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Studies on Ketene and Its Derivatives. LXXIII.[1] Synthesis of Pyrido[1,2-*a*]-pyrimidin-4-one and Pyrido[1,2-*a*]*sym*-triazin-4-one Derivatives

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Ethyl N-(2-pyridyl)formimidate (Va) reacted with diketene to give 3-acetyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (VIIa) and ethyl 2-(2-pyridylaminomethylene)acetoacetate (VIIIa).

Reaction of diketene with ethyl N-(2-pyridyl)acetimidate (Vb) and ethyl N-(2-pyridyl)propionimidate (Vc) afforded 4*H*-pyrido[1,2-*a*]pyrimidine derivatives (VIIb and VIIc), respectively. Similarly 2-benzylideneaminopyridine (VIa) reacted with diketene to give 3-acetyl-4-hydroxy-2-phenyl-4*H*-pyrido-[1,2-*a*]pyrimidine (XI).

On the other hand, reaction of trimethylsilyl isocyanate with Va, Vb, and Vc gave rise to 4*H*-pyrido[1,2-*a*]-*sym*-triazin-4-one derivatives (XIXa, XIXb, and XIXc), respectively. Reaction of phenyl isocyanate with VIa afforded 2,3-diphenyl-4*H*-pyrido[1,2-*a*]-*sym*-2,3-dihydrotriazin-4-one (XX).

In the previous paper of this series, we have reported that diketene reacted with imidates such as ethyl benzimidate (I) and Schiff bases such as N-benzylideneaniline (II) to give 2-ethoxy-6-methyl-2-phenyl-3,4-dihydro-2H-1,3-oxazin-4-one (III)[3] and 2-benzylideneacetoacetanilide (IV),[4] respectively. The reactions involve the addition of diketene to the C=N double bond of I and II forming a six and four membered cyclic intermediate followed by prototropy to give III and IV, respectively.

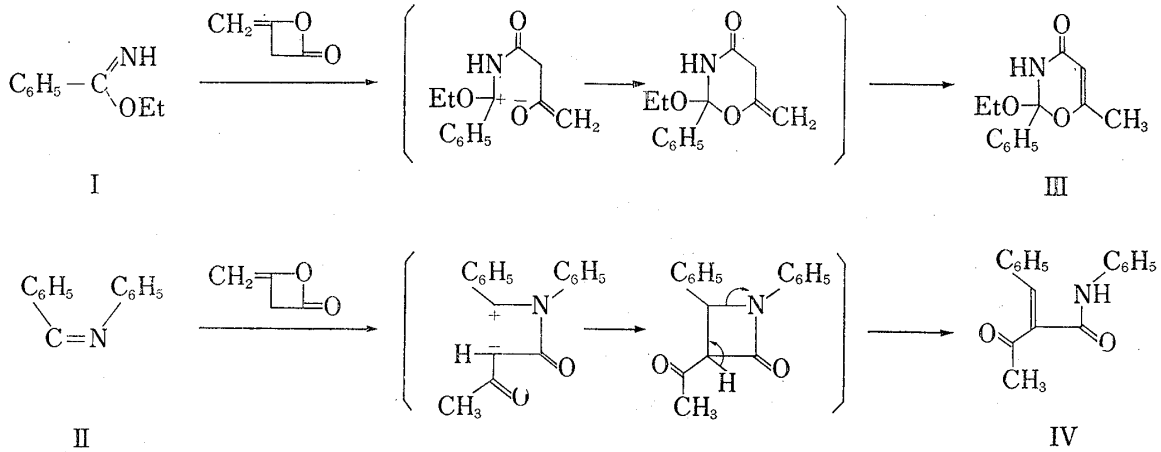


Chart 1

As a continuation of the study we investigated the reaction of diketene with N-(2-pyridyl)-imidate (V) and 2-benzylideneaminopyridine (VI) in an effort to prepare the pyridyl-1,3-oxazine and benzylideneacetoacetamidopyridine derivatives, and found that the reactions did not lead to the expected oxazine and acetoacetamido derivatives, but lead pyrido[1,2-*a*]-pyrimidone derivatives presumably by the 1,4-dipolar addition reaction.

1) Part LXXII: T. Kato, Y. Yamamoto, and M. Kondo, *Heterocycles*, **4**, 293 (1975).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **15**, 1334 (1967).
4) T. Kato and Y. Yamamoto, *Chem. Pharm. Bull.* (Tokyo), **13**, 959 (1965).

Moreover, it appeared to be of interest to investigate further the scope of this reaction with isocyanates in place of diketene, because isocyanates are known as active dipolarphiles, which another object of this paper.

1. Reaction of Diketene with N-(2-Pyridyl)imidates (V) and 2-Benzylideneaminopyridine (VI)

Reaction of ethyl N-(2-pyridyl)formimidate (Va, R=H) with diketene gave the known compound, 3-acetyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (VIIa, R=H), mp 152° (lit.[5] mp 152°), and ethyl 2-(2-pyridylaminomethylene)acetoacetate (VIIIa), mp 89°, in 38% and 51% yield, respectively. Structural assignment was made on the basis of elemental analysis, infrared (IR) and nuclear magnetic resonance (NMR) spectral data. Reflux of the solution of VIIIa in acetic anhydride afforded VIIa in 88% yield. Reaction of Va with ethyl acetoacetate afforded VIIIa in good yield.

Similar reaction of ethyl N-(2-pyridyl)acetimidate (Vb, R=CH_3) afforded 3-acetyl-2-methyl -4*H*-pyrido[1,2-*a*]pyrimidin-4-one (VIIb, R=CH_3) in 65% yield besides the formation of 2-acetamidopyridine (IXb, R=CH_3) in 22% yield. Treatment of VIIb with concentrated sulfuric acid gave rise to the deacetylated product, which was characterized as 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (Xb) by the comparison with an authentic sample.[6]

Similarly, ethyl N-(2-pyridyl)propionimidate (Vc, R=C_2H_5) reacted with diketene to give 3-acetyl-2-ethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (VIIc, R=C_2H_5) and 2-propionamidopyridine (IXc, R=C_2H_5) in 72% and 14% yield.

When 2-benzylideneaminopyridine (VIa, R=H) was allowed to react with diketene, yellow crystals of mp 211°, $C_{16}H_{14}O_2N_2$ (XI), were obtained in 76% yield. Elemental analysis indicated the product being the adduct of diketene and VIa. From NMR and IR spectral data, 3-acetyl-4-hydroxy-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidine (XI) was proposed as the structure of this adduct. Oxidation of XI with chloranil afforded 3-acetyl-2-phenyl-4*H*-pyrido[1,2-*a*]-pyrimidin-4-one (XII).

Similar reaction of 2-(1-phenylethylidene)aminopyridine (VIb, R=CH_3) with diketene resulted in the recovery of the starting materials.

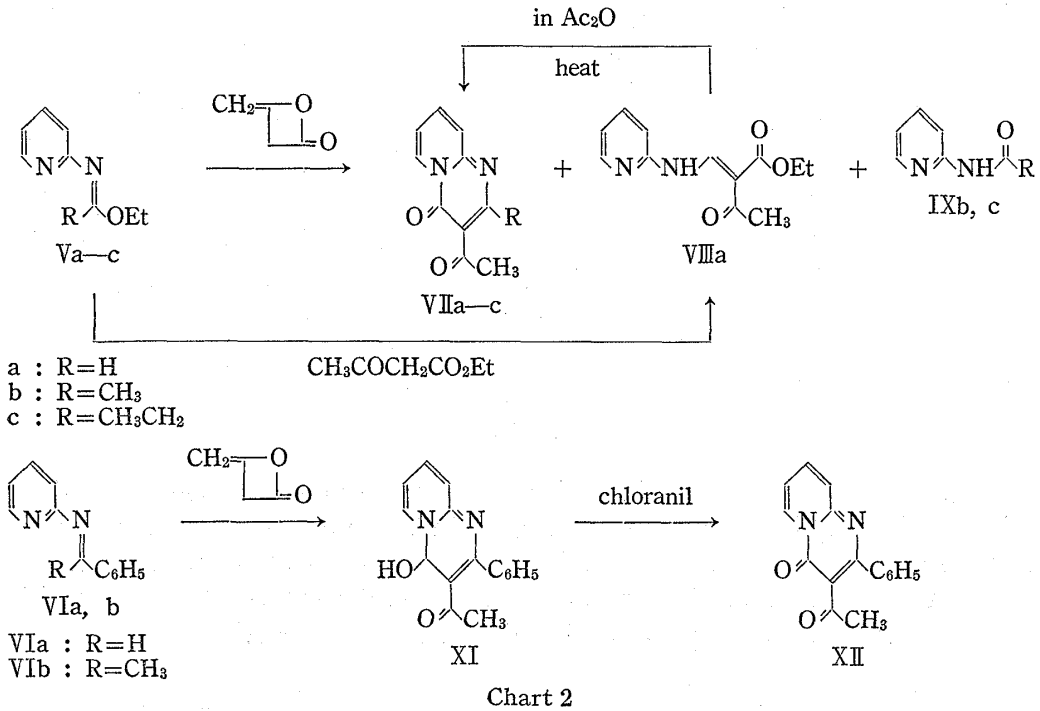


Chart 2

5) H. Antaki, *J. Am. Chem. Soc.*, **80**, 3066 (1958).
6) T. Kato, H. Yamanaka, N. Katagiri, and S. Masuda, *Chem. Pharm. Bull.* (Tokyo), **20**, 142 (1972).

Although the mechanism of the formation of these products is not clear at present, likely pathways are shown in Chart 3. Namely, the electrophilic addition of the carbonyl carbon of diketene to the ring nitrogen of V would form the dipolar intermediate XIII which cyclizes to the dihydropyrido[1,2-*a*]pyrimidone intermediate (XIV) followed by the elimination of EtOH to give VII. (path-a). If the electrophilic addition of diketene occurrs at the imidate nitrogen, the four membered cyclic intermediate (XVI) will form *via* the dipolar ionic intermediate XV. Ring fission of XVI accompanied with prototropy gives rise to VIIIa (path-b).[7]

Another probable mechanism for the formation of VIIIa will be proposed as follows: ethyl acetoacetate, produced from diketene and EtOH which was isolated during the formation of VIIa, reacts with Va to give VIIIa.

According to the similar procedure given for VII from V, the electrophilic attack of diketene to the ring nitrogen of VIa gives rise to the adduct XVII, the dipolar cycloaddition of which affords the pyrido-pyrimidone intermediate (XVIII), which by prototropy is transformed to XI.

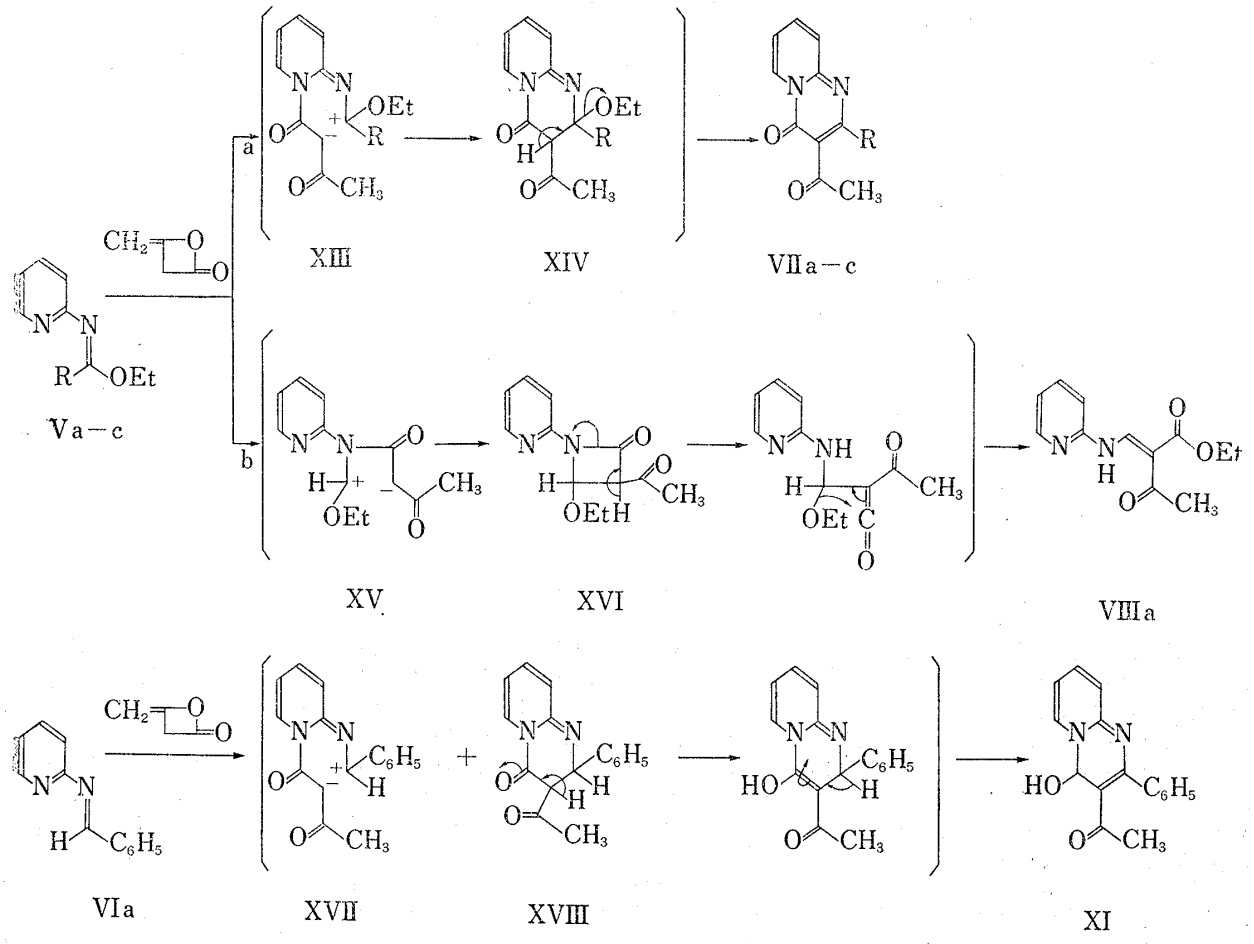


Chart 3

2. Reaction of Isocyanates with N-(2-Pyridyl)imidates (V) and 2-Benzylideneaminopyridine (VIa)

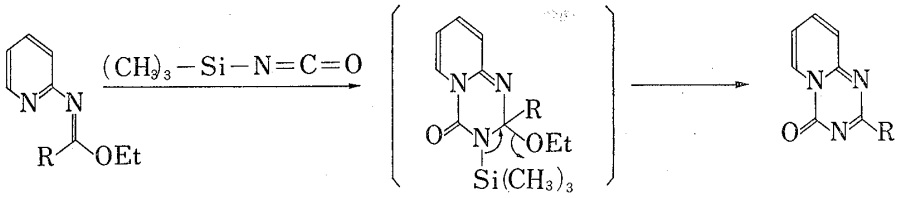
When ethyl N-(2-pyridyl)formimidate (Va, R=H) was allowed to react with trimethylsilyl isocyanate at room temperature, colorless needles of mp 210°, $C_7H_5ON_3$ (XIXa, R=H), were obtained in good yield. Elemental analysis and spectral data uniquely suggested the structure

7) T. Kato, *Accounts of Chem. Research*, **7**, 265 (1974).

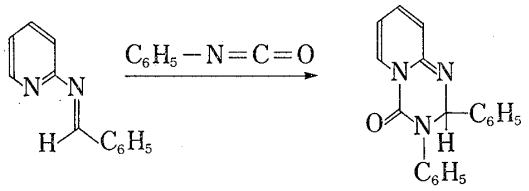
being 4*H*-pyrido[1,2-*a*]-*sym*-triazin-4-one. Similarly, ethyl N-(2-pyridyl)acetimidate (Vb, R=CH_3) and ethyl N-(2-pyridyl)propionimidate (Vc, R=C_2H_5) reacted with trimethylsilyl isocyanate to give good yields of 2-methyl-4*H*-pyrido[1,2-*a*]-*sym*-triazin-4-one (XIXb, R=CH_3) and 2-ethyl-4*H*-pyrido[1,2-*a*]-*sym*-triazin-4-one (XIXc, R=C_2H_5), respectively.

Though the similar reaction of 2-benzylideneaminopyridine (VIa, R=H) with trimethylsilyl isocyanate did not afford any product corresponding to the pyridotriazine derivative such as XIX, the reaction of VIa with phenyl isocyanate gave rise to an adduct, $C_{19}H_{15}ON_3$ (XX), in 83% yield, which was identified as 2,3-diphenyl-4*H*-pyrido[1,2-*a*]-*sym*-2,3-dihydrotriazine-4-one on the basis of elemental analysis and spectral data.

Similar reaction of Va—c with phenyl isocyanate gave crystalline substances in pretty good yield, however, they were very unstable and purification by recrystallization or chromatography failed.



Va—c XIXa—c



VIa XX

Chart 4

Experimental

IR spectra were measured by a Nippon-Bunko Model IR-S spectrophotometer. NMR spectra were determined on a Hitachi-Perkin Elmer R=20 spectrophotometer at 60 MHz. Values are given in ppm relative to tetramethylsilane as an internal standard. Abbreviations are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. All melting points were uncorrected.

Reaction of Diketene with Ethyl N-(2-Pyridyl)formimidate (Va, R=H)——A mixture of Va (1.5 g, 0.01 mole) and diketene (3.4 g, 0.04 mole) was allowed to stand at room temperature for 3 days. Crystals separated were collected by suction, and recrystallized from EtOH to orange needles of mp 151—152° (VIIa) (lit.[5] mp 152°). Yield, 0.5 g.

The filtrate was condensed to dryness, and the resulting residue was purified by silica gel column chromatography using a mixture of petroleum ether and ether (1: 1) and then acetone as eluants. From the petroleum ether–ether eluant a crystalline substance was obtained. Recrystallization from petroleum ether–ether gave colorless prisms of mp 89—90° (VIIIa). Yield, 1.2 g (51%). *Anal.* Calcd. for $C_{12}H_{14}O_3N_2$ (VIIIa): C, 61.52; H, 6.02; N, 11.96. Found: C, 61.62; H, 6.03; N, 12.15. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690, 1630. NMR ($CDCl_3$) ppm: 1.35 (3H, t, J=6.75 Hz), 2.58 (3H, s), 4.28 (2H, q, J=6.75 Hz), 6.80—8.50 (4H, m), 9.18 (1H, d, J=11.4 Hz), 12.70 (1H, d, J=11.4 Hz).

The acetone eluted fraction afforded 0.2 g of VIIa. Total yield of VIIa was 0.7 g (38%).

Ethyl 2-(2-Pyridylaminomethylene)acetoacetate (VIIIa)——A mixture of Va (1.5 g) and ethyl acetoacetate (2 g) was allowed to stand at room temperature for 3 days. The reaction mixture was condensed *in vacuo*, and the crystalline residue was purified by recrystallization from ether–petroleum ether to give 1.9 g (88%) of VIIIa.

Cyclization of VIIIa to VIIa——A solution of VIIIa (0.5 g) in Ac_2O (5 ml) was refluxed for 20 min. After removal of Ac_2O by vacuum distillation, the reaction mixture was washed with ether to give a crystalline

residue. Purification by recrystallization from EtOH gave 0.35 g (88%) of VIIa.

Reaction of Diketene with Ethyl N-(2-Pyridyl)acetimidate (Vb, R=CH_3)——A mixture of Vb (1.6 g) and diketene (3.4 g) was allowed to stand at room temperature for 3 days. Crystals separated were collected by suction. Recrystallization from MeOH afforded yellow needles of mp 159° (VIIb). Yield, 0.5 g. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$ (VIIb): C, 65.33; H, 4.98; N, 13.86. Found: C, 65.45; H, 4.65; N, 13.83. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (sh), 1670, 1630. NMR ($CDCl_3$) ppm: 2.59 (3H, s), 2.68 (3H, s), 7.08—8.07 (3H, m), 9.10 (1H, m).

The filtrate was chromatographed on a silica gel column using petroleum ether, ether and acetone as eluants. The petroleum ether–ether (3: 1) eluted fraction gave 0.6 g of ethyl acetoacetate. The ether eluted fraction gave 2-acetamidopyridine (IXb), mp 69° (lit.[8] mp 67°). The acetone elution gave 0.7 g of VIIb. Total yield of VIIb was 1.2 g (65%).

2-Methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one——A solution of VIIb (0.2 g) in 70% H_2SO_4 (10 ml) was heated at 140° for 3 hr. The reaction mixture was poured into ice-water, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ solution was condensed, and the resulting residue was recrystallized from ether to pale yellow needles of mp 120°, undepressed on admixture with an authentic sample prepared according to the literature.[6]

Reaction of Diketene with Ethyl N-(2-Pyridyl)propionimidate (Vc, R=C_2H_5)——A mixture of Vc (3.6 g) and diketene was allowed to stand at room temperature for 4 days. After removal of excess diketene by vacuum distillation, the resulting residue was extracted with ether. The ether soluble fraction was purified by silica gel column chromatography using petroleum ether and ether as eluants. From the petroleum ether–ether (3: 1) fraction, 0.9 g of ethyl acetoacetate was isolated. The 1: 1 mixture of petroleum ether and ether gave 0.4 g (14%) of 2-propionamidopyridine (IXc), mp 62°.[8] The ether elution gave pale yellow prisms of mp 90° (VIIc). Yield, 1.9 g (72%). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$ (VIIc): C, 66.65; H, 5.59; N, 12.96. Found: C, 66.78; H, 5.72; N, 12.93. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700 (sh), 1668, 1630. NMR ($CDCl_3$) ppm: 1.31 (3H, t, J=7.2 Hz), 2.70 (3H, s), 2.88 (2H, q, J=7.2 Hz), 7.10—8.10 (3H, m), 9.15 (1H, m).

Reaction of Diketene with 2-Benzylideneaminopyridine (VIa, R=H)——Diketene (1.3 g) was added dropwise to VIa (1.8 g) under ice-cooling with stirring for 5 hr. The reaction mixture, which solidified, was filtered. The crystalline substance was washed with a small amount of cold MeOH. Recrystallization from absolute MeOH gave yellow needles of mp 211° (decomp.) (XI). Yield, 2.0 g (76%). *Anal.* Calcd. for $C_{16}H_{14}O_2N_2$ (XI): C, 72.16; H, 5.30; N, 10.52. Found: C, 71.96; H, 5.47; N, 10.36. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 2700—3300, 1685, 1645. NMR (DMSO-d_6) ppm: 3.38 (3H, s), 5.72 (1H, d, J=3 Hz), 6.70—8.00 (8H, m), 8.70 (1H, m), 9.92 (1H, d, J=3 Hz).

3-Acetyl-2-phenyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (XII)——A suspension of XI (0.27 g, 0.001 mole) and chloranil (0.25 g, 0.001 mole) in benzene (20 ml) was refluxed for 1 hr. The reaction mixture was extracted with 10% HCl. The HCl solution was neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ solution was condensed, and the resulting residue was purified by recrystallization from MeOH to pale brown needles of mp 158° (XII). Yield, 0.2 g (74%). *Anal.* Calcd. for $C_{16}H_{12}O_2N_2$ (XII): C, 72.71; H, 4.58; N, 10.60. Found: C, 72.84; H, 4.80; N, 10.75. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1668, 1635. NMR ($CDCl_3$) ppm: 2.47 (3H, s), 7.00—8.00 (8H, m), 9.10 (1H, m).

4*H*-Pyrido[1,2-*a*]-*sym*-triazin-4-one (XIXa, R=H)——A mixture of Va (R=H) (3.0 g, 0.02 mole) and trimethylsilyl isocyanate was stirred at room temperature for 2 days. Crystals separated were collected by suction. Recrystallization from acetone gave colorless needles of mp 210° (XIXa, R=H). Yield, 2.4 g (81%). *Anal.* Calcd. for $C_7H_5ON_3$ (XIXa): C, 57.14; H, 3.43; N, 28.56. Found: C, 56.99; H, 3.56; N, 28.97. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1715, 1638. NMR (CF_3CO_2H) ppm: 7.90—9.00 (3H, m), 8.68 (1H, s), 9.40 (1H, m).

The filtrate was distilled to give a colorless oil of bp 62°, $(CH_3)_3SiOEt$. Yield, 0.4 g (17%).

2-Methyl-4*H*-pyrido[1,2-*a*]-*sym*-triazin-4-one (XIXb, R=CH_3)——Following the similar procedure as above, ethyl N-(2-pyridyl)acetimidate (Vb, R=CH_3) (3.3 g) was allowed to react with trimethylsilyl isocyanate (2.3 g) to give colorless needles (AcOEt) of mp 165° (XIXb, R=CH_3). Yield, 2.8 g (88%). *Anal.* Calcd. for $C_8H_7ON_3$ (XIXb): C, 59.62; H, 4.38; N, 26.07. Found: C, 59.54; H, 4.53; N, 25.71. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1635. NMR ($CDCl_3$) ppm: 2.58 (3H, s), 7.26—8.30 (3H, m), 9.03 (1H, m).

2-Ethyl-4*H*-pyrido[1,2-*a*]-*sym*-triazin-4-one (XIXc, R=C_2H_5)——Following similar procedure described above, ethyl N-(2-pyridyl)propionimidate (Vc, R=C_2H_5) (3.6 g) was allowed to react with trimethylsilyl isocyanate (2.3 g) to give colorless leaves (AcOEt) of mp 148° (XIXc, R=C_2H_5). Yield, 2.6 g (74%). *Anal.* Calcd. for $C_9H_9ON_3$ (XIXc): C, 61.70; H, 5.18; N, 23.99. Found: C, 62.06; H, 5.35; N, 24.15. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1710, 1638. NMR ($CDCl_3$) ppm: 1.36 (3H, t, J=7.8 Hz), 2.80 (2H, q, J=7.8 Hz), 7.22—8.28 (3H, m), 9.04 (1H, m).

2,3-Diphenyl-4*H*-pyrido[1,2-*a*]-*sym*-2,3-dihydrotriazin-4-one (XX)——A mixture of 2-benzylideneaminopyridine (VIa, R=H) (1.8 g) and phenyl isocyanate (1.2 g) was stirred at room temperature for 1 hr. Crystals separated were collected by suction. Purification by recrystallization from cold absolute MeOH gave yellow needles of mp 90°. Yield, 2.5 g (83%). *Anal.* Calcd. for $C_{19}H_{15}ON_3$ (XX): C, 75.73; H, 5.02;

8) A.L. Mndzhoyan and V.G. Afrikyan, *Ser. Khim. Nauk.*, **10**, 143 (1957).

N, 13.95. Found: C, 76.09; H, 5.23; N, 13.89. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1700, 1650. NMR ($CDCl_3$) ppm: 5.70—7.50 (14H, m), 7.80 (1H, m).

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