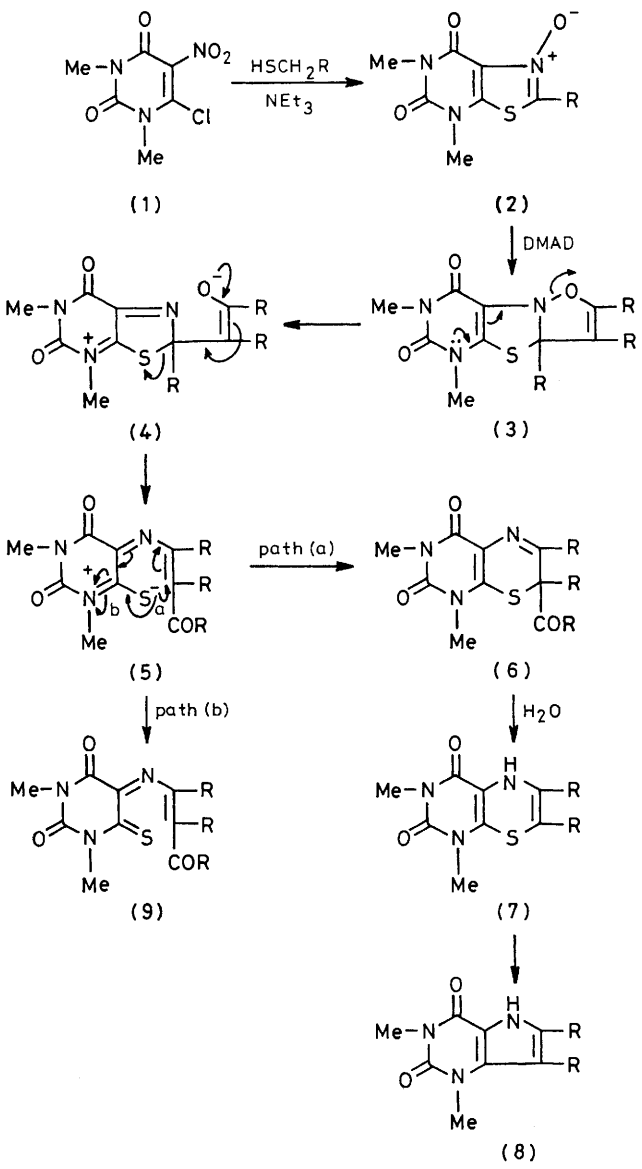
1,3-Dipolar Cycloaddition of a Thiazolo[5,4-*d*]pyrimidine 1-Oxide to Dimethyl Acetylenedicarboxylate. New Ring Transformation to a Pyrrolo-[3,2-*d*]pyrimidine *via* a Pyrimido[4,5-*b*][1,4]thiazine

By KEITARO SENGA,* MISUZU ICHIBA, HASHIME KANAZAWA, and SADAO NISHIGAKI

(*Pharmaceutical Institute, School of Medicine, Keio University*, 35, *Shinanomachi, Shinjuku-ku, Tokyo* 160, *Japan*)

Summary 1,3-Dipolar cycloaddition of a thiazolo[5,4-*d*]-pyrimidine 1-oxide to dimethyl acetylenedicarboxylate resulted in the ring transformation of the thiazole moiety to give a pyrrolo[3,2-*d*]pyrimidine *via* a pyrimido-[4,5-*b*][1,4]thiazine.

1,3-DIPOLAR cycloadditions of heterocyclic *N*-oxides, particularly involving ring transformations, are important in chemistry from both the theoretical and practical viewpoint. We have recently reported that the 1,3-dipolar cycloaddition of pyrimido[5,4-*e*]-*asym*-triazines with acetylenic esters causes a facile ring transformation of the *asym*-triazine moiety to give pyrrolo[3,2-*d*]pyrimidines.[1] On the basis of these findings, we have now investigated the reaction of a thiazolo[5,4-*d*]pyrimidine 1-oxide (**2**) with dimethyl acetylenedicarboxylate (DMAD), and have found that the thiazole moiety undergoes a new ring transformation to give a pyrrolo[3,2-*d*]pyrimidine *via* a pyrimido-[4,5-*b*][1,4]thiazine. The pyrrolopyrimidine and pyrimido-thiazine ring systems are of biological interest, since their structures are closely related to purine and pteridine, respectively.



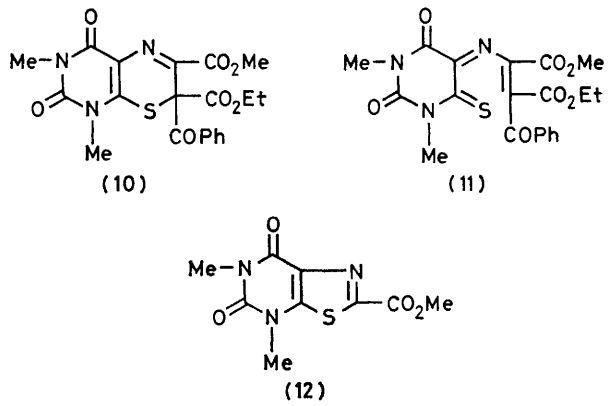
SCHEME. R = CO_2Me.

The starting material (**2**) was readily prepared in a single step by the method used for the synthesis of benzothiazole *N*-oxides,[2] *i.e.*, the dropwise addition of triethylamine (0·1 mol) to a stirred mixture of the chloro-nitrouracil (**1**)[3] (0·05 mol) and methyl thioglycolate (0·05 mol) in ethanol (30 ml) over a period of 1 h at −5 °C caused the separation of (**2**) [m.p. 147—148 °C, 50%, $\lambda_{max.}$ (EtOH) 315 (log ϵ 3·86), 278 (3·98), 268sh (3·88), and 255 nm (3·87)].†

Refluxing of (**2**) (0·001 mol) with DMAD (0·001 mol) in methanol (5 ml) for 10 h resulted in the formation of the pyrimidothiazine (**7**) [m.p. 158—159 °C, 38%, $\lambda_{max.}$ (EtOH) 370 (log ϵ 3·43), 313 (3·89), and 258 nm (4·04)], the pyrrolopyrimidine (**8**)[1] [m.p. 248—249 °C, 17%, $\lambda_{max.}$ (EtOH) 307 (log ϵ 4·22), 273 (4·28), and 230 nm (4·57)], and the thiobarbituric acid (**9**) [m.p. 194—196 °C, 2%, $\lambda_{max.}$ (EtOH) 345 (log ϵ 4·33) and 280sh nm (3·65)]. The compound (**8**) was readily precipitated out from the reaction mixture, while the compounds (**7**) and (**9**) were isolated by fractional recrystallization of the concentrated filtrate from ethyl acetate.

As shown in the Scheme, this new ring transformation presumably involves the initial formation of the adduct (**3**) by a 1,3-dipolar cycloaddition. The cleavage of the isoxazoline ring to give (**4**), followed by C–S bond fission to give (**5**), and subsequent disproportionation by either path (a) or (b) would yield (**6**) and (**9**), respectively. Liberation of the methoxalyl group of (**6**) probably as monomethyl oxalate owing to the water present in the solvent (or DMAD) employed would yield (**7**), and the following ring contraction by loss of sulphur would then give (**8**) as a final product.

Actually, as expected from a precedent that certain pyrimidothiazines closely related to (**7**) undergo thermal ring contraction to give pyrrolopyrimidines,[4] the last step was conducted (in 75% yield) by refluxing of (**7**) with methanol for 3 h. Presumably, the driving force for this reaction is that the formally anti-aromatic 1,4-thiazine ring is transformed into the formally aromatic pyrrole ring. That water participates in the conversion of (**6**) into (**7**) is supported by the fact that refluxing of (**2**) with DMAD in 5% aqueous methanol caused a pronounced improvement in the yield of (**8**) (71%). Moreover when this reaction was interrupted for 1 h, (**7**) was obtained in 56% yield. Although attempted isolation of the intermediates, particularly (**3**)‡ and (**6**), was unsuccessful presumably owing to their high reactivity, the existence of (**6**) at least was suggested by the evidence that the reaction of (**2**) with ethyl phenylpropiolate resulted in the isolation of the anticipated pyrimidothiazine (**10**) [m.p. 175—176 °C, 36%, $\lambda_{max.}$ (EtOH) 366 (log ϵ 4·08) and 256 nm (4·68)] as a stable compound along with the thiobarbituric acid (**11**) [m.p. 201—202 °C, 15%, $\lambda_{max.}$ (EtOH) 331 nm (log ϵ 4·59)].



† All compounds gave satisfactory elemental analyses and spectral properties (i.r., n.m.r., and mass) consistent with the assigned structures.

‡ An adduct of type (**3**) has been obtained previously in the reaction of 2-ethoxycarbonylbenzothiazole *N*-oxide with DMAD (see ref. 2).

In contrast with (**6**), (**9**) is rather stable, *i.e.*, refluxing of (**9**) with methanol or toluene for prolonged periods resulted in the recovery of unchanged (**9**). Additionally, it should be noted that the reaction of thiazolopyrimidine (**12**) [m.p. 214—216 °C, 96%, $\lambda_{max.}$ (EtOH) 310 (log ϵ 4·16) and 270sh nm (3·87)], obtained by the reduction of (**2**) with aqueous sodium dithionite, with DMAD in methanol did not give any ring-transformed product, and the starting material was recovered.

Thanks are due to Mr. K. Nagahara of Kitasato University for elemental analyses and n.m.r. spectra, and to Dr. K. Ishii and Mr. K. Chiba of this school for mass spectra.

(*Received, 15th December* 1980; *Com.* 1329.)

[1] K. Senga, M. Ichiba, and S. Nishigaki, *J. Org. Chem.*, 1979, **44**, 3830.
[2] K. Wagner, H. Heitzer, and L. Oehlmann, *Chem. Ber.*, 1973, **106**, 640.
[3] T. K. Liao and C. C. Cheng, *J. Heterocycl. Chem.*, 1965, **1**, 212.
[4] H. Fenner and H. Motshall, *Tetrahedron Lett.*, 1971, 4185.