The Synthesis and ^{1}H Nuclear Magnetic Resonance Spectra of 3,6-Dihydro-1,2-oxazines

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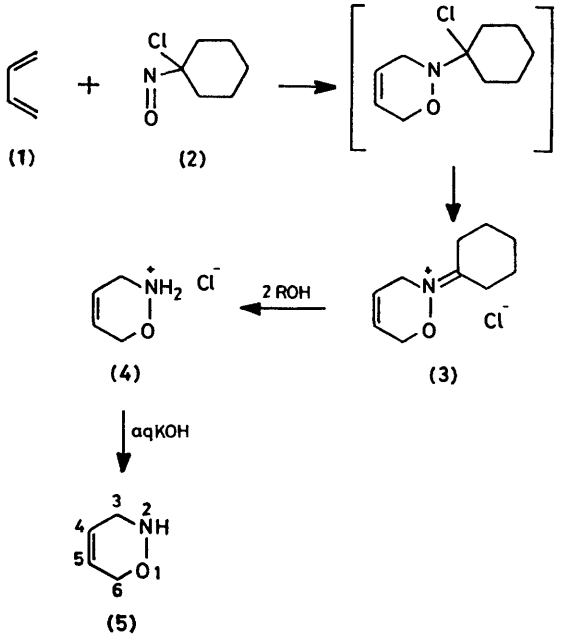
The synthesis of 40 derivatives of 3,6-dihydro-1,2-oxazine making use of the Diels–Alder reaction of 1-chloro-1-nitrosocyclohexane is described. Unambiguous assignment of the structures of the oxazines was possible by means of ^{1}H n.m.r. spectra through decoupling experiments. The adducts from isoprene and 2-phenylbutadiene are mixtures of isomers, the major products having 5-methyl and 4-phenyl groups respectively. *N*-Alkylation of the primary Diels–Alder adducts to give *N*-alkyl-substituted derivatives (R = Me, Et, Pr^i, Bz, CO_2Et) is also reported.

DIHYDRO-OXAZINES are potentially extremely versatile synthetic intermediates which have been used in the preparation of tetrahydro-oxazines,[1] amino-alcohols,[2] and pyrroles.[3] They are also interesting compounds in their own right and have yielded information about nitrogen inversion barriers,[4] conformations of cyclohexene systems,[5] conformational equilibria in cyclohexene systems,[6] and long range ^{1}H–^{1}H coupling constants.[7] Because of their potential synthetic utility,[1-3] and our interests in their conformational properties,[4-7] we decided to re-open the study of their synthesis.

The best method for preparing dihydro-1,2-oxazines is by the Diels–Alder reaction of derivatives of buta-1,3-diene (1) with 1-chloro-1-nitrosocyclohexane (2) (Scheme).[3,8,9] This reaction, which is generally conducted in the presence of ethanol, is believed to proceed *via* the immonium salt (3) which undergoes alcoholysis to the hydrochloride (4). The free base (5) can be liberated by treatment of the hydrochloride with aqueous potassium hydroxide. We decided to extend the scope of this reaction using previously untried butadienes, and also to attempt to prepare *N*-alkyl derivatives, very few of which had previously been reported.[1,10,11]



SCHEME

In this paper we describe our synthetic studies of the Diels–Alder reaction of 1-chloro-1-nitrosocyclohexane with buta-1,3-diene, isoprene, piperylene, 2,3-dimethylbuta-1,3-diene, 1-phenylbuta-1,3-diene, 2-phenylbuta-1,3-diene, 1-phenyl-2-methylbuta-1,3-diene, and 3-phenylpenta-1,3-diene. The regioselectivity of the addition reaction is traced by structural examination of the products using ^{1}H n.m.r. techniques and, in some instances, chemical degradation. Physical and analytical data on the compounds synthesised are reported in Table 1. Proton chemical shifts and coupling constants of the dihydro-oxazine derivatives and n.m.r. data of some resulting cleavage products are given in Supplementary Publication No. SUP 22609 (7 pp.).†

1-*Substituted Dienes.*—The Diels–Alder reaction with piperylene and 1-phenylbutadiene produced adducts with the methyl and phenyl substituents located in position 6 of the oxazine ring [(9) and (23) respectively], as shown by ^{1}H decoupling experiments. First, the CH_2N resonances had twice the intensity of the CH_2O resonances. Furthermore on decoupling the olefinic proton the CH_2N resonances appeared as broadened AB quartets consistent with them arising from protons *cis* and *trans* to the C(6) substituent.

The exclusive formation of 6-substituted oxazines is consistent with steric effects playing an important role in the addition reaction. The nitroso-group, acting as a dienophile, carries a bulky substituent, 1-chlorocyclohexyl, which will approach the least substituted end of the diene.

2-*Substituted Dienes.*—The reaction of isoprene with (2) gave a mixture of two isomeric adducts, 4-methyl and 5-methyl (14), with the latter being the major product. The structure of (14) was proved by decoupling experiments.[1] The predominant formation of this compound (80%) has also been reported by other authors.[1,12]

2-Phenylbutadiene also produced a mixture of isomeric adducts (28), although in this case the 4-substituted derivative predominated (*ca.* 70%). We were able to

† For details of Supplementary Publications see Notice to Authors, No. 7, in *J.C.S. Perkin I*, 1978, Index issue.

TABLE 1

Physical and analytical data

3,6-Dihydro-1,2-oxazine	Substituent on carbon	Substituent on nitrogen	B.p. (°C) [*p*/mmHg]	M.p. (°C) of picrate	Analysis: Required (%) C	H	N	Found (%) C	H	N
(5)	H	H	47—48 [8]	167—169	38.2	3.2	17.85	37.65	3.05	17.55 [a]
(6)	H	Me	58—59 [100]	111—113	40.25	3.65	17.05	40.25	3.75	16.95 [a]
(7)	H	Et	70—71 [100]	87—89	42.1	4.1	16.35	42.2	4.0	16.15 [a]
(8)	H	Pr^i	78—79 [100]	123—125	*m/e* 127.0997			*m/e* 127.0997		
(9)	6-Me	H	48—49 [15]	141—143	44.3	7.4	10.35	44.4	7.45	10.2 [b]
(10)	6-Me	Me	51—52 [50]	102—104	42.1	4.1	16.35	41.75	4.1	16.15
(11)	6-Me	Et	62—64 [50]	82—84	43.8	4.5	15.75	43.8	4.3	15.55
(12)	6-Me	Pr^i	44—45 [15]	84—86	45.3	5.1	15.1	45.35	5.1	15.1 [a]
(13)	6-Me	CO_2Et	80—82 [6]		[c]					
(14)	5-Me	H	46—48 [6]	166—168	40.25	3.65	17.05	40.45	3.9	16.65 [a]
(15)	5-Me	Me	58—59 [50]	133—135	42.1	4.1	16.35	42.3	4.0	16.05 [a]
(16)	5-Me	Et	66—70 [47]	71—73	*m/e* 127.0998			*m/e* 127.0998		
(17)	5-Me	Pr^i	56—58 [15]	117—119	*m/e* 141.1161			*m/e* 141.1154		
(18)	4,5-Me_2	H	50—51 [3]	186—188	48.15	8.0	9.35	47.85	7.95	9.35 [b]
(19)	4,5-Me_2	Me	74—76 [50]	132—134	43.8	4.5	15.75	44.05	4.6	15.4 [a]
(20)	4,5-Me_2	Et	90—94 [50]	120—122	45.4	4.85	15.15	45.35	4.95	14.95 [a]
(21)	4,5-Me_2	Pr^i	69—70 [15]	85—87	46.85	5.2	14.6	46.8	5.25	14.25 [a]
(22)	4,5-Me_2	CO_2Et	100—103 [3]		[c]					
(23)	6-Ph	H	112—114 [2.5]	126—128	60.75	6.05	7.1	60.95	6.25	7.25 [b]
(24)	6-Ph	Me	86—88 [2.5]	140—142	50.5	3.95	13.85	50.6	4.0	13.65 [a]
(25)	6-Ph	Et	98—100 [2.5]	144—146	57.65	4.3	13.4	57.55	4.4	13.25 [a]
(26)	6-Ph	Pr^i	104—106 [2]	145—147	*m/e* 203.1310			*m/e* 203.1311		
(27)	6-Ph	CO_2Et	146—148 [2.5]		[c]					
(28)	4,(5)-Ph	H [d]	68—72 (m.p.)		74.55	6.85	8.7	74.5	6.95	8.6
(29)	4,(5)-Ph	Me [d]	82—84 [3]	64—66	75.4	7.4	8.0	75.35	7.3	8.05
(30)	4,(5)-Ph	Et [d]	98—101 [2]	88—92	76.2	7.95	7.4	75.95	7.95	7.2
(31)	4,(5)-Ph	Pr^i [d]	110—112 [2]		76.85	8.35	6.9	77.0	8.35	6.8
(32)	4,(5)-Ph	Bz [d]	76—80 (m.p.)		81.25	6.75	5.55	81.1	6.9	5.6
(33)	4,(5)-Ph	CO_2Et [d]	164—168 [2.5]		[c]					
(34)	4-Ph	H [e]	100—102 (m.p.)		74.55	6.85	8.9	74.5	7.05	8.5
(35)	4-Ph	Me [e]								
(36)	5-Ph-6-Me	H	58—59 (m p.)		62.4	6.6	6.6	62.35	6.7	6.55
(37)	5-Ph-6-Me	Me	96—98 [2.5]		*m/e* 189.1154			*m/e* 189.1156		
(38)	5-Ph-6-Me	Et	108—110 [2.5]		76.85	8.35	6.9	76.75	8.25	6.85
(39)	5-Ph-6-Me	Pr^i	119—120 [2]	111—113	53.8	4.95	12.55	54.1	5.05	12.45 [a]
(40)	5-Ph-6-Me	CO_2Et	156—158 [2.5]							
(41)	5-Me-6-Ph	H	126—128 [3]		62.4	6.6	6.6	62.65	6.75	6.6 [b]
(42)	5-Me-6-Ph	Me	98—102 [3]	164—166	76.2	7.95	7.4	76.1	7.95	7.35
(43)	5-Me-6-Ph	Et	103—106 [3]	123—125	52.8	4.6		53.1	4.75 [a]	
(44)	5-Me-6-Ph	Pr^i	100—102 [2]	128—130	77.05	9.15	6.4	77.1	8.9	6.3
(45)	5-Me-6-Ph	CO_2Et	142—146 [3]							

[a] Picrate. [b] Hydrochloride. [c] No analytical data available. Compounds identified by mode of formation and ^1H n.m.r. spectra. [d] Mixture of 4- and 5-phenyl derivatives. [e] 4-Phenyl derivative separated from the mixture of both isomers by column chromatography. Isomer identified by its ^1H n.m.r. spectrum.

obtain a pure sample of the 4-phenyl derivative by column chromatography, but were unable to obtain the 5-phenyl derivative uncontaminated by the 4-phenyl isomer. Therefore, our results refer to the mixture, whose signals from the ring hydrogens were clearly separated in the n.m.r. spectra. In the major isomer, decoupling of the CH_2O resonance showed the olefinic hydrogen as a triplet with a splitting of *ca.* 1.6 Hz to CH_2N, which appeared as a doublet. The value of 1.6 Hz is suggestive of an allylic coupling, putting the phenyl at position 4 in the ring. This is further confirmed upon decoupling of the CH_2O resonance which showed the olefinic hydrogen as a triplet with a vicinal coupling of *ca.* 3.0 Hz to 6-H. Similar decoupling experiments on the minor component confirmed it to be the 5-phenyl derivative.

Steric hindrance can hardly be expected to be a factor of paramount importance in reactions of 2-substituted butadienes. The transition state leading to the 4-substituted products may be slightly more hindered than the other giving the 5-substituted isomers. However, during the reaction of 2-phenylbutadiene with nitrosobenzene the 4-phenyl isomer is the predominant product (>95%).[6] Furthermore the reaction of nitrosoaromatic compounds with isoprene [6,13] or chloroprene [13,14] yields the 4-substituted isomer. These results suggest that steric factors are a more decisive influence for (2) than for nitrosoaromatic compounds.[15]

1,2-*Disubstituted Butadienes.*— 1-Phenyl-2-methylbutadiene reacts with (2) to give a single adduct (41), whose structure was confirmed as follows. Decoupling the *C*-methyl group reduced the CHO resonance to a quartet, consistent with a doublet of triplets with similar couplings. The doublet could be attributed to an allylic coupling of −1.7 Hz to the olefinic hydrogen and the triplet to a homoallylic coupling of 2.2 Hz with the CH_2O group. The olefinic hydrogen appeared as a barely resolved sextet with allylic and vicinal couplings of −1.7 and 3.7 Hz respectively.* When the oxazine was converted into the amino-alcohol by N–O bond cleavage

* There is a negligible chemical shift difference between the 3-hydrogens.

the ^1H spectrum of the product was also consistent with the assigned structure.

A similar argument can be applied to the adduct of (2) with 3-phenylpenta-1,3-diene, which was shown to be the 5-phenyl-6-methyl isomer (36).

In these reactions with 1,2-disubstituted buta-1,3-dienes it is again clear that steric hindrance is important in deciding the regioselectivity of the reaction.

N-Alkyl Derivatives.—*N*-Alkyl derivatives were prepared from the initial adducts by standard methods. *N*-Methylation was carried out by the Eschweiller–Clark technique, using formalin in formic acid. Ethylation and isopropylation were performed by using the alkyl bromides in methanol. Benzylation was accomplished by use of benzyl chloride and potassium carbonate. *N*-Ethoxycarbonylation was carried out using ethyl chloroformate and potassium carbonate in ethanol.

The n.m.r. spectra of the *N*-alkyl derivatives are, in their overall features, very similar to those of the initial adducts, and are reported in SUP 22609.

EXPERIMENTAL

Representative syntheses are described below. Other compounds were all synthesised by similar methods, differing only in the quantities employed and occasionally in the solvent (Table 2).

1-Chloro-1-nitrosocyclohexane.[16]—Cyclohexanone oxime was treated with a stream of dry chlorine, while the flask was cooled in ice. The blue liquid which formed was washed several times with water to remove acid, and after drying ($CaCl_2$) it was distilled at 61—62° and 13 mmHg or 35° and 5 mmHg. **CAUTION!** There is a danger of explosion if the pressure is allowed to rise during distillation.

3-Phenylpenta-1,3-diene.[17]—α-Phenylcrotonaldehyde, b.p. 116—118° at 13 mmHg, prepared from benzaldehyde, acetaldehyde, water, ethanol, and crystalline sodium acetate, was treated with CH_3MgBr. The complex formed was hydrolysed with ammonium chloride and ice to 3-phenylpent-3-en-4-ol, b.p. 99—101° at 8 mmHg. The alcohol was dehydrated with potassium hydrogensulphate at 140° and 160 mmHg in the presence of hydroquinone to give 3-phenylpenta-1,3-diene, b.p. 72—75° at 12 mmHg.

TABLE 2

Addition of buta-1,3-dienes to 1-chloro-1-nitrosocyclohexane

Substituent in buta-1,3-diene	Reaction conditions: Solvent [a]	Temp. (°C) [b]	Time (h)	Yield (%)	M.p. (°C)
H	B–Et	10—12	72	42.5	
1-Me	B–Et	O	96	46.8	138—140
2-Me	B–Et	RT	48	31.6	
2,3-Me_2	E–Et	RT	48	39.5	150—152 (lit.,[8] 149—150)
1-Ph	B–Et	RT	5	52.6	147—149 [d] (lit.,[2] 150.5)
2-Ph	B–Et	RT	1	58 [c]	184—186 [d]
1-Me-2-Ph	E–Et	O	72	32.5	167—169 [d]
1-Ph-2-Me	E–Et	O	24	73.0	173—175 [d]

[a] Solvents: B = benzene; E = ether; Et = ethanol. [b] RT = room temperature (*ca.* 28—30 °C in tropical climate). [c] Mixture of two structural isomers. [d] Recrystallization from Pr^iOH.

6-Methyl-5-phenyl-3,6-dihydro-1,2-oxazinium Chloride.—A solution of 1-chloro-1-nitrosocyclohexane (33.57 g, 0.227 mol), ether (80 ml), and ethanol (28.6 ml) was cooled in ice and then added to the solution of 3-phenylpenta-1,3-diene (32.77 g, 0.227 mol) in ether (40 ml). The mixture was left in ice for 72 h. Crystals of the hydrochloride appeared after *ca.* 5 h. After 72 h the crystals of the hydrochloride were filtered off, washed with ether, and dried *in vacuo*, yield 15.6 g (32.4%), m.p. 167—169°.

6-Methyl-5-phenyl-3,6-dihydro-1,2-oxazine.—The oxazine hydrochloride (9.6 g, 0.045 mol) was dissolved in the minimum amount of water cooled in ice and an aqueous solution of potassium hydroxide was added. The liberated amine was extracted with ether and dried (Na_2SO_4). When the ether was evaporated, the crystalline solid obtained was dried *in vacuo*, yield 5.38 g (67.47%), m.p. 58—59°; $\nu_{max.}$ (mull) 3 290, 3 220, 3 075, 3 050, 3 040, 2 990, 2 950, 2 925, 2 900, 2 875, 2 850, 2 825, 1 600, 1 560, 1 500, 1 445, 1 420, 890, 830, 795, 760, 700, and 660 cm^{-1}.

2,6-Dimethyl-5-phenyl-3,6-dihydro-1,2-oxazine.—6-Methyl-5-phenyl-3,6-dihydro-1,2-oxazine (1.21 g, 0.007 mol) was dissolved in formalin (8 ml), the solution was cooled, and formic acid (13.8 g, 0.3 mol) was added slowly. The mixture was stirred and refluxed for 2 h, cooled, and then made alkaline by the addition of a solution of sodium hydroxide. The product was extracted with ether, washed with water until neutral, dried (Na_2SO_4), the ether removed, and the residue distilled at 96—98° and 2.5 mmHg, yield 0.93 g (84.3%); $\nu_{max.}$ (film) 3 080, 3 050, 2 975, 2 950, 2 900, 2 875, 2 825, 1 500, 1 470, 1 450, 895, 760, and 700 cm^{-1}.

2-Ethyl-6-methyl-5-phenyl-3,6-dihydro-1,2-oxazine.—The free amine (36) (0.92 g, 0.005 mol) was dissolved in methanol (6 ml) and ethyl bromide (1.13 g, 0.001 mol) and potassium carbonate (0.46 g, 0.004 mol) were added. The mixture was heated under reflux for 5 h, cooled, filtered, and methanol distilled off. From the residue the amine was extracted with ether, the ethereal solution was dried (Na_2SO_4), and the ether evaporated. The product distilled at 108—110° and 2.5 mmHg, yield 0.81 g (75.7%); $\nu_{max.}$ (film) 3 070, 3 040, 2 990, 2 950, 2 925, 2 850, 2 810, 1 600, 1 495, 1 450, 890, 760, and 700 cm^{-1}.

2-Isopropyl-6-methyl-5-phenyl-3,6-dihydro-1,2-oxazine.—The free base (36) (1.1 g, 0.006 mol) was treated with 2-bromopropane (2.48 g, 0.02 mol) in methanol, under similar conditions as described for the ethyl derivative. The product distilled at 119—120° and 2 mmHg, yield 0.94 g (68.9%); $\nu_{max.}$ (film) 3 070, 3 045, 2 990, 2 950, 2 860, 2 805, 1 600, 1 495, 1 450, 865, 760, and 700 cm^{-1}.

2-Ethoxycarbonyl-6-methyl-5-phenyl-3,6-dihydro-1,2-oxazine.—A mixture of the hydrochloride (36) (2.75 g, 0.013 mol), ethyl chloroformate (2.2 g, 0.02 mol), potassium carbonate (4.54 g, 0.036 mol) and ethanol (60 ml) was stirred and heated under reflux for 1 h, then left overnight. The solution was filtered, treated with ether, the ethereal solution washed with water, dried (Na_2SO_4), and the ether evaporated. The product distilled at 156—158° and 2.5 mmHg, yield 1.91 g (59.5%); $\nu_{max.}$ (film) 3 080, 3 005, 2 950, 1 710, 1 450, 770, and 710 cm^{-1}.

2-Benzyl-4(5)-phenyl-3,6-dihydro-1,2-oxazine.—4(5)-Phenyl-3,6-dihydro-1,2-oxazine (18) (2.48 g, 0.015 mol) dissolved in methanol (6 ml), benzyl chloride (5.8 g, 0.045 mol), and potassium carbonate (3.18 g, 0.024 mol) were heated under reflux for 4 h. After cooling, the mixture was filtered, methanol distilled off, and the residue was washed

with water in order to remove an excess of benzyl chloride. The benzyl derivative of the oxazine was extracted with ether and the ethereal solution was dried (Na_2SO_4). When the ether was evaporated crystals of the product were obtained, m.p. 76—80°, $\nu_{max.}$ (Nujol) 3 080, 3 050, 2 930, 2 895, 2 860, 2 840, 1 625, 1 575, 1 500, 1 460, 1 430, 1 385, 1 345, 860, 800, 760, 730, 700, and 660 cm^{-1}.

5-Amino-3-phenylpent-3-en-2-ol (46).—The free base (36) (1.35 g, 0.007 mol), dissolved in glacial acetic acid (35 ml), was treated with zinc dust while the solution was stirred vigorously. The mixture was heated for 1 h at 50 °C on a water-bath, and the zinc was filtered off and washed with glacial acetic acid. The filtrate was made alkaline and the amine was extracted with chloroform. The chloroform solution was washed with water and dried (Na_2SO_4), the chloroform was removed by distillation, and the product distilled at 159—163° and 2 mmHg.

4-Amino-2-methyl-1-phenylbut-2-enol.—The oxazine (41) was converted into 4-amino-2-methyl-1-phenylbut-2-enol as for (36). The product distilled at 142—144° and 2 mmHg.

I.r. Spectra.—I.r. spectra were run on a Perkin-Elmer model 720 spectrophotometer in Kumasi. For solid samples hexachlorobutadiene was used as solvent.

N.M.R. Spectra.—N.m.r. spectra were recorded for *ca.* 10% solutions in $CDCl_3$ or D_2O–CD_3OD on either a Perkin-Elmer R32 operating at 90 MHz or a Varian A60 spectrometer at 60 MHz, both equipped with a standard variable temperature accessories. Spectra were run mainly at Stirling (R32) and partly at McMaster University, Hamilton, Ontario (A60). Chemical shifts are given in p.p.m. (δ) or Hz downfield from tetramethylsilane as internal reference. For easier interpretation of spectra, overlapping multiplets were resolved by spin–spin decoupling using a Varian HA-100D proton stabilized n.m.r. spectrometer, operating at 100 MHz (McMaster University), or the R32 spectrometer.

Mass Spectra.—Mass spectra were recorded on a JEOL D-100 mass spectrometer at Stirling.

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