of benzoylacetamide, take either of the two. If we suppose that each compound follows the easiest mode, the relation $\mathbf{B}\gtrsim\mathbf{A}>\mathbf{E}>\mathbf{C}$, is observed between the four modes. However, for the same supposition, a different relation, $\mathbf{A}>\mathbf{C}\gtrsim\mathbf{B}>\mathbf{E}$, is derived from the results obtained from reactions of **3** with several active methylenes.[14,15] The most important factor characterizing the mode still remains undetermined. However, the reactions of **2** and **3** with active methylenes are useful for synthesizing pyridine or pyrimidine derivatives.

Experimental

The melting points of all products were measured in capillary tubes with a Mettler FPI apparatus at the rate 2 °C/min. The IR spectra were measured in KBr pellets with a JASCO DS-403G spectrometer. The molecular

Table 1. Pyridine derivatives (**5**, **7**, **8**, and **10—17**)

Compound	Reaction conditions[a]	Solvent for recrystn.	Mp (°C)	Yield (%)	Mol. wt	Elemental analysis Found (Calcd) (%) C	H	N	Cl	IR (cm^{-1})
5	A	EtOH	144.5	73	376	79.68 (79.77	4.18 4.29	7.54 7.52)		2205, 1756, 1592, 1576, 1531, 1431, 1229, 1111.
7	C	EtOH	141.8	70	423	75.21 (75.58	4.73 5.00	3.30 3.31)		1757, 1720, 1593, 1576, 1527, 1265, 1232, 1102.
8	A	DMF	>300	57		79.24 (79.38	4.32 4.45	10.26 10.29)		3020, 2800, 2210, 1640, 1573, 1530, 1499, 1222.
10	C	NaOH-HCl[b]	183.9	82		75.13 (75.22	5.24 5.37	4.36 4.39)		3050, 2700, 1721, 1621, 1570, 1530, 1246, 1108.
11	A	AcOH	172.6	35	411	87.42 (87.56	5.24 5.15	3.36 3.40)		1663, 1570, 1530, 1492, 1441, 1261.
12	A	AcOH	225.6	78	332	87.03 (86.70	4.96 4.86	8.33 8.50)		2210, 1569, 1532, 1491, 1374.
13	B	MeCN	233.0	92	350	82.35 (82.26	5.09 5.17	7.88 7.99)		3469, 3278, 3156, 1648, 1570, 1532, 1492, 1366.
14	A	AcOH	195.0	46	352	76.24 (76.39	4.53 4.58	7.59 7.95)		1587, 1577, 1540, 1491, 1363.
15	A	MeCN	250.3	68		78.38 (78.58	3.91 4.12	7.85 7.61	9.65 9.66)	2212, 1582, 1566, 1529, 1490, 1088, 1012, 836.
16	A	MeCN	195.4	40		75.01 (75.07	3.99 3.97	2.92 3.08	14.76 14.47)	1674, 1582, 1529, 1493, 1090, 1011, 924, 833.
17	A	NaOH-HCl	266.5	10		81.95 (82.03	4.88 4.88	3.99 3.99)		3020, 2700, 1665, 1615, 1570, 1525, 1497, 1257.

a) A: Under refluxing, B: Left to stand at room temp., C: Conversion of the butadiene. b) Reprecipitated by pouring the solution in aqueous sodium hydroxide into dilute hydrochloric acid.

Table 2. 1-Benzoylamino-1,3-diphenyl-4,4-disubstituted butadienes (**6**, **9**, and **18**)

Compound	Substituent	Mp (°C)	Yield (%)	Elemental analysis Found (Calcd) (%) C	H	N	IR (cm^{-1})	NMR (δ)
6	$COOC_2H_5$ $COOC_2H_5$	115.3	46	74.35 (74.18	5.97 5.80	3.01 2.98)	3380, 1720, 1676, 1601, 1470, 1217, 1104.	0.94(t, 3H), 1.29(t, 3H), 3.96(q, 2H), 4.30(q, 2H), 7.30(m, 17H).
9	$COOC_2H_5$ $CONH_2$	187.2	35	73.52 (73.79	5.52 5.27	6.36 6.37)	3430, 3160, 1716, 1663, 1484, 1232, 1056.	0.81(t, 3H), 3.28(s, 1H), 3.82(q, 2H), 6.80(s, 1H), 7.30(m, 15H), 9.43(s, 2H).
18	$COOC_2H_5$ COC_6H_5	128.4	53	79.27 (79.02	5.54 5.43	3.01 2.79)	3430, 1713, 1695, 1600, 1466, 1219, 1112.	1.08(t, 3H), 4.14(q, 2H), 6.90(s, 1H), 7.30(m, 21H).

weights were determined with a Hitachi RMU6E mass spectrometer equipped with a direct inlet and operating at an ionization electron energy of 70 eV. The NMR spectra were obtained in deuteriochloroform with a Varian XL-100 spectrometer with tetramethylsilane as an internal standard.

Genaral Procedures for the Reaction of 2 with Active Methylene Compounds. 2 mmol of **2** was added to a solution of 2 mmol of an active methylene compound and 3 mmol of triethylamine in 10 ml of dioxane. The mixture was stirred for ten minutes, and then either (A): refluxed for an hour, or (B): allowed to stand for a week at room temperature. The resulting mixture was poured into dilute hydrochloric acid. The precipitate was collected by filtration, and purified by recrystallization from an appropriate solvent. Results for the pyridine derivatives (**5**, **7**, **8**, and **10**—**17**) are given in Table 1. The butadienes were always obtained under the reaction conditions, B, and purified by recrystallization from methanol. Results for the butadienes are given in Table 2.

Conversion of Butadienes to Pyridines (7 and 10). 0.50 g of **6** was heated to above its melting point, *i.e.*, 140—150 °C for 20 min, and 0.5 g of **9** was treated at 180—190 °C for 2 hr (Table 1). **18** was treated in a similar way to that given above, at 150—160 °C for 4 hr, but recovered as such.

2-Benzoyloxy-3-cyano-4,6-diphenylpyridine (5) from 2-Chloro-3-cyano-4,6-diphenylpyridine. A solution of 1.00 g of 2-chloro-3-cyano-4,6-diphenylpyridine and 1.00 g of benzoic acid in 5 ml of pyridine was allowed to stand at room temperature for two days. The solvent was evaporated *in vacuo*, and the residue was washed with dilute hydrochloric acid and aqueous sodium hydroxide, and then recrystallized from ethanol to yield 0.22 g (16%) of **5**; mp 144.4 °C. The IR spectrum and molecular weight agreed completely with those of **5** derived from **2** with methyl cyanoacetate. Found: C, 79.83; H, 4.39; N, 7.53%. Calcd for $C_{25}H_{18}N_2O_2$: C, 79.77; H, 4.29; N, 7.53%.

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