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Syntheses of Heterocyclic Compounds from Benzamidine, Aldehydes, and Hydrogen Cyanide*1,*2,*3

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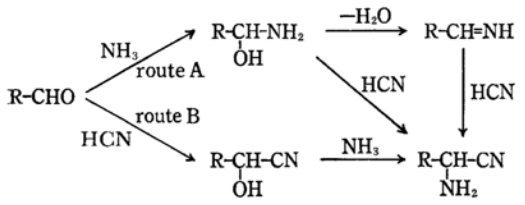
The reactions of benzamidine with several aldehydes in the presence of hydrogen cyanide were studied, using an aqueous methanol as a solvent. When formaldehyde or acetaldehyde was used as an aldehyde component, α-hydroxyalkyldiphenyl-*s*-triazines were obtained, while when benzaldehyde, *p*-chlorobenzaldehyde, or furfural was used, the corresponding 4-arylmethylidenamino-2,5-diphenyloxazoles were obtained. However, under the same reaction conditions, *m*-nitrobenzaldehyde afforded dimethyl azoxybenzene-3,3'-dicarboxylate.

An α-aminonitrile, an intermediate of the Strecker synthesis of α-amino acid, can usually be prepared in a good yield from an aldehyde, hydrogen cyanide, and ammonia, though it is not obvious through which the following routes of the reaction proceeds:



If an amidine behaves similarly to ammonia in this reaction, Compound I may be formed and I may cyclize further to an imidazole derivative. Contrary to this expectation, however, when an aromatic aldehyde was used as an aldehyde component, an oxazole derivative VI was obtained, and when an aliphatic aldehyde was used, a triazine derivative, VII, was obtained, as is shown in the following chart.

The structures of VI and VII were confirmed from the following experimental evidence. Compound VIa ($C_{22}H_{16}ON_2$, mp 156—157°C) had no absorption band in the N–H region in its infrared spectrum and gave an equimolar amount of benzaldehyde 2,4-dinitrophenylhydrazone when it was treated with a solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid at room temperature for 24 hr. Furthermore, the steam distillation of VIa in the presence of concentrated hydrochloric acid gave benzaldehyde, benzoic acid, and mandelic acid as a result of hydrolysis. These facts exclude any structures other than VIc. Compound XI, which is an isomer of VIa and which was synthesized by Lichtenberger,[1] has, accidentally, the same melting point as VIa. However, the Compound XI prepared by the method described in the literature was found to be surely different from Compound VIa, for a mixed-melting-point determination showed a depression and the features of the infrared spectra were different.

Since Compounds VIb and VIc have infrared and ultraviolet spectra similar to those of VIa, and since they gave one mole of 2,4-dinitrophenylhydrazone of *p*-chlorobenzaldehyde and of furfural respectively, they must also be oxazole derivatives. Compounds VIIa and VIIb, which were obtained by the reaction with formaldehyde and acetaldehyde respectively, had ultraviolet spectra similar to that of methyl diphenyl-*s*-triazine, and their oxidation with potassium permanganate yielded the known diphenyl-*s*-triazine carboxylic acid. Hence, the presence of a triazine ring having two phenyl groups in VIIa and VIIb was established. The presence of the O–H group in VIIa and VIIb was confirmed by the absorption band at 3480 cm^{-1} in their infrared spectra and by the formation of the acetyl derivative, IX, from VIIa and of the phenylcarbamate, X, from VIIb, respectively.

The question now arises of why aromatic and aliphatic aldehydes yielded different products. The formations of VI and VII might indicate that the addition reaction of hydrogen cyanide to an aliphatic or aromatic aldehyde predominates over the addition of benzamidine to the aldehyde, and that the hydroxyl group of the cyanhydrine formed

*1 Part IV of "Studies of the Syntheses of Heterocyclic Compounds."

*2 Part III: E. Haruki, T. Inaike and E. Imoto, This Bulletin, **41**, 1361 (1968).

*3 Presented at the 18th Annual Meeting of the Chemical Society of Japan, Osaka, April, 1965.

1) J. Lichtenberger, *Bull. Soc. Chim. France*, **1956**, 1184.

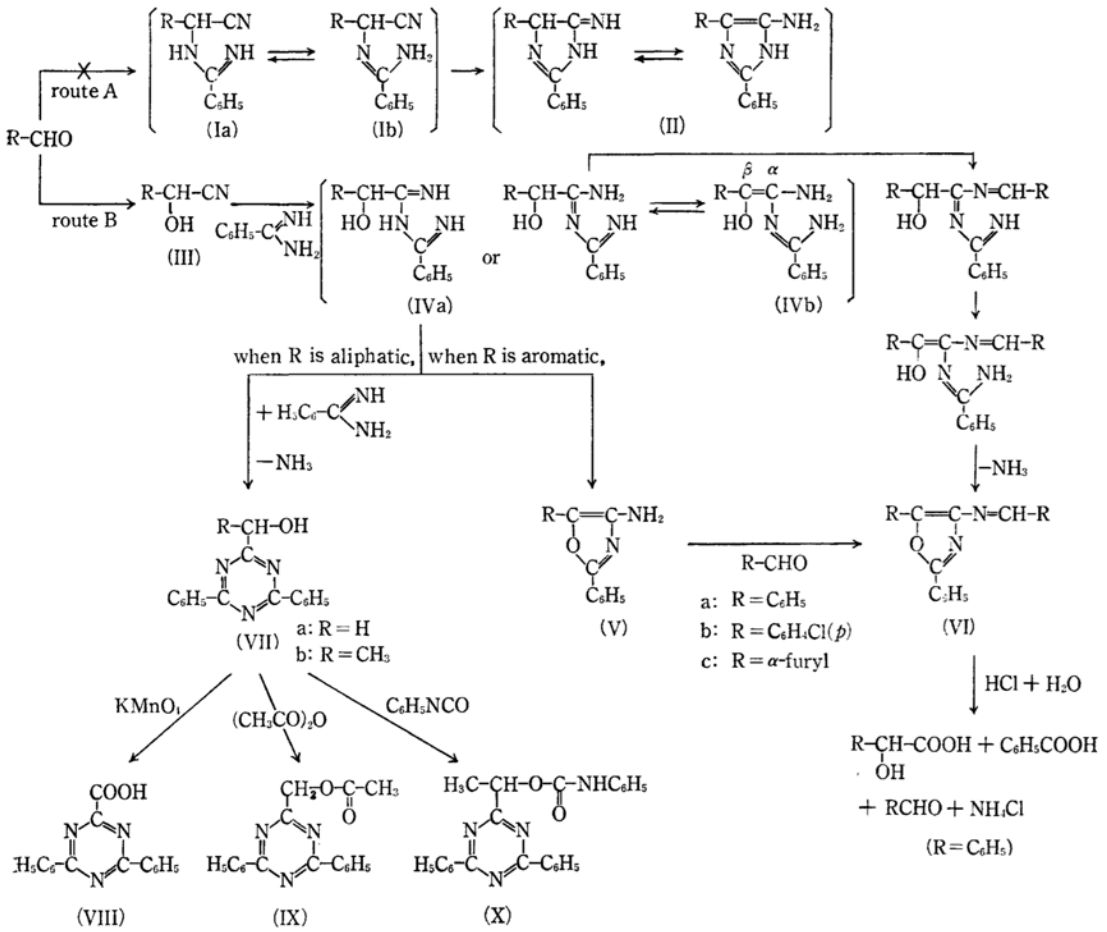
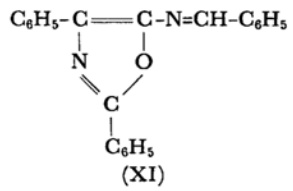


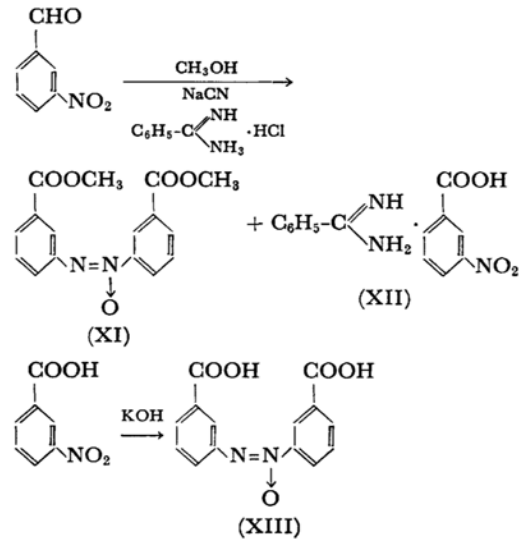
Chart 1.



(XI)

was not replaced by the amino group of benzamidine, because of the lower nucleophilicity of benzamidine than that of ammonia. Under these conditions, benzamidine may be forced to react with the cyano group to form IVa. When R in IVa is aromatic, IVb would be more probable than IVa because of its larger degree of conjugation.

Since the carbon atom to which the hydroxyl group attaches in IV corresponds to the β-carbon atom of a vinylamine system, as in IVb, one of the tautomers of IV, this carbon atom may be attacked by a nucleophile only with great difficulty. For this reason, the nucleophilic attack of the hydroxyl group on the carbon atom of the amidino group would occur more easily to produce an oxazole ring. When R in IVa is aliphatic, the IVb tautomer is not always more favorable than IVa, and IVa may react with another molecule of benzamidine to form triazine derivatives, VIIa and VIIb.



m-Nitrobenzaldehyde in aqueous methanol reacted with sodium cyanide in the presence of an equimolar amount of benzamidine hydrochloride in a manner completely different from that in the reactions described above. In this case, dimethyl azoxybenzene-3, 3'-dicarboxylate (XI) and benzamidinium nitrobenzoate (XII) were produced. However, in this reaction benzamidine seems to act only as a base, because *m*-nitrobenzaldehyde and sodium cyanide in methanol without benzamidine hydrochloride also reacted to yield the same compound, XI. Compound XI was hydrolysed to azoxybenzene-3,3'-carboxylic acid (XII), which was identified by comparison with an authentic sample prepared from *m*-nitrobenzoic acid and potassium hydroxide.

Though the reaction of nitrobenzaldehyde with sodium cyanide seems to be very interesting, the details of this reaction will be reported elsewhere, for this reaction has no relation with the subject reported on this paper.

Experimental

General Method for the Preparating of Oxazole Derivatives. A solution of an aldehyde (0.02—0.04 mol) in methanol (10 m*l*) and a solution of sodium cyanide (0.01 mol) in water (20 m*l*) were mixed with a solution of benzamidine hydrochloride (0.1 mol) in methanol under ice-cooling, after which the reaction mixture was allowed to stand for few days. After about one day a small amount of crystals precipitated. After standing for three days, the crystals precipitated were collected by filtration and recrystallized from the solvents shown in Table 1. The melting points, the yields, and the results of the elemental analyses of the products obtained are shown in Table 1.

Hydrolysis of the Oxazole Derivatives. *a) Under Mild Conditions.* A solution of VIa (103.2 mg) in 50 m*l* of 2 N hydrochloric acid and a small amount of methanol was mixed with a saturated solution of 2,4-dinitrophenylhydrazine in 2 N hydrochloric acid. After the mixture has stood for 24 hr at room temperature while being stirred, benzaldehyde 2,4-dinitrophenylhydrazone was collected by filtration and weighed (94.6 mg, yield, 95%) after drying.

b) Under Severe Conditions. The steam distillation of a mixture consisting of 3.3 g (0.01 mol) of VIa and 20 m*l* of concentrated hydrochloric acid gave at first about 0.7 g (0.007 mol) of benzaldehyde. After the complete distillation of the benzaldehyde, benzoic acid was distilled out gradually; the total amount was 1.1 g (0.009 mol). The residue of distillation was evaporated to dryness, and the residue was extracted with ether to give 1.1 g (0.007 mol) of mandelic acid. The benzoic acid and mandelic acid obtained above were identified by comparison with respective authentic samples, while the benzaldehyde obtained was identified as its 2,4-dinitrophenylhydrazone.

c) Hydrolyses of VIb and VIc under Mild Conditions. Hydrolyses of VIb and VIc were performed similarly to that of VIa. *p*-Chlorobenzaldehyde 2,4-dinitrophenylhydrazone was obtained from VIb in a yield of 92%, while furfural 2,4-dinitrophenylhydrazone was obtained from VIc in a yield of 71%.

A General Method for the Preparation of *α*-Hydroxyalkyldiphenyl-*s*-triazine (VII). A solution of 0.04 mol of sodium cyanide (1.6 g) in 10 m*l* of water was added, portion by portion and under ice-cooling, to a solution of 0.07 mol of an aliphatic aldehyde in 10 m*l* of methanol. Into this mixture there was then stirred, drop by drop, under ice-cooling, a

TABLE 1

	Yield (%)	Mp °C	Solvent for recrystallization	Analysis C%	Analysis H%	Analysis N%	λ_{max}^{EtOH} (mμ)	ε_{max}
VIa (R=C_6H_5)	32	156—157	Ethanol-Benzene	81.65 (81.46)	5.15 (4.97)	8.99 (8.64)	334	5.7×10^4
VIb (R=C_6H_4Cl-*p*)	35	189—190	Ethanol-Benzene	67.26 (67.21)	3.43 (3.59)	6.90 (7.12)	337	2.6×10^4
VIc (R= )	28	133—134	Benzene	70.93 (71.04)	4.09 (3.98)	9.16 (9.21)	352	6.0×10^4

Values in parentheses are calculated for $C_{22}H_{16}ON$ (VIa), $C_{22}H_{14}ONCl_2$ (VIb) and $C_{18}H_{12}O_3N_2$ (VIc).

TABLE 2.

Product	Yield, g (%)	Mp, °C	Mol Wt	Analysis C%	Analysis H%	Analysis N%
VIIa (R=H)	1.5 (34)	122—124	250*	72.33 (72.98)	5.15 (4.98)	15.50 (15.50)
VIIb (R=CH_3)	1.4 (31)	114—115	280**	73.37 (73.63)	5.46 (5.45)	14.97 (15.15)

* This value was measured by the depression of melting point of nitrobenzene.

** This value was measured by the depression of the melting point of benzene. Analytical values in parentheses are calculated for $C_{16}H_{13}ON_3$ (VIIa) and $C_{17}H_{15}ON_3$ (VIIb).

solution of 5.0 g of benzamidine hydrochloride in 10 ml of methanol, and then 20 ml of water were added. The stirring was continued for 1 hr, after while the reaction mixture was allowed to stand at room temperature for three days. The crystals precipitated were collected by filtration. The concentration of the filtrate gave a further small amount of the same crystals. These crystals were combined and recrystallized from an ethanol-water.

Acetylation of VII. A solution of 1.0 g of VIIa in 10 ml of dry benzene was mixed with 5 ml of acetic anhydride and then refluxed for 3 hr. The evaporation of the solvents gave crystals, which were then recrystallized from ethanol; mp 112—114°C, yield 69%.

Found: C, 70.74; H, 4.86; N, 13.39%. Calcd for $C_{18}H_{15}O_2N_3$: C, 70.80; H, 4.95; N, 13.76%.

An attempt to prepare the acetyl derivative of VIIb was unsuccessful; only the starting material was recovered in a yield of 80%.

Preparation of Phenylurethane of VIIb. A mixture of VIIb (0.5 g), phenylisocyanate (0.3 ml), pyridine (one drop), and dioxane (5 ml) was warmed for 30 min. The solvent was evaporated to give colorless needles with a mp of 169—170°C. The yield was 0.5 g (70%).

Found: C, 72.46; H, 5.32; N, 14.02%. Calcd for $C_{24}H_{20}O_2N_4$: C, 72.71; H, 5.09; N, 14.13%.

Oxidation of VIIa and VIIb to VIII with Potassium Permanganate. A solution of potassium permanganate (0.5 g) and potassium hydroxide (0.5 g) in 20 ml of water was mixed with VIIa (0.1 g), and the resulting mixture was refluxed for 2 hr. The reaction mixture was filtered while hot. When the filtrate was cooled, potassium diphenyl-*s*-triazinecarboxylate was obtained as a precipitate. The acidification of the filtrate yielded a precipitate of diphenyl-*s*-triazinecarboxylic acid, which was identified by comparison with an authentic sample of this acid, which had been prepared by oxidation of methyldiphenyl-*s*-triazine[2] with potassium permanganate (which had in turn been prepared from benzamidine hydrochloride and acetic anhydride by the method described in the literature[2]).

Preparation of Dimethyl Azoxybenzene-3,3'-dicarboxylate (XI). *a) In the Presence of Benzamidine.* A solution of sodium cyanide (0.04 mol) in water (10 ml) was added, drop by drop, to a solution of *m*-nitrobenzaldehyde (4.53 g, 0.03 mol) in methanol (70 ml), and then to this mixture there was added a solution of benzamidine hydrochloride (5.0 g, 0.03 mol) in methanol (10 ml). The reaction mixture was stirred at 35—40°C for 4 hr. The crystals which precipitated on cooling were recrystallized from ethanol-benzene to produce 0.9 g of colorless needles with a mp of 132—133°C.

Found: C, 61.36; H, 4.47; N, 8.60%. Calcd for $C_{16}H_{14}O_5N_2$: C, 61.14; H, 4.49; N, 8.91%.

The filtrate was evaporated to dryness, and the solid obtained was recrystallized from ethanol to give benzamidinium *m*-nitrobenzoate with a mp of 237—239°C (yield 5.0 g, 60%).

Found: C, 58.54; H, 4.61; N, 14.85%. Calcd for $C_{14}H_{13}O_4N_3$: C, 58.53; H, 4.56; N, 14.63%.

b) In the Absence of Benzamidine. Sodium cyanide (1.0 g, 0.025 mol) was added to a solution of *m*-nitrobenzaldehyde (1.0 g, 0.007 mol) in methanol (20 ml). After the addition was complete, an exothermic reaction soon began to take place and a large amount of a pale yellow powder started to precipitate. After the heat evolution had ceased, the precipitates were collected by filtration, washed thoroughly with water, and recrystallized from an ethanol-benzene mixture to produce colorless needles with a mp of 132—133°C in a yield of 70%. The needles showed no depression upon a mixed-melting-point determination with Compound XI, obtained above. The aqueous solution which had been obtained by washing the precipitate was acidified with hydrochloric acid to give a small amount of *m*-nitrobenzoic acid (mp 140—141°C), which was identified by comparison with an authentic sample.

2) A. Pinner, *Ber.*, **17**, 2512 (1884); **25**, 1642 (1892).