Notes

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Studies on Ketene and Its Derivatives. LXXXIV.[1] Reaction of Diketene with Tetrazole Derivatives

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Reaction of diketene with 5-phenyltetrazole (I) gave rise to 2-acetonyl-5-phenyl-1,3,4-oxadiazole (VII), and 3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2,6-dimethyl-4-pyrone (VIII). On the other hand, when this reaction was carried out in acetic acid with reflux, 2-methyl-5-phenyl-1,3,4-oxadiazole (IX) and 1,1-diacetyl-2-benzoylhydrazine (X) were obtained.

Reaction of diketene with 5-aminotetrazole (III) resulted in the formation of 7-methyltetrazolo[1,5-*a*]pyrimidin-5(8*H*)-one (XI).

Reaction of 5-phenyltetrazole (I) with acylating agents was reported to give 2-methyl-5-phenyl-1,3,4-oxadiazole (II, R=CH_3).[3] The first stage of the reaction involves the acylation of compound (I) to give 2-acyl-5-phenyltetrazole (A). Elimination of nitrogen from this intermediate gives rise to the 1,3-dipolar intermediate (B), which is transformed into another canonical structure (C) followed by cyclization to give the oxadiazole (II).

Reaction of tetrazole derivatives with compounds having C≡C or C≡N triple bond was also reported to give the corresponding pyrazole or triazole derivatives.[4,5] In these reactions the 1,3-dipolar intermediate corresponding to the structure B, formed by the elimination of nitrogen from tetrazole, is considered as the reactant, which adds to dipolarphiles to give pyrazole or triazole derivative.

On the other hand, it is reported that 5-aminotetrazoles (III, IV) reacted with acylating agents such as acetic anhydride to give the 1,3,4-oxadiazole derivatives (V, VI).[6–8] In this reaction, the intermediate is considered not to be the 1,3-dipolar type structure corresponding to B, but the nitrene structure (E). Namely, the first stage of the reaction might well involve the acylation of the amino group of the tetrazole (III, IV) to give acetamidotetrazole derivative (D), which by the elimination of nitrogen is transformed into the nitrene intermediate (E). Migration of acetamido group of the nitrene (E) gives rise to the carbodimide intermediate (F), recyclization of which, accompanied with protoropy, affords the oxadiazole (V, VI).

Observing these facts, our attention was focused on the investigations on the reaction of 5-phenyl and 5-aminotetrazole with diketene as an acylating agent, which is the subject of the present paper.

When a mixture of 5-phenyltetrazole (I) and diketene was heated at 85—90°, a vigorous reaction occurred with evolution of nitrogen. After working up, except than the recovery of the starting tetrazole, 2-acetonyl-5-phenyl-1,3,4-oxadiazole (VII) and 3-(5-phenyl-1,3,4-oxadiazol-2-yl)-2,6-dimethyl-4-pyrone (VIII) were obtained in 38% and 9% yields, respec-

1) Part LXXXIII: T. Kato, T. Chiba, and S. Tanaka, *J. Heterocyclic Chem.*, **13**, 461 (1976).
2) Location: *Aobayama, Sendai, 980, Japan.*
3) R. Huisgen, *Angew. Chem.*, **72**, 359 (1960).
4) R. Huisgen, M. Siedel, J. Sauer, J. McFarland, and G. Wallbrllisch, *J. Org. Chem.*, **24**, 892 (1959).
5) R. Huisgen, J. Sauer, and M. Seidel, *Chem. Ber.*, **94**, 2503 (1961).
6) R.M. Herbst and J.E. Klingbeil, *J. Org. Chem.*, **23**, 1912 (1958).
7) R. Stable, *Chem. Ber.*, **62**, 1118 (1929).
8) F. Einberg, *J. Org. Chem.*, **32**, 3687 (1967).

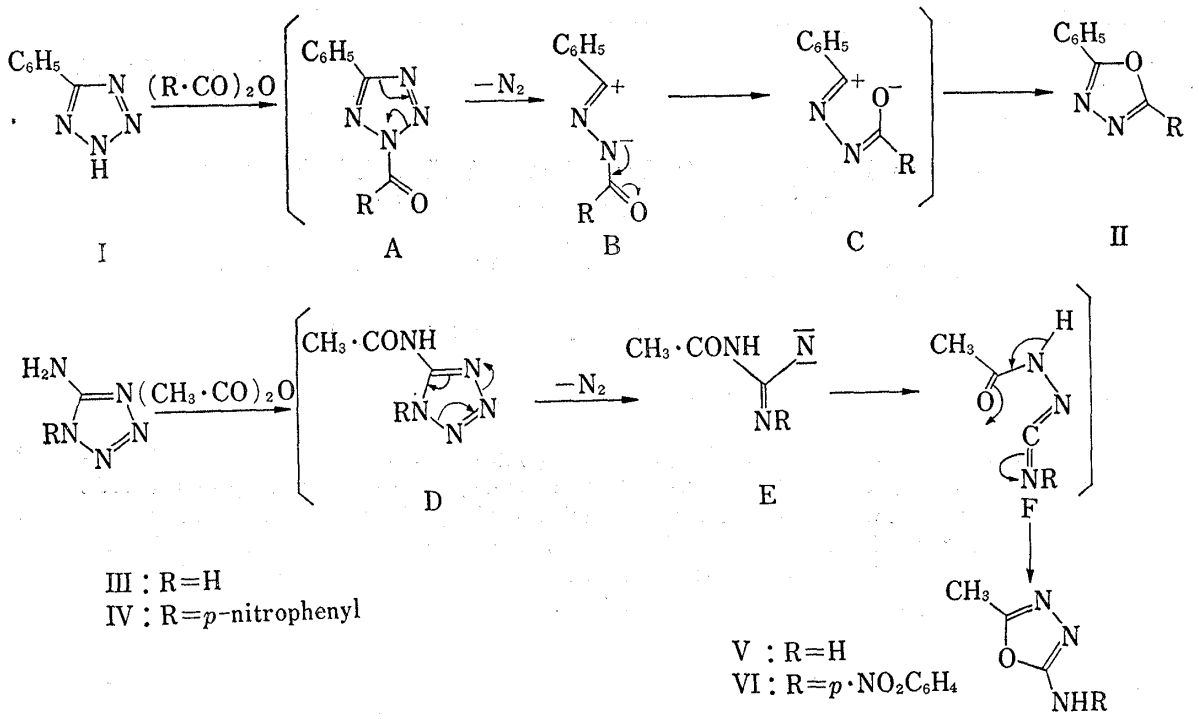

Chart 1

tively. Structural assignment was done on the basis of elemental analysis and the spectroscopic data detailed in the experimental part.

Further reaction of compound (VII) with diketene gave rise to a 49% yield of compound (VIII), which on acid hydrolysis, was converted into 2,6-dimethylpyrone.

However, when the reaction was carried out in acetic acid under reflux, the products were 2-methyl-5-phenyl-1,3,4-oxadiazole (IX), and 1,1-diacetyl-2-benzoylhydrazine (X). These

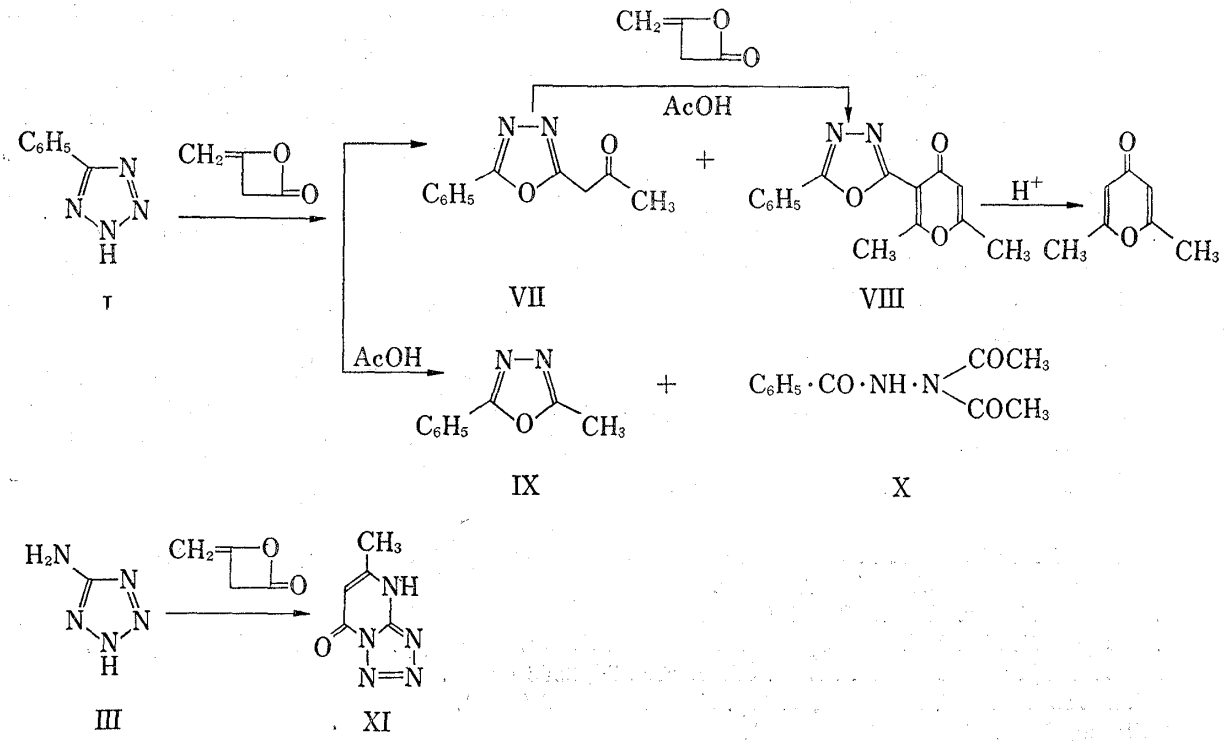

Chart 2

compounds were identified unequivocally by comparison with the respective authentic samples prepared according to the methods described in the literatures.[9,10]

Reaction of 5-aminotetrazole with diketene did not give the corresponding oxadiazole derivative, but gave a known compound, 7-methyltetrazolo[1,5-*a*]pyrimidin-5(8*H*)-one (XI)[11] in almost quantitative yield.

In consideration of the formation of 2-alkyl-5-phenyl-1,3,4-oxadiazole (II) from compound (I) and acylating agent, a similar mechanism can be given for the formation of 2-acetonyl-5-phenyl-1,3,4-oxadiazole (VII). Namely, electrophilic attack of diketene to the ring nitrogen at the 2-position of the tetrazole (I) affords 2-acetoacetyl-5-phenyltetrazole (A, R=CH_2COCH_3), which by loss of nitrogen is converted into the 1,3-dipolar intermediate (B, R=CH_2COCH_3), cyclization of which readily gives rise to compound (VII).

The formation of compound (VIII) is considered in view of the reported reaction of 2-acetonylquinoline with diketene to give 3-(2-quinolyl)-2,6-dimethyl-4-pyrone.[12]

Formation of compound (IX) in acetic acid is explained in view of the fact that reaction of diketene with acetic acid gives acetic anhydride *via* the mixed anhydride ($AcCH_2CO_2Ac$). Acetylation with either acetic anhydride or the mixed anhydride gives the same 1,3-dipolar intermediate (B, R=CH_3), which is transformed to the compound IX along path a. Addition of acetic acid to the 1,3-dipolar intermediate (B, R=CH_3) affords the enol acetate intermediate (G), acetyl migration of which gives rise to compound (X). Similar reaction was reported by Huisgen, *et al.*[5] Namely, 2,5-diphenyltetrazole (XII) reacts with benzoic acid to give 1,2-dibenzoyl-1-phenylhydrazine (XIII), in which reaction the enol benzoate intermediate corresponding to the enol acetate (G) and its acyl migration would be involved.

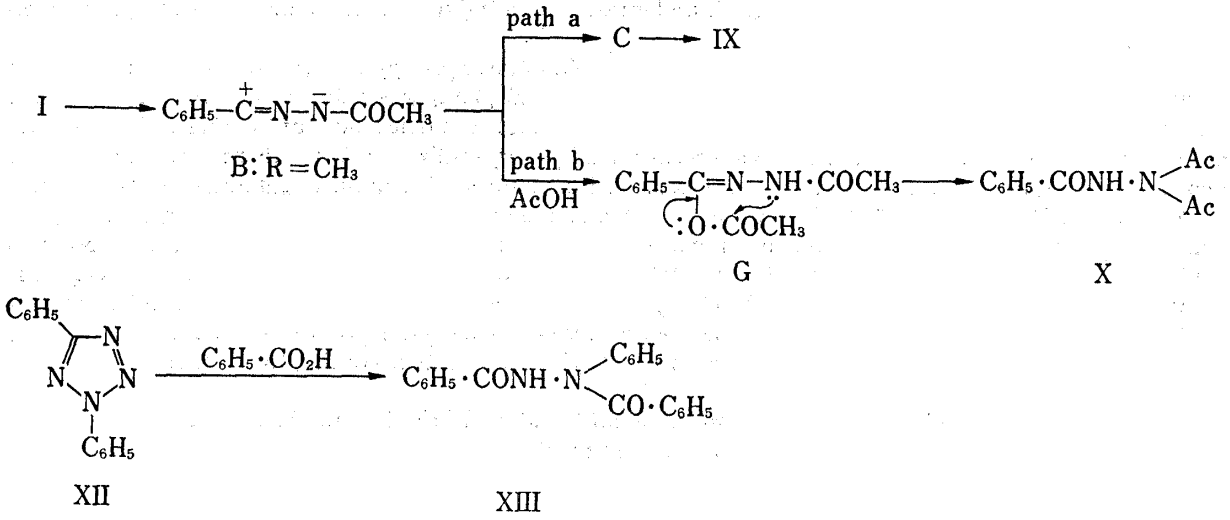

Chart 3

Reaction of 5-aminotetrazole (III) with diketene is considered to proceed by the aceto-acetylation of the ring nitrogen at the 1-position of the tetrazole (III) followed by cyclization and dehydration to give compound (XI).

Experimental

Reaction of Diketene with 5-Phenyltetrazole——1) A suspension of 5-phenyltetrazole (I) (0.73 g, 0.005 mole) in diketene (5 g, 0.06 mole) was heated at 85—90°. After 5 min a vigorous reaction with the evolution

9) R. Huisgen and M. Siedel, *Chem. Ber.*, **94**, 2509 (1961).
10) G. Heller, *J. Prakt. Chem.*, [2] **120**, 59 (1929).
11) L.E. Brady and R.M. Herbst, *J. Org. Chem.*, **24**, 922 (1959).
12) T. Kato, H. Yamanaka, T. Sakamoto, and T. Shiraishi, *Chem. Pharm. Bull.* (Tokyo), **22**, 1206 (1974).

of nitrogen and carbon dioxide occurred. The reaction mixture was allowed to stand at room temperature to give a thick-brown solid. The solid was taken up in chloroform, and submitted to silica gel column chromatography using petroleum ether, benzene, benzene–ether (1: 1), and ethyl acetate as eluants. The petroleum ether and the first benzene elutions gave dehydroacetic acid. The second benzene elution gave 0.15 g of the starting tetrazole.

The benzene–ether (1: 1) fractions were collected and condensed to dryness. The colorless crystals obtained were purified by recrystallization from ether–petroleum ether to give 0.38 g (38%) of colorless prisms, mp 139—140°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$ (VII): C, 65.33; H, 4.98; N, 13.86. Found: C, 65.29; H, 5.07; N, 13.87. IR ν_{max}^{KBr} cm^{-1}: 3000, 2960, 1710, 1590. NMR ($CDCl_3$) ppm: 2.31 (3H, s), 4.08 (2H, s), 7.40—8.10 (5H, m, ring protons).

From the ethyl acetate fraction, after condensation, yellow crystals were obtained, which were purified by recrystallization from benzene to give 0.11 g (9%) of colorless prisms, mp 229—230°. *Anal.* Calcd. for $C_{15}H_{12}O_3N_2$ (VIII): C, 67.15; H, 4.51; N, 10.44. Found: C, 66.92; H, 4.62; N, 10.59. IR ν_{max}^{KBr} cm^{-1}: 1673, 1640, 1582. NMR ($CDCl_3$) ppm: 2.53 (3H, s), 2.72 (3H, s), 6.45 (1H, s), 7.50—8.20 (5H, m, ring protons).

2) A suspension of 5-phenyltetrazole (I) (1.46 g, 0.01 mole) and diketene (2.52 g, 0.03 mole) in acetic acid (15 ml) was refluxed for 4 hr. The reaction mixture was then condensed under reduced pressure. The oily residue was extracted with *n*-hexane. The residual solid was purified by recrystallization from benzene to give 0.11 g (5%) of colorless prisms, mp 149° (lit. mp 152°).[10] *Anal.* Calcd. for $C_{11}H_{12}O_3N_2$ (X): C, 55.99; H, 5.49; N, 12.72. Found: C, 60.23; H, 5.46; N, 12.79. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3420, 3380, 1730, 1700 (shoulder), NMR ($CDCl_3$) ppm: 2.42 (6H, s), 7.30—7.95 (5H, m, ring protons), 8.82 (1H, br. s).

The *n*-hexane extract was condensed under reduced pressure. The crystals obtained were purified by recrystallization from *n*-hexane to give 0.83 g (41% yield) of colorless plates, mp 63—65° (IX), undepressed on admixture with an authentic sample of 2-methyl-5-phenyl-1,3,4-oxadiazole (XX) prepared according to the literature.[3]

Reaction of Diketene with 2-Acetonyl-5-phenyl-1,3,4-oxadiazole (XIX)——A mixture of 2-acetonyl-5-phenyl-1,3,4-oxadiazole (VII) (0.1 g, 0.0005 mole) and diketene (0.168 g, 0.002 mole) in acetic acid (3 ml) was refluxed for 4 hr. The reaction mixture was then condensed under reduced pressure. The oily residue was triturated with ether. The crystals obtained were purified by recrystallization from benzene to give 0.07 g (52% yield) of colorless prisms, mp 229—230°, undepressed on admixture with an authentic sample of compound VIII prepared in the above run.

Acid Hydrolysis of 3-(5-Phenyl-1,3,4-oxadiazol-2-yl)-2,6-dimethyl-4-pyrone (VIII)——A suspension of compound VIII (0.05 g, 0.00018 mole) in 10% hydrochloric acid (3 ml) was refluxed for 6 hr. The reaction mixture was cooled, and extracted with chloroform. The extract was dried over anhydrous sodium sulfate and condensed to dryness. The residual solid was purified by recrystallization from ether to give 0.01 g (40%) of colorless plates, mp 133°, undepressed on admixture with an authentic sample of 2,6-dimethyl-4-pyrone.

Reaction of Diketene with 5-Aminotetrazole——A mixture of 5-aminotetrazole monohydrate (III) (0.51 g, 0.005 mole) and diketene (1.68 g, 0.02 mole) in acetic acid (5 ml) was heated at 80—85° for 1 hr, allowed to stand at room temperature overnight. The crystals separated were collected and purified by recrystallization from EtOH to give 0.75 g (95%) of colorless prisms, mp 236—239° (decomp.). IR and NMR spectra of this compound were identical in every respect with those of 7-methyltetrazolo[1,5-*a*]pyrimidin-5(8*H*)-one (XI) prepared by the reaction 5-aminotetrazole with ethyl acetoacetate according to the literature.[11]

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