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

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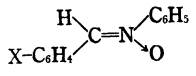
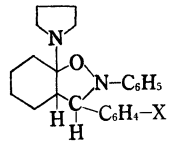
In a preliminary communication[1] it has been shown that 4,5-tetra(or tri)methylene-2,3-diphenyl-5-pyrrolidino(or morpholino)isoxazolidine was formed by the reaction of benzylideneaniline *N*-oxide(diphenylnitrone) (Ia : X=H) with 1-pyrrolidino (or morpholino)-1-cyclohexene (or cyclopentene) in dimethylformamide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



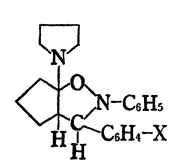
I



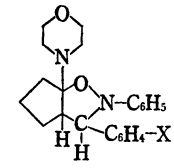
II

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.

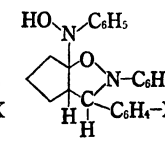
1-Morpholino-1-cyclopentene was rather sluggish against Ia in DMF at room temperature, and cycloadduct, 4,5-trimethylene-2,3-diphenyl-5-morpholinoisoxazolidine (IVa: X=H) was obtained in 4.2% yield after prolonged heating at 40°C. The main product in this reaction, however, was another isoxazolidine,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



III



IV



V

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 m*l*) 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 m*l*) 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	Found	Calcd	Mol. formula	UV: $\lambda_{max}^{ethanol}$ (ε)
a)	H	72	74.8	147—148	Colorless plates*1	C	79.32	79.27	$C_{23}H_{28}N_2O$	251 (11500)
						H	8.24	8.10		
						N	7.89	8.04		
b)	*p*-CH_3	24	31.1	165—167	Colorless needles*1	C	79.61	79.51	$C_{24}H_{30}N_2O$	252.5 (6700)
						H	8.40	8.34		
						N	7.56	7.73		
c)	*p*-CH_3O	67	35.9	131—132	Colorless needles*1	C	76.06	76.15	$C_{24}H_{30}N_2O_2$	229.5 (27100)
						H	8.02	7.99		253 (10100)
						N	7.32	7.40		
d)	*p*-$(CH_3)_2N$	53	poor	172—174.5	Colorless needles*2	C	76.44	76.69	$C_{25}H_{33}N_3O$	257 (24500)
						H	8.21	8.49		
						N	10.77	10.73		
e)	*p*-Cl	53	51.3	164—166	Colorless needles*1	C	72.31	72.14	$C_{23}H_{27}ClN_2O$	223.5 (15100)
						H	7.17	7.11		250.5 (11700)
						N	6.95	7.32		
f)	*p*-Br	72	73.3	171—172	Colorless needles*1	C	64.31	64.63	$C_{23}H_{27}BrN_2O$	220 (17100)
						H	6.39	6.37		249.5 (12100)
						N	6.56	6.56		
g)	*p*-CN	46	54.1	164—165	Colorless needles*1	C	77.22	77.18	$C_{24}H_{27}N_3O$	238.5 (26300)
						H	7.32	7.29		
						N	11.23	11.25		
h)	*p*-NO_2	53	42.0	172—173	Yellow plates*1	C	70.07	70.20	$C_{23}H_{27}N_3O_3$	254 (22000)
						H	6.92	6.92		
						N	10.58	10.68		
i)	*m*-NO_2	65	88.8	180—182	Yellow plates*1	C	70.09	70.20	$C_{23}H_{27}N_3O_3$	251.5 (20200)
						H	6.88	6.92		
						N	10.67	10.68		
j)	*p*-CH_3OCO	42	42.0	142—143	Colorless needles*3	C	74.14	73.86	$C_{25}H_{30}N_2O_3$	245 (33800)
						H	7.59	7.44		
						N	6.82	6.89		

*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	Found	Calcd	Mol. formula	UV: $\lambda_{max}^{ethanol}$ (ε)
a)	H	34*1	49.9	102.8	Colorless needles	C	78.74	79.00	$C_{22}H_{26}N_2O$	254.5(8900)
						H	7.62	7.84		
						N	8.28	8.38		
b)	*p*-CH_3	43*2	43.1	119.5—121	Colorless needles	C	79.08	79.27	$C_{23}H_{28}N_2O$	254.5(11150)
						H	8.21	8.10		
						N	8.19	8.04		
c)	*p*-CH_3O	49*2	59.5	121.7—123.7	Colorless needles	C	75.72	75.79	$C_{23}H_{28}N_2O_2$	230(17100) 255(7800)
						H	7.79	7.74		
						N	7.72	7.69		
d)	*p*-$(CH_3)_2N$	64*3	8.0	128—130	Reddish crystals*4	C	76.42	76.36	$C_{24}H_{31}N_3O$	264(23750)
						H	8.41	8.28		
						N	10.96	11.13		
e)	*p*-Cl	42*2	63.3	124—125	Colorless needles	C	71.95	71.63	$C_{22}H_{25}ClN_2O$	224(14250) 251(5800)
						H	6.98	6.83		
						N	7.25	7.59		
f)	*p*-Br	43*2	60.2	129—131	Colorless plates	C	63.99	63.92	$C_{22}H_{25}BrN_2O$	224(23000) 249(10200)
						H	6.39	6.10		
						N	6.66	6.78		
g)	*p*-CN	61*3	75.1	162—164	Colorless grains	C	76.91	76.85	$C_{23}H_{25}N_3O$	237(25150)
						H	7.15	7.01		
						N	11.69	11.69		
h)	*p*-NO_2	45*3	12.0	122—123	Yellow crystals	C	69.68	69.63	$C_{22}H_{25}N_3O_3$	264(14700)
						H	6.43	6.64		
						N	10.86	11.08		
i)	*m*-NO_2	41*3	60.6	125—127	Yellow plates	C	69.58	69.63	$C_{22}H_{25}N_3O_3$	256.5(17500)
						H	6.75	6.64		
						N	11.00	11.08		

*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 m*l*) 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: $\lambda_{max}^{ethanol}$ 247 mμ (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: $\lambda_{max}^{ethanol}$ 254.5 mμ (ε 8100).

The Reaction between *p*-Methoxybenzylideneaniline *N*-Oxide (Ic: X=*p*-CH_3O) 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 m*l* of DMF, 3-*p*-methoxyphenyl-4,5-trimethylene-2-phenyl-5-(*N*-phenylhydroxyamino)isoxazolidine (Vc: X=*p*-CH_3O) 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: $\lambda_{max}^{ethanol}$ 230 (ε 22300) and 246 mμ (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, CH_3O); 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*-CH_3O) could be isolated.