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Studies on Heteroaromaticity. XXI.[1] 1,3-Dipolar Cycloaddition of *N*-Phenyl-*C*-(6-uracilyl)nitrone

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N-Phenyl-*C*-(6-uracilyl)nitrone (II) was prepared in 80% yield from orotaldehyde (I) and phenylhydroxylamine. II underwent 1,3-dipolar cycloaddition reactions with several ethylenic and acetylenic compounds to afford the corresponding isoxazolidines (IIIa—f) and isoxazolines (IVg—i). Similar reactions of II with phenyl isocyanate, carbon disulfide and with enamine were carried out successfully. The structural elucidation of these products was done on the basis of their NMR spectra.

The 1,3-dipolar cycloaddition reactions of nitrones with olefins are known to supply a general synthetic method of isoxazolidines.[2] Many papers have been published on this line, but little has been documented on the nitrones of nitrogen heteroaromatic systems except on ring nitrogen *N*-oxide.[3] A recent publication of the most convenient preparative method for orotaldehyde (I) among hitherto reported ones[4] opened a new synthetic route for preparing new chemical species involving an uracil moiety. This paper is concerned with the 1,3-dipolar cycloaddition of *N*-phenyl-*C*-(6-uracilyl)nitrone (II), a nitrone readily prepared from orotaldehyde (I).

Results and Discussion

Orotaldehyde (I) was treated with phenylhydroxylamine in ethanol according to the general procedure for preparing nitrones[5] to give a nitrone II in 80% yield; II was stable in the air but reactive enough to undergo the 1,3-dipolar cycloaddition reactions with several ethylenic and acetylenic compounds to afford the corresponding isoxazolidines (IIIa—f) and isoxazolines (IVg—i) respectively, as shown in Tables 1 and 2.

As is obvious from Table 1, the 1,3-dipolar cycloaddition of II to α,β-unsaturated carbonyl compounds such as b, c and f, aryl-conjugated alkenes such as d and e, and non-conjugated alkene such as a proceeded similarly with high yields, but it was necessary for a to be heated for a longer time than when b was used. In each case, the reaction time was seemingly parallel to the reactivity of the used dipolarophile. In fact, the reaction with maleic anhydride, which is regarded as one of the strongest dipolarophiles,[6] resulted in the formation of intractable tars even on cooling, and the reaction with *trans*-stilbene, which is a weak dipolarophile, resulted in recovering the starting materials even on heating the reaction mixture for 1 day. With acetylenic compounds, the reactions were carried out in dioxane instead of dimethylformamide (DMF) for avoiding the reaction of DMF with such acetylenic compounds.[7] As illustrated in Table 2, the yields were generally lower than those with ethylenic compounds, presumably because of their lower reactivity as dipolarophiles and higher tendency to the thermal polymerization. In fact, the thermal polymerization was clearly observed in the reactions of II with dimethyl acetylenedicarboxylate, propargyl bromide, ethyl phenylpropiolate and chlorocyanoacetylene,[8] all resulted in the thermal polymerization of used alkynes and in recovering II, except those with propargyl alcohol (g), cyanoacetylene (h)[9] and phenylacetylene (i), which afforded the corresponding isoxazolines (IVg—i) as indicated in Table 2.

Conversion of II to III is clearly observed in the

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[1] Part XX of this series: T. Sasaki and T. Yoshioka, this Bulletin, **42**, 258 (1969).

[2] R. Huisgen, R. Grashey and J. Sauer, "Cycloaddition Reactions of Alkenes" in 'The Chemistry of Alkenes', S. Patai, Ed., Interscience Publishers, New York, N. Y. (1964), p. 861.

[3] R. Grashey, R. Huisgen and H. Leitmann, *Tetrahedron Letters*, **1960**, 9; W. E. Noland and D. A. Jones, *Chem. & Ind.*, **1962**, 363; H. Seidl and R. Huisgen, *Tetrahedron Letters*, **1963**, 2022.

[4] K-Y. Zee-Cheng and C. C. Cheng, *J. Heterocyclic Chem.*, **4**, 163 (1967).

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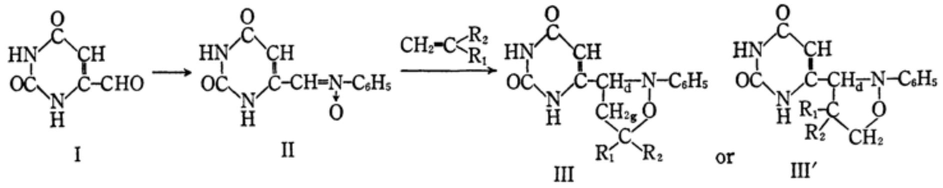
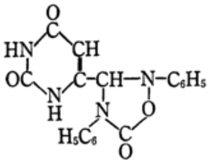
[6] H. Seidl, Ph. D. Thesis, University of Munich, 1963. Ref. 2, p. 865.

[7] E. Winterfeldt, *Angew. Chem.*, **79**, 389 (1967).

[8] E. Kloster-Jensen, *Acta Chem. Scand.*, **18**, 1629 (1964).

[9] C. H. Moureu and J. Ch. Bongrand, *Compt. Rend.*, **151**, 946 (1920); *Arch. Chim.*, (9), **14**, 53 (1920); S. Murahashi, T. Takizawa, S. Kurioka and S. Maikawa, *Nippon Kagaku Zasshi (J. Chem. Soc. Japan, Pure Chem. Sect.)*, **77**, 1689 (1956); L. J. Krebaum, *J. Org. Chem.*, **31**, 4103 (1966).





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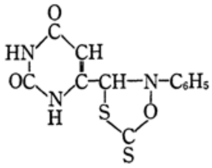

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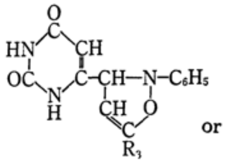

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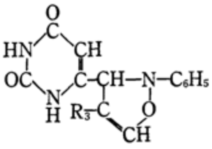

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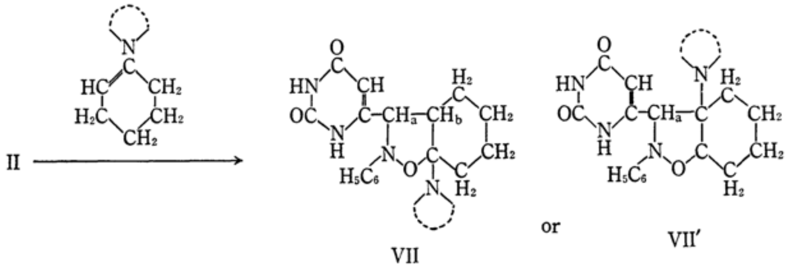

TABLE 1. ISOXAZOLIDINES (III)

	Dipolarophile $CH_2=CR_1R_2$ R₁	R₂	Reaction time hr	Yield %	Product (mp,*1 °C)	Microanalyses Found (Calcd) C	H	N	MeOH UV λ_{max} mμ (log ε)
a	H	CH_2OH	12	100	IIIa (206—209)	58.32 (58.12	5.27 5.23	14.32 14.53)	237(3.18) 260(3.06)
b	H	$COOCH_3$	5	100	IIIb (204—209)	56.49 (56.78	4.86 4.77	12.98 13.24)	236(3.11) 254(3.09)
c	H	$CONH_2$	7	100	IIIc (190—196)	55.43 (55.63	4.44 4.67	18.36 18.54)	236(3.12) 258(3.06)
d	H	C_6H_5	9	100	IIId (206—210)	68.07 (68.05	4.97 5.11	12.31 12.53)	238(3.26) 258(3.11)
e	H	C_5H_4N	8	100	IIIe (210—214)	64.44 (64.28	4.55 4.79	16.57 16.66)	234(3.18) 256(3.12)
f	CH_3	$COOCH_3$	5	86	IIIf (200—204)	57.63 (58.00	4.93 5.17	12.57 12.68)	244(3.18)

*1 decomp.

TABLE 2. ISOXAZOLINES (IV)

	Dipolarophile $HC\equiv CR_3$ R₃	Reaction time hr	Yield %	Product (mp, °C)	Microanalyses Found (Calcd) C	H	N	MeOH UV λ_{max} mμ (log ε)
g	CH_2OH	24	62	IVg (188—189)	55.63 (55.81	4.08 4.35	18.67 18.60)	241 (3.98)
h	CN	24	48	IVh (181—183)	59.61 (59.57	3.43 3.57	20.01 20.19)	241 (3.92)
i	C_6H_5	48	61	IVc (192—194)	68.47 (68.46	4.48 4.45	12.44 12.61)	242 (4.14)

comparison of their ultraviolet and infrared spectra; in the ultraviolet spectra as indicated in Fig. 1 and Table 1, which IIIa—e show the similar patterns of absorptions except IIIf, all indicating hypsochromic shifts compared with that of II. This suggests interruption of the conjugation between the pyrimidine ring and a substituent at the 6-position in II by the conversion. In the infrared spectra, disappearance of a $\nu_{N\rightarrow O}$ absorption[10] after the conversion also supports the occurrence of the 1,3-dipolar cycloaddition. In the ultraviolet spectral comparison of III and IV, slightly bathochromic shifts of IV indicate the increase in unsaturation of IV, but other general patterns resemble each other as shown in Tables 1 and 2.

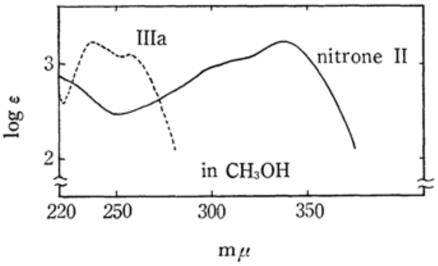

Fig. 1. UV absorption spectra of II and IIIa.

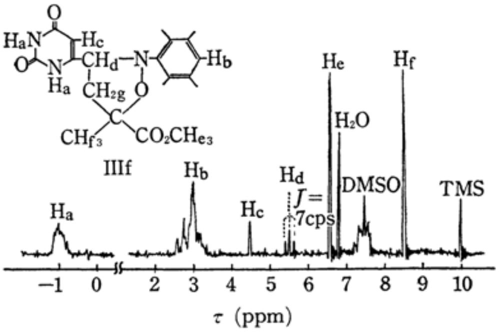

Fig. 2. NMR spectrum of IIIf (DMSO-d_6).

For III, there are two possible structures, III and III′, depending on two different directions of addition. In the NMR spectrum in DMSO-d_6, a signal due to H_d was observed at 5.37τ as a triplet, (J=7.0 cps), as shown in Fig. 2, and consequently IIIf was concluded to be a correct structure.*[1] Similarly, appearance of a H_d signal at 5.25 τ as a quartet supports IIId structure. The fact that no reaction had occurred between II and ethyl cinnamate even on heating for a longer time may be explained by the steric hindrance of a bulky phenyl group attached to the vinyl carbon of the cinnamate.

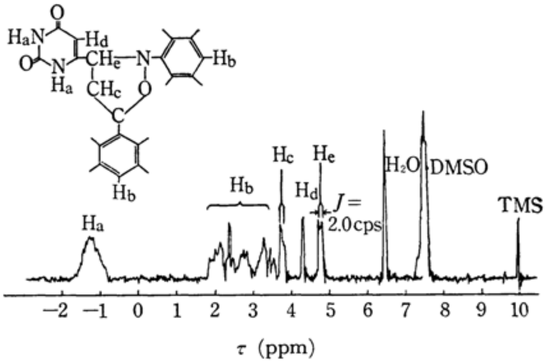

Fig. 3. NMR spectrum of IVi.

The structural elucidation of IV was carried out on the basis of their NMR spectra. For example, IVi was confirmed to be a 5-substituted isoxazoline from its NMR spectrum as shown in Fig. 3.

For further investigation of the reactivity of this nitrone, II was treated with heterocumulenes like phenyl isocyanate, carbon disulfide, phenyl isothiocyanate, benzoyl isocyanate and benzoyl isothiocyanate, and with enamines. Among these dipolarophiles, the first two and the last one were successfully subjected to the 1,3-dipolar cycloaddition; in the reaction with phenyl isocyanate, a catalytic amount of triethylamine was added to the reaction mixture, since without triethylamine, no reaction had occurred. In the reaction with carbon disulfide, the yield of the product was below 10%. A recent publication of the formation of isoxazolidines by the reactions of enamines with diphenylnitrone[11] prompted us to report our results. The reaction of II with 1-morpholino-1-cyclohexene was carried out in a sealed tube under nitrogen, because the same reaction in the air resulted in the formation of intractable tars.

For the reaction product of II with the enamine, there are two possible structures, VII and VII′, assumable, depending on two directions of addition. Appearance of a signal due to H_a at 4.56 τ in the NMR spectrum in DMSO-d_6 indicates that VII is preferable to VII′. The coupling constant J_{ab} was 3.8 cps, which is different from the value reported by Nomura and his coworkers.[11]

Experimental

All the melting points are uncorrected. Infrared spectra were determined on a Nippon Bunko IR-S type spectrometer and electronic spectra were obtained with a Nippon Bunko optical rotary dispersion recorder,

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[10] L. G. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y. (1958), pp. 115, 305.

*[1] For IIIf, a signal due to H_d should be a triplet or a quartet by the presence of vicinal protons. H_g, on the contrary, for IIIf′, it should be a singlet because of the absence of a vicinal proton.

[11] Y. Nomura, F. Furusaki and Y. Takeuchi, This Bulletin, **40**, 1740 (1967).

[12] W. Schulze and Wullitzer, *J. prakt. Chem.*, **33**, 50 (1966).

Model ORD/UV-5. NMR spectra were determined on a Varian A-60 spectrometer, with tetramethylsilane as an internal standard and the peak positions are expressed by τ-values.

***N*-Phenyl-*C*-(6-uracilyl)nitrone (II).** Orotaldehyde (I)4) (1 g) was suspended in 30 m*l* of ethanol and 0.8 g of phenylhydroxylamine was added to this suspension. The reaction mixture was refluxed for 2 hr until the suspension of I went into solution. After cooling, the precipitates were filtered and recrystallized from ethanol to give II as yellow needles, mp 280—285°C. IR (KBr) cm^{-1}: 1060 ($\nu_{N\rightarrow O}$). NMR (DMSO-d$_6$)τ: -1.20 (2H, broad, NH), 1.49 (1H, singlet, –C$\underline{\text{H}}$–N–), 2.0—2.5 (5H, multiplet, phenyl protons), 3.35 (1H, singlet, 5-C–H).

Found: C, 57.39; H, 3.63; N, 17.98%. Calcd for $C_{11}H_9O_3N_3$: C, 57.14; H, 3.92; N, 18.18%.

All attempts for preparing II from 6-methyluracil by the reported procedures12) were unsuccessful.

2-Phenyl-3-(6-uracily)-5-hydroxymethylisoxazolidine (IIIa). To a suspension of 0.2 g of II in 20 m*l* of dry DMF was added 0.5 m*l* of allyl alcohol with stirring. The mixture was heated at 85°C for 12 hr with occasional stirring until the suspension went into solution. After cooling, excess allyl alcohol and DMF were removed under reduced pressure to afford 0.23 g of IIIa as colorless crystals. The mps, yields, elemental analyses and ultraviolet spectra of the reaction products with several ethylenic compounds are summarized in Table 1.

2-Phenyl-3-(6-uracilyl)-5-hydroxymethylisoxazoline (IVg). To a suspension of 0.2 g of II in 20 m*l* of dry dioxane was added 0.5 m*l* of propargyl alcohol. The mixture was fused in a glass tube and heated at 100°C for 1 hr until a clear solution was obtained. After removing an excess amount of propargyl alcohol and dioxane under reduced pressure, the oily residue was dissolved in methanol and a crystalline material precipitated upon addition of ether was recrystallized from tetrahydrofuran to yield IVg as colorless crystals. The yields, mps, elemental analyses and ultraviolet spectral data of the reaction products with several acetylenic compounds are summarized in Table 2.

2-Phenyl-3-(6-uracilyl)-4-phenyl-1,2,4-oxadiazole-5-one (V). Three drops of triethylamine was added to a suspension of 0.3 g of II in 15 m*l* of dioxane and 0.12 m*l* of phenyl isocyanate. The mixture was fused in a glass tube and heated at 85°C for 2 days until a clear solution was obtained. After removing the distillable parts from the reaction mixture under reduced pressure on a water bath, the residue was extracted with 1 m*l* of ethyl acetate-acetone (1 : 1). Solvents were removed from the extract and the residue was recrystallized from benzene-ethyl acetate to afford 0.28 g (62%) of a 1 : 1 adduct (V) as pale yellow crystals, mp 254°C. IR (KBr): 1825 cm^{-1} (ν_{CO}). UV λ_{max}^{MeOH} mμ (log ε): 366 (3.00), 256 (3.84), 222 (4.18).

Found: C, 61.31; H, 3.79; N, 16.00%. Calcd for $C_{18}H_{14}O_4N_4$: C, 61.71; H, 4.03; N, 15.99%.

4-(6-Uracilyl)-5-phenyl-1,3,5-oxathiazole-2-thione (VI). To a suspension of 0.3 g of II in a mixture of 2 m*l* of carbon disulfide and 15 m*l* of dry dioxane was added 3 drops of triethylamine. The mixture was fused in a glass tube filled up with nitrogen and heated at 85°C for 3 days. Work-up as above afforded a 1 : 1 adduct (VI) in 10% yield. Mp 218°C after recrystallization from ethyl acetate. IR (KBr): 1300 cm^{-1} (ν_{CS}). UV λ_{max}^{MeOH} mμ (log ε): 308 (3.75, shoulder), 253 (3.88, shoulder), 253 (3.88, shoulder).

Found: C, 46.16; H, 3.42; N, 12.99%. Calcd for $C_{12}H_9O_3N_3S_2$: C, 46.89; H, 2.95; N, 13.67%.

Reaction of II with 1-Morpholino-1-cyclohexene. A mixture of 0.3 g of II and 0.5 g of 1-morpholino-1-cyclohexene was added to 15 m*l* of dioxane. The resulting mixture was fused in a glass tube filled up with nitrogen and heated at 85°C for 3 days. After removing the distillable parts from the reaction mixture under reduced pressure on a water bath, the residue was dissolved in 5 m*l* of benzene. Upon addition of ether, 0.36 g (72%) of a 1 : 1 adduct (VII) precipitated as brown crystals, mp 203°C. UV λ_{max}^{MeOH} mμ (log ε): 265 (4.09, shoulder), 245 (4.26). NMR (DMSO-d$_6$)τ: 2.49—3.24 (multiplet, phenyl protons), 4.17 (singlet, 5-C–H), 4.56 (doublet, *J*=3.8 cps, 3-C–H), 7.0—7.7 (multiplet, morpholine ring protons), 8.0—9.0 (multiplet, cyclohexane ring protons).

Found: C, 63.70; H, 6.90; N, 13.82%. Calcd for $C_{21}H_{26}O_4N_4$: C, 63.30; H, 6.58; N, 14.06%.

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