

The Synthesis of 5-Aminoisoxazolidines by the 1,3-Dipolar Cycloaddition Reaction of Nitrones with Enamines

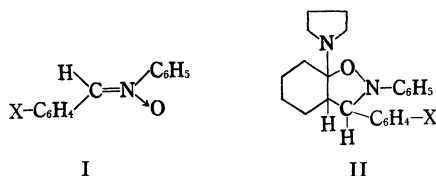
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In a preliminary communication¹⁾ it has been shown that 4,5-tetra(or tri)methylene-2,3-diphenyl-5-pyrrolidino(or morpholino)isoxazolidine was formed by the reaction of benzyldeneaniline *N*-oxide(diphenylnitrone) (Ia: X=H) with 1-pyrrolidino (or morpholino)-1-cyclohexene (or cyclopentene) in dimethylformamide (DMF) at room temperature. The present note deals with the synthesis of a number of isoxazolidines by the nitrono-enamine cycloaddition in detail.

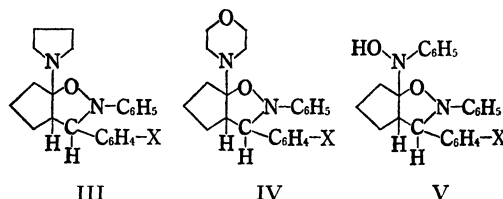
Isoxazolidines IIb—j, with a substituent on 3-phenyl group were synthesized from the corresponding nitrones I and 1-pyrrolidino-1-cyclohexene. The results together with UV spectral data are summarized in Table 1.



The reaction between I and 1-pyrrolidino-1-cyclopentene also gave 2,3-diaryl-4,5-trimethylene-5-pyrrolidinoisoxazolidines IIIa—i. Low yields of III together with the formation of a substantial amount of tar were observed at room temperature. The reaction temperature was controlled to obtain the best results which are tabulated in Table 2.

1-Morpholino-1-cyclopentene was rather sluggish against Ia in DMF at room temperature, and cycloadduct, 4,5-trimethylene-2,3-diphenyl-5-morpholinoisoxazolidine (IVa: X=H) was obtained in 4.2% yield after prolonged heating at 40°C. The main product in this reaction, however, was another isoxazolidine, which was identified as

4,5-trimethylene-2,3-diphenyl-5-(*N*-phenylhydroxy-amino)isoxazolidine (Va: X=H, yield 12.9%) from elementary analysis, IR and above all, NMR spectra. Tsuge *et al.*²⁾ also reported that 4,5-tetramethylene-2,3-diphenyl-5-(*N*-phenylhydroxy-amino)isoxazolidine was formed by heating Ia and 1-morpholino-(or 1-piperidino)-1-cyclohexene in boiling benzene.



Experimental

UV and IR spectra were taken on a Hitachi EPS-2 and a Perkin Elmer 125 spectrophotometer, respectively. NMR spectra were determined in dimethyl sulfoxide-*d*₆ on a JEOL JNM-4H-100 spectrometer at 100 MHz with tetramethylsilane as the internal standard.

All melting points were uncorrected.

2,3-Diaryl-4,5-tetramethylene-5-pyrrolidinoisoxazolidines (IIa—j). A DMF (30 ml) solution of diphenylnitrone (Ia) (5.92 g, 0.03 mol) and 1-pyrrolidino-1-cyclohexene (5.45 g, 0.036 mol) was stirred at room temperature for 72 hr under a nitrogen stream. After removal of the solvent *in vacuo*, the residue was recrystallized from ethanol to afford 4,5-tetramethylene-2,3-diphenyl-5-pyrrolidinoisoxazolidine (IIa) (7.84 g, 74.8%). In a similar manner IIb—j were obtained from the corresponding nitrones and 1-pyrrolidino-1-cyclohexene. The results are summarized in Table 1.

2,3-Diaryl-4,5-trimethylene-5-pyrrolidinoisoxazolidines (IIIa—i). A DMF (30 ml) solution of Ia (3.94 g, 0.02 mol) and 1-pyrrolidino-1-cyclopentene (3.30 g, 0.024 mol) was prepared with ice-cooling and

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

2) O. Tsuge, M. Tashiro and Y. Nishihara, *Tetrahedron Lett.*, **1967**, 3769.

TABLE 1. 2,3-DIARYL-4,5-TETRAMETHYLENE-5-PYRROLIDINOISOXAZOLIDINES(II) OBTAINED BY THE REACTION OF I WITH 1-PYRROLIDINO-1-CYCLOHEXENE

II	X	Reaction time (hr)	Yield (%)	Mp (°C)	Appearance	Elementary analysis		Mol. formula	UV: $\lambda_{\max}^{\text{ethanol}}$ (e)
						Found	Calcd		
a)	H	72	74.8	147—148	Colorless plates*1	C 79.32 H 8.24 N 7.89	79.27 8.10 8.04	C ₂₃ H ₂₈ N ₂ O	251 (11500)
b)	<i>p</i> -CH ₃	24	31.1	165—167	Colorless needles*1	C 79.61 H 8.40 N 7.56	79.51 8.34 7.73	C ₂₄ H ₃₀ N ₂ O	252.5 (6700)
c)	<i>p</i> -CH ₃ O	67	35.9	131—132	Colorless needles*1	C 76.06 H 8.02 N 7.32	76.15 7.99 7.40	C ₂₄ H ₃₀ N ₂ O ₂	229.5 (27100) 253 (10100)
d)	<i>p</i> -(CH ₃) ₂ N	53	poor	172—174.5	Colorless needles*2	C 76.44 H 8.21 N 10.77	76.69 8.49 10.73	C ₂₃ H ₃₃ N ₃ O	257 (24500)
e)	<i>p</i> -Cl	53	51.3	164—166	Colorless needles*1	C 72.31 H 7.17 N 6.95	72.14 7.11 7.32	C ₂₃ H ₂₇ ClN ₂ O	223.5 (15100) 250.5 (11700)
f)	<i>p</i> -Br	72	73.3	171—172	Colorless needles*1	C 64.31 H 6.39 N 6.56	64.63 6.37 6.56	C ₂₃ H ₂₇ BrN ₂ O	220 (17100) 249.5 (12100)
g)	<i>p</i> -CN	46	54.1	164—165	Colorless needles*1	C 77.22 H 7.32 N 11.23	77.18 7.29 11.25	C ₂₄ H ₂₇ N ₃ O	238.5 (26300)
h)	<i>p</i> -NO ₂	53	42.0	172—173	Yellow plates*1	C 70.07 H 6.92 N 10.58	70.20 6.92 10.68	C ₂₃ H ₂₇ N ₃ O ₃	254 (22000)
i)	<i>m</i> -NO ₂	65	88.8	180—182	Yellow plates*1	C 70.09 H 6.88 N 10.67	70.20 6.92 10.68	C ₂₃ H ₂₇ N ₃ O ₃	251.5 (20200)
j)	<i>p</i> -CH ₃ OCO	42	42.0	142—143	Colorless needles*3	C 74.14 H 7.59 N 6.82	73.86 7.44 6.89	C ₂₅ H ₃₀ N ₂ O ₃	245 (33800)

*1 Recrystallized from ethanol.

*2 Purified by column (silica gel) chromatography (benzene-cyclohexane) followed by recrystallization from ethanol.

*3 Purified by column (silica gel) chromatography (dichloromethane) followed by recrystallization from methanol.

TABLE 2. 2,3-DIARYL-4,5-TRIMETHYLENE-5-PYRROLIDINOISOXAZOLIDINES(III) OBTAINED BY THE REACTION OF I WITH 1-PYRROLIDINO-1-CYCLOPENTENE

III	X	Reaction time (hr)	Yield (%)	Mp (°C)	Appearance	Elementary analysis		Mol. formula	UV: $\lambda_{\max}^{\text{ethanol}}$ (ϵ)
						Found	Calcd		
a)	H	34*1	49.9	102.8	Colorless needles	C 78.74 H 7.62 N 8.28	79.00 7.84 8.38	$C_{22}H_{26}N_2O$	254.5 (8900)
b)	<i>p</i> -CH ₃	43*2	43.1	119.5–121	Colorless needles	C 79.08 H 8.21 N 8.19	79.27 8.10 8.04	$C_{23}H_{28}N_2O$	254.5 (11150)
c)	<i>p</i> -CH ₃ O	49*2	59.5	121.7–123.7	Colorless needles	C 75.72 H 7.79 N 7.72	75.79 7.74 7.69	$C_{23}H_{28}N_2O_2$	230 (17100) 255 (7800)
d)	<i>p</i> -(CH ₃) ₂ N	64*3	8.0	128–130	Reddish crystals*4	C 76.42 H 8.41 N 10.96	76.36 8.28 11.13	$C_{24}H_{31}N_3O$	264 (23750)
e)	<i>p</i> -Cl	42*2	63.3	124–125	Colorless needles	C 71.95 H 6.98 N 7.25	71.63 6.83 7.59	$C_{22}H_{25}ClN_2O$	224 (14250) 251 (5800)
f)	<i>p</i> -Br	43*2	60.2	129–131	Colorless plates	C 63.99 H 6.39 N 6.66	63.92 6.10 6.78	$C_{22}H_{25}BrN_2O$	224 (23000) 249 (10200)
g)	<i>p</i> -CN	61*3	75.1	162–164	Colorless grains	C 76.91 H 7.15 N 11.69	76.85 7.01 11.69	$C_{23}H_{25}N_3O$	237 (25150)
h)	<i>p</i> -NO ₂	45*3	12.0	122–123	Yellow crystals	C 69.68 H 6.43 N 10.86	69.63 6.64 11.08	$C_{22}H_{25}N_3O_3$	264 (14700)
i)	<i>m</i> -NO ₂	41*3	60.6	125–127	Yellow plates	C 69.58 H 6.75 N 11.00	69.63 6.64 11.08	$C_{22}H_{25}N_3O_3$	256.5 (17500)

*1 The reaction mixture was stirred for 10 hr under ice-cooling and then at room temperature.

*2 The reaction mixture was stirred for 4 hr under ice-cooling and then at room temperature.

*3 The reaction mixture was stirred for 24 hr under ice-cooling and then at 8°C.

*4 Purified by column (silica gel) chromatography (benzene-cyclohexane) followed by recrystallization from ethanol.

stirred for 10 hr. The stirring was continued for an additional 24 hr at room temperature. The oil obtained by evaporating the solvent *in vacuo* was taken up in ethanol and the solution was allowed to stand in a refrigerator overnight. The precipitate was collected and recrystallized from ethanol to give 4,5-trimethylene-2,3-diphenyl-5-pyrrolidinoisoxazolidine (IIIa) (3.20 g, 49.9%).

Similarly IIIb–i were obtained from the corresponding nitrones and 1-pyrrolidino-1-cyclopentene. The data together with the reaction conditions are listed in Table 2.

The Reaction between Diphenylnitrone (Ia) and 1-Morpholino-1-cyclopentene. A DMF (30 ml) solution of the nitrone Ia (3.94 g, 0.02 mol) and 1-morpholino-1-cyclopentene (3.68 g, 0.024 mol) was stirred at 40°C for 72 hr under a nitrogen stream, and treated as mentioned above. 4,5-Trimethylene-2,3-diphenyl-5-(*N*-phenylhydroxyamino)isoxazolidine (Va: X=H), sparingly soluble in hot ethanol, was isolated as colorless plates, mp 134.5°C (dec.); yield 1.03 g (12.9%).

Found: C, 77.25; H, 6.75; N, 7.54%. Calcd for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52%.

UV: $\lambda_{\max}^{\text{ethanol}}$ 247 m μ (ϵ 11500). IR (KBr): 3320 cm^{-1} (ν OH). NMR: τ 2.6–3.4 (15H, multiplet, aromatic protons); 5.09 (1H, doublet, $J_{3,4}$ =8.0, Hz, 3-H); 6.38 (1H, doublet, $J_{3,4}$ =8.0 Hz, 4-H); 6.73 (1H, singlet, OH); 7.9–8.8 (6H, multiplet, trimethylene

protons).

From the ethanol-soluble fraction, 4,5-trimethylene-2,3-diphenyl-5-morpholinoisoxazolidine (IVa: X=H) was, after purification by chromatography (alumina-benzene), obtained as colorless needles, mp 125–126°C, yield 0.34 g (4.2%).

Found: C, 74.83; H, 7.51; N, 8.00%. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.40; H, 7.48; N, 7.99%.

UV: $\lambda_{\max}^{\text{ethanol}}$ 254.5 m μ (ϵ 8100).

The Reaction between *p*-Methoxybenzylidenaniline *N*-Oxide (Ic: X=*p*-CH₃O) and 1-Morpholino-1-cyclopentene. From 6.82 g (0.03 mol) of the nitrone Ic and 5.52 g (0.036 mol) of 1-morpholino-1-cyclopentene in 50 ml of DMF, 3-*p*-methoxyphenyl-4,5-trimethylene-2-phenyl-5-(*N*-phenylhydroxyamino)isoxazolidine (Vc: X=*p*-CH₃O) was obtained, mp 136–138°C (dec.) (from ethanol); yield 2.28 g (40.0%).

Found: C, 73.93; H, 6.70; N, 6.85%. Calcd for $C_{25}H_{26}N_2O_3$: C, 74.60; H, 6.51; N, 6.96%.

UV: $\lambda_{\max}^{\text{ethanol}}$ 230 (ϵ 22300) and 246 m μ (ϵ 15800). NMR: τ 2.65–3.35 (14H, multiplet, aromatic protons); 5.15 (1H, doublet, $J_{3,4}$ =8.0 Hz, 3-H); 6.32 (3H, singlet, CH₃O); 6.47 (1H, doublet, $J_{3,4}$ =8.0 Hz, 4-H); 6.72 (1H, singlet, OH); 7.8–8.2 (6H, multiplet, trimethylene protons).

In this reaction, no 5-morpholinoisoxazolidine IVc (X=*p*-CH₃O) could be isolated.