Isoxazoline Derivatives. Part VI.[1] Regioselectivity in the 1,3-Dipolar Cycloaddition of Nitrile Oxides to αβ-Unsaturated Ketones

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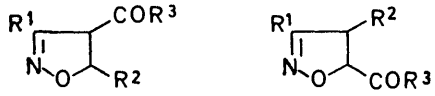
1,3-Cycloadditions of nitrile oxides to αβ-unsaturated ketones have been studied. In most cases a mixture of the two regioisomeric 3-substituted 4- and 5-acyl-Δ^2-isoxazolines was obtained. The individual compounds were characterised by chemical and/or spectroscopic methods. Effects of steric and electronic factors on the cycloadditions are discussed.

1,3-DIPOLAR cycloadditions are usually regarded as concerted reactions,[2,3] although a diradical intermediate has recently been proposed.[4,5]

Reaction with an unsymmetrically substituted dipolarophile would be expected to lead to one or both of two orientational isomers (or regioisomers). Usually only one isomer is isolated, but sometimes a mixture of the two is formed. Both electronic and steric factors contribute to the orientation in the transition state, but their relative importance is difficult to evaluate. In some cases,[6,7] separation of the electronic from the steric component has been attempted; the semiquantitative treatment of nitrilimine cycloadditions[8] is of particular significance. Nevertheless, in spite of the extensive literature on 1,3-dipolar cycloadditions, no general rule has so far been proposed to rationalise the direction of addition, and the orientation phenomena have been said to represent the 'biggest unsolved problem in the field'.[3] More experimental data therefore seem desirable; we report here the behaviour of αβ-unsaturated ketones in their cycloadditions with nitrile oxides.

Nitrile oxides are reported to yield a mixture of two orientational isomers in cycloadditions with indene,[9] αβ-unsaturated esters,[10-13] and ω-nitrostyrenes.[14] Among the hitherto reported cycloadditions with vinyl ketones[15-21] and their monoaryl derivatives,[22,23] only *p*-nitrobenzylidene-acetone and -acetophenone[23] are claimed to give a mixture of the two regioisomers (but without indication of ratios).

We have tested the behaviour of several αβ-unsaturated ketones (ethylideneacetophenone, benzylideneacetone, and chalcones and their heterocyclic analogues, all of which have a *trans*-configuration, as well as cycloalk-2-enones, which possess a *cis*-transoid structure) toward several nitrile oxides. In almost all cases the cycloaddition led to the two regioisomeric Δ^2-isoxazoline ketones (a) and (b). (Table 1).



(1a)-(53a) (1b)-(53b)

METHODS AND RESULTS

The nitrile oxides were prepared by the *in situ* technique from the corresponding hydroximic acid chlorides, except for the stable nitrile oxides, which were used as such. All the cycloaddition reactions were run under comparable conditions. The structures of the orientational isomers were elucidated both by chemical and by spectroscopic methods. Table 1 lists the results obtained with αβ-unsaturated ketones of general formula $R^2CH{=}CH{\cdot}COR^3$.

The ready base-promoted ring cleavage of 5-acyl-Δ^2-isoxazolines[20,21] to give nitriles and α-diketones is a well-known reaction. The corresponding 4-acyl-Δ^2-isoxazolines are more stable toward bases and do not yield α-diketones. The reaction with triethylamine is therefore diagnostic for the 5-acyl structure, and can be also used as a spot test for monitoring chromatographic separations (yellow spot only for the 5-acyl isomer).

In some cases, the acylisoxazolines were identified through dehydrogenation with *N*-bromosuccinimide[24] to the corresponding isoxazoles.

Structural assignments based on chemical methods have been confirmed and extended by n.m.r. spectro-

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TABLE 1

Regioisomeric 4- and 5-acyl-Δ^2-isoxazolines from nitrile oxides R^1CNO and $\alpha\beta$-unsaturated ketones $R^2CH{=}CH{\cdot}COR^3$

Cycloadduct	R^1	R^2	R^3	Isomeric ratio (a) : (b)	(% Total yield)
		(a) Cycloalkenones			
(1)	Ph	$[CH_2]_2$		91 : 9	(85)
(2)	p-$O_2N{\cdot}C_6H_4$	$[CH_2]_2$		$\geqslant$95 : *a*	(96)
(3)	p-$MeO{\cdot}C_6H_4$	$[CH_2]_2$		90 : 10	(93)
(4)	2,4,6-$Me_3C_6H_2$	$[CH_2]_2$		$\geqslant$95 : *a*	(93)
(5)	Ph	$[CH_2]_3$		75 : 25	(85)
(6)	2,4,6-$Me_3C_6H_2$	$[CH_2]_3$		$\geqslant$95 : *a*	(94)
(7)	Ph	$[CH_2]_4$		65 : 35	(95)
(8)	p-BrC_6H_4	$[CH_2]_4$		79 : 21	(76)
(9)	p-$O_2N{\cdot}C_6H_4$	$[CH_2]_4$		82 : 18	(78)
(10)	p-$MeO{\cdot}C_6H_4$	$[CH_2]_4$		79 : 21	(82)
(11)	Ph	$CMe_2{\cdot}CH_2{\cdot}CH_2$		$\geqslant$95 : *a*	(70)
		(b) Benzylideneacetones			
(12)	Me	Ph	Me	45 : 55	(44)
(13)	Ph	Ph	Me	59 : 41	(92)
(14)	p-ClC_6H_4	Ph	Me	55 : 45	(85)
(15)	p-BrC_6H_4	Ph	Me	56 : 44	(80)
(16)	m-$O_2N{\cdot}C_6H_4$	Ph	Me	56 : 44	(85)
(17)	p-$O_2N{\cdot}C_6H_4$	Ph	Me	62 : 38	(80)
(18)	2,6-$Cl_2C_6H_3$	Ph	Me	67 : 33	(85)
(19)	p-MeC_6H_4	Ph	Me	58 : 42	(82·5)
(20)	p-$MeO{\cdot}C_6H_4$	Ph	Me	52 : 48	(91·5)
(21)	2,4,6-$Me_3C_6H_2$	Ph	Me	20 : 80	(90)
(22)	2,4,6-Me_3-3,5-Cl_2C_6	Ph	Me	14 : 86	(90)
(23)	2,4,6-$(MeO)_3C_6H_2$	Ph	Me	80 : 20	*b*
(24)	Bz	Ph	Me	82 : 18	(55)
(25)	Ph	2,4,6-$Me_3C_6H_2$	Me	20 : 80	*b*
(26)	Ph	2,4,6-$(MeO)_3C_6H_2$	Me	85 : 15	(86)
(27)	2,6-$Cl_2C_6H_3$	2,4,6-$(MeO)_3C_6H_2$	Me	57 : 43	*b*
(28)	2,4,6-$Me_3C_6H_2$	2,4,6-$Me_3C_6H_2$	Me	*a* : $\geqslant$95	*b*
(29)	2,4,6-$Me_3C_6H_2$	2,4,6-$(MeO)_3C_6H_2$	Me	35 : 65	*b*
(30)	Ph	Ph	Et	48 : 52	(79)
		(c) Chalcones			
(31)	Ph	Ph	Ph	29 : 71	(80)
(32)	2,4,6-$Me_3C_6H_2$	Ph	Ph	25 : 75	(92)
(33)	Ph	p-BrC_6H_4	Ph	23 : 77	(73)
(34)	Ph	p-MeC_6H_4	Ph	27 : 73	(90)
(35)	Ph	p-$MeOC_6H_4$	Ph	27 : 73	(90)
		(d) Chalcone hetero-analogues			
(36)	Ph	Ph	2-Furyl	43 : 57	(95)
(37)	2,4,6-$Me_3C_6H_2$	Ph	2-Furyl	30 : 70	(94·5)
(38)	Ph	Ph	2-Thienyl	43 : 57	(96)
(39)	2,4,6-$Me_3C_6H_2$	Ph	2-Thienyl	13 : 87	(72)
(40)	2,4,6-$Me_3C_6H_2$	2-Furyl	Ph	62 : 38	(92)
(41)	Ph	2-Thienyl	Ph	63 : 37	(95)
(42)	Ph	2-Furyl	2-Furyl	88 : 12	(87)
(43)	2,4,6-$Me_3C_6H_2$	2-Furyl	2-Furyl	87 : 13	(75)
(44)	Ph	2-Furyl	2-Thienyl	76 : 24	(97)
(45)	2,4,6-$Me_3C_6H_2$	2-Furyl	2-Thienyl	70 : 30	(55)
(46)	Ph	2-Thienyl	2-Furyl	87 : 13	(96)
(47)	Ph	2-Thienyl	2-Thienyl	70 : 30	(91·5)
		(e) Ethylideneacetophenones			
(48)	Ph	Me	Ph	32 : 68	*b*
(49)	2,6-$Cl_2C_6H_3$	Me	Ph	60 : 40	*b*
(50)	2,4,6-$Me_3C_6H_2$	Me	Ph	45 : 55	*b*
		(f) Acetals			
(51)	Ph	Cyclopent-2-enone ethylene acetal		90 : 10	(67)
(52)	2,4,6-$Me_3C_6H_2$	Cyclopent-2-enone ethylene acetal		$\geqslant$95 : *a*	(75)
(53)	Ph	Cyclohept-2-enone ethylene acetal		43 : 57	(54)

[a] Not detectable in the reaction mixture. [b] Total yield not exactly evaluable.

TABLE 2

^{1}H N.m.r. data (δ in p.p.m.; J in Hz) [a]

Compound	H-4	H-5	$J_{4,5}$	$\Delta\delta_{5,4}$	Compound	H-4	H-5	$J_{4,5}$	$\Delta\delta_{5,4}$
				(a) Cycloalkenones					
(1a)	4·075d	5·49m	8·8	1·415	(1b)	4·43m	4·82d	10·0	0·39
(2a) [b]	4·60d	5·65m	9·3	1·05	(2b)				
(3a)	4·10d	5·50m	8·7	1·40	(3b)		4·78d		
(4a)	3·91d	5·50m	9·2	1·59	(4b)				
(5a)	4·23d	5·12m	9·6	0·89	(5b)	4·20m	4·68d	9·4	0·48
(6a)	4·14d	5·14m	10·5	1·00	(6b)				
(7a)	4·41d	5·00m	12·0	0·59	(7b)	3·95m	5·12d	11·3	1·17
(8a)	4·95d	5·05m	12·0	0·10	(8b)				
(9a) [b]	5·3m				(9b) [b]	4·40m	5·60d	11·3	1·20
(10a)	4·40d	5·00m	11·3	0·60	(10b)	4·0m	5·10d	10·7	1·10
(11a)	4·25d	4·60dd	10·2	0·35	(11b)				
				(b) Benzylideneacetones					
(12a)	4·05d	5·72d	7·5	1·67	(12b)	4·43d	4·70d	4·7	0·27
(13a)	4·45d	5·87d	5·08	1·42	(13b)	4·69d	4·95d	3·7	0·26
(14a) [c]	4·22d	5·77d	4·8	1·55	(14b) [c]	4·66d	4·96d	4·0	0·30
(15a)	4·43d	5·68d	5·0	1·25	(15b)	4·83d	5·08d	4·2	0·25
(16a)	4·58d	5·93d	5·3	1·35	(16b)	4·90d	5·13d	4·3	0·23
(17a)	4·56d	5·94d	5·6	1·38	(17b)	4·87d	5·12d	4·5	0·25
(18a) [c]	4·55d	6·15d	8·6	1·60	(18b) [c]	4·98d	5·08d	5·3	0·10
(19a)	4·40d	5·80d	5·0	1·40	(19b)	4·70d	5·0d	3·9	0·30
(20a)	4·37d	5·79d	5·0	1·42	(20b)	4·72d	5·0d	3·9	0·28
(21a)	4·52d	5·57d	8·6	1·05	(21b)	4·88d	5·16d	3·6	0·28
(22a) [c]	4·27d	6·12d	9·3	1·85	(22b) [c]	4·78d	5·11d	3·4	0·33
(23a)	4·49d	6·01d	6·8	1·52	(23b)				
(24a)	4·67d	5·83d	8·5	1·16	(24b)	4·93d	5·11d	5·4	0·18
(25a)					(25b) [c]	4·77d	5·40d	7·5	0·63
(26a)	4·66d	6·40d	7·2	1·74	(26b)	4·92d	5·55d	9·3	0·63
(27a)	5·32d	6·75d	12·0	1·43	(27b)	5·34d	5·86d	7·2	0·52
(28a)					(28b) [c]	4·95d	5·47d	4·7	0·52
(29a)					(29b)	5·25d	5·69d	6·7	0·44
(30a)	4·24d	5·70d	5·0	1·46	(30b)	4·65d	4·98d	4·0	0·33
				(c) Chalcones					
(31a)	5·35d	5·75d	7·0	0·4	(31b)	5·41d	5·65d	4·5	0·24
(32a)	5·30d	6·40d	8·0	1·1	(32b)	5·27d	6·02d	4·5	0·75
(33a)	5·41d	5·80d	6·5	0·39	(33b)	5·51d	5·70d	4·5	0·19
(34a)	5·48d	5·78d	6·5	0·30	(34b)	5·44d	5·70d	4·5	0·26
(35a)	5·48d	5·72d	7·0	0·24	(35b)	5·38d	5·70d	4·5	0·32
				(d) Chalcone hetero-analogues					
(36a)	5·18d	5·85d	6·5	0·67	(36b)	5·29d	5·39d	3·0	0·1
(37a)	5·17d	6·33d	8·5	1·16	(37b)	5·17d	5·81d	4·5	0·64
(38a)	5·15d	5·85d	7·0	0·7	(38b)	5·37d	5·47d	4·0	0·1
(39a)	5·09d	6·31d	8·0	1·22	(39b)	5·18d	5·78d	4·0	0·60
(40a)	5·72d	6·30d	7·7	0·58	(40b)	5·55d		6·0	
(41a)	5·50d	5·95d	6·5	0·45	(41b)	5·66d	5·78d	5·0	0·12
(42a)	5·47d	5·85d	7·0	0·38	(42b)	5·5d	5·65d	5·0	0·15
(43a)	5·64d	6·45d	8·0	0·81	(43b)	5·35d	5·83d	4·0	0·4
(44a)	5·47d	5·80d	7·0	0·33	(44b)	5·5d	5·67d	4·5	0·17
(45a)	5·40d	6·29d	7·0	0·89	(45b)	5·45d	5·95d	6·0	0·5
(46a)	5·35d	6·1d	6·5	0·75	(46b)	5·45d	5·63d	4·5	0·18
(47a)	5·30d	6·05d	7·0	0·75	(47b)	5·45d	5·70d	4·5	0·25
				(e) Ethylideneacetophenones					
(48a)	4·95m				(48b)	4·40m	5·48d	4·8	1·08
(49a)	5·16d	5·61m	6·9	0·45	(49b)	4·43m	5·50d	8·0	1·07
(50a)	4·83d	5·24m	8·0	0·41	(50b)	4·18m	5·24d	6·8	1·06
				(f) Acetals					
(51a)		5·2m			(51b)		4·64d	8·6	
(52a)		5·25m			(52b)				
(53a)		4·77m			(53b)		4·68d	10·7	
	5-Benzoyl-3-phenyl-Δ²-isoxazoline				3·95(A) [d]	5·80(X) [d]	J_{AX} 7·3		
					3·45(B) [d]		J_{BX} 11·3		
	5-Acetyl-3-phenyl-Δ²-isoxazoline				3·60(A) [d]	5·04(X) [d]	J_{AX} 7·0		
					3·48(B) [d]		J_{BX} 11·0		

[a] Spectra recorded in $CDCl_3$ unless otherwise stated. [b] $(CD_3)_2SO$ solution. [c] CCl_4 solution. [d] The capital letter in brackets refers to the ABX system of a 3,5-disubstituted Δ²-isoxazoline.

scopy. Previous n.m.r. studies[9,17,25-28] proved this technique to be useful for structural assignment of Δ^2-isoxazoline derivatives, especially in the case of *cis–trans*-isomers. A proton in the 5-position absorbs at lower field than a 4-proton, owing to the paramagnetic shift caused by the adjacent oxygen atom; the chemical shifts of both protons depend further on the nature of the substituents.

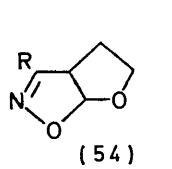
N.m.r. spectroscopy has now been used to distinguish between 4-acyl-Δ^2-isoxazolines [structures (a)] and 5-acyl-Δ^2-isoxazolines [structures (b)]. As shown in Table 2, which gives the spectral data pertinent to the 4- and the 5-protons of the acylisoxazolines, the differences between the chemical shifts of the two protons ($\delta_5 - \delta_4 = \Delta\delta_{5,4}$) show remarkable regularities within the same group of compounds. In the case of the acetylisoxazolines [(12)—(29)], $\Delta\delta_{5,4}$ is always notably larger for the 4-acylisoxazolines than for the 5-acyl isomers (the values range between 1·05 and 1·85 for the former and 0·10 and 0·63 for the latter). With acylisoxazolines derived from chalcones and their hetero-analogues [(31)—(47)], the same pattern is observed, with one exception (35), but here the differences are smaller, although still sufficient for diagnostic purposes. However, a *para*-substituent on an aryl group in the 4- or 5-position may lower the value, and in one case [*p*-MeO, (35)] the $\Delta\delta_{5,4}$ value is actually larger for the 5-acyl than for the 4-acyl isomer. With methyl-benzoylisoxazolines [(48)—(50)] this last observation ($\Delta\delta_{5,4}$ 5-acyl > $\Delta\delta_{5,4}$ 4-acyl) is the general rule. These regularities in the chemical shifts of 4- and 5-acylisoxazolines are understandable in terms of the deshielding effects of the groups involved if we admit a rough additivity of the substituent parameters.

Coupling constants are also valuable in the structural assignments, since for all isoxazolines derived from arylmethyleneacetones and chalcones and their hetero-analogues, the $J_{4,5}$ values are always larger for the 4-acylisoxazolines than for the 5-acylisoxazolines. The values of $J_{4,5}$ for monocyclic acylisoxazolines are spread over a wide range (3·0—12·0 Hz), but are consistent with the hitherto reported values for *trans*-protons in Δ^2-isoxazolines.[25-28] The condensed acylisoxazolines, prepared from cycloalkenones, show larger $J_{4,5}$ values (8·8—12·0 Hz), consistent with their *cis*-orientation. No exception to the rigid *cis*-stereospecificity of the addition was observed.*

The reaction mixtures usually contained, besides the two isoxazoline ketones, variable amounts of starting material and, in the case of aromatic nitrile oxides, small amounts of the dimer, *i.e.* the 3,4-diarylfurazan oxide. Usually the separation was achieved through column chromatography, but the isomeric ratios reported in Table 1 were deduced from n.m.r. spectroscopy. Whenever possible, the reported values were corroborated by quantitative chromatographic separation. The individual regioisomers thus obtained, whenever isolable in pure form, were stable under the reaction conditions.

DISCUSSION

In order to evaluate the role of electronic factors in determining the orientation of cycloaddition, it is essential to make use of asymmetrically activated dipolarophiles, having equal or almost equal steric hindrance on both ends of the unsaturated system. Such requirements are essentially fulfilled, for example, by 2,3-dihydrofuran and by but-2-enolides, which are known to react with nitrile oxides to give only one of the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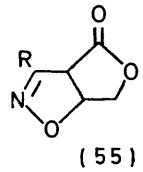
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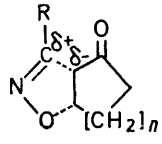
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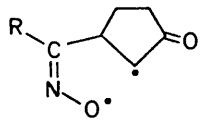

(57)

two possible isomers, *i.e.* the bicyclic furo[3,2-*d*]isoxazole (54) [29] and furo[3,4-*d*]isoxazol-4-one (55) [30] derivatives, respectively. Whereas the orientation in the former adduct can be equally well explained by both the concerted and the diradical mechanisms, the orientation in the latter case points towards a concerted process.

From this point of view, the results obtained with cyclopent-2-enone (Table 1) and its ethylene acetal are particularly interesting. Whereas in a previous report [31] only one bicyclic isoxazoline ketone, of unspecified structure, was obtained from the cycloaddition of benzonitrile oxide and cyclopentenone in ethereal solution, a mixture of the two orientational isomers has now been obtained either from the ketone or from its acetal. The large preponderance of the 4-ketone is best explained by a concerted process with charge unbalance in the transition state (56; $n = 1$). A diradical route seems less likely, because in this case the most likely intermediate would be (57). Consistent with the better delocalisation of the partial positive

* A recent systematic examination of the mass spectra of 4- and 5-acyl-Δ^2-isoxazolines revealed different fragmentation patterns for the two regioisomeric series (A. Selva, personal communication). The foregoing structural attributions based on n.m.r. spectroscopy were fully confirmed.

[25] M. C. Aversa, G. Cum, and M. Crisafulli, *Gazzetta*, 1968, **98**, 42.

[26] G. Bianchi, P. Grünanger, and A. Perotti, *Tetrahedron Letters*, 1964, 2157.

[27] A. Perotti, G. Bianchi, and P. Grünanger, *Chimica e Industria*, 1966, **48**, 492; Atti Convegno risonanze magnetiche, CNR, Pavia, 1966.

[28] R. Sustmann, R. Huisgen, and H. Huber, *Chem. Ber.*, 1967, **100**, 1802.

[29] R. Paul and S. Tchelitcheff, *Bull. Soc. chim. France*, 1962, 2215; 1963, 140.

[30] R. Metelli and G. F. Bettinetti, *Synthesis*, 1970, 365. Recently, negligible amounts of the regioisomer have been isolated in some cases (G. F. Bettinetti, unpublished results).

[31] N. Barbulescu and P. Grünanger, *Gazzetta*, 1962, **92**, 138.

charge in (56), mesitonitrile oxide gives a still higher yield of the major isomer (4a).*

In changing from five-membered through six- to seven-membered cycloalkenes, the proportion of the minor isomer increases progressively [*cf.* (5b) and (7b)]. This variation may be due both to an increased conformational mobility and to a reduced stabilisation of the partial negative charge α to the carbonyl group in (56). The exclusive formation of the isomer (11a) in the cycloaddition of benzonitrile oxide to 4,4-dimethylcyclohex-2-enone is mainly due to steric hindrance.†

The results of the cycloaddition with acyclic αβ-unsaturated ketones ‡ are less straightforward, and only some general trends are worth mentioning. The cycloaddition of benzo- or mesito-nitrile oxide to mesityl oxide led to only one isomer, *i.e.* 3-phenyl- and 3-mesityl-4-acetyl-5,5-dimethyl-Δ^2-isoxazolines respectively (see Experimental section), easily predictable both on steric and on electronic criteria. As Table 1 shows, in all other cycloaddition reactions a product mixture was obtained, in which sometimes approximately equal amounts of the two possible isomers were present.

When a heteroaromatic group, such as furyl or thienyl, is directly bonded to the ethylenic linkage, the 4-acylisoxazoline is largely prevalent in the mixture. In contrast, when the heteroaromatic ring is bonded to the carbonyl group and in the case of chalcones, ArCH=CH·COAr', the ratios are displaced in favour of the 5-acyl isomer. The nature of the aromatic residue bound to the carbonyl group does not seem to affect the isomeric ratio notably.

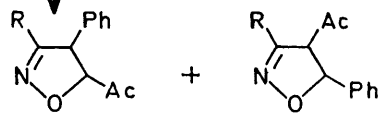
With benzylideneacetone nearly equal amounts of the two isomers are often obtained. Different benzonitrile oxides have been tested, and the nature of the *para*-substituent has been shown to affect the isomer ratio only slightly. The reversibility of orientation is particularly striking in the limit cases: mesitonitrile oxide afforded the 5-acyl isomer (21b) predominantly, whereas 2,4,6-trimethoxybenzonitrile oxide gave the 4-acyl isomer (23a) as major component. The same effect is observed when the substituent is directly linked to the dipolarophilic double bond. With ethylideneacetophenone the isomeric ratio is *ca.* 1 : 1.

In order to gain a deeper insight into the nature of the transition state, we examined the effect of solvent, the influence of which on regioselectivity in nitrile oxide cycloaddition reactions has been little studied. So far, only a slight influence of the solvent polarity on the cycloaddition of mesitonitrile oxide to methyl propiolate has been recorded.[14] Our preliminary results on the cycloadditions of mesitonitrile oxide and 2,6-dichlorobenzonitrile oxide to benzylidene acetone are reported in Table 3. In both cases a notable shift toward the 4-acyl isomer, much more marked with the former 1,3-dipole than with the latter, parallels the increasing polarity of the solvent.§ If we admit a concerted mechanism, this fact means that the process toward the 5-acylisoxazoline is more 'synchronous', whereas the transition state leading to the 4-acyl isomer bears more highly developed partial charges owing to equal bond formation.¶ The 'charge-unbalanced' transition

TABLE 3 [a]

Solvent effects

RCNO + PhCH=CH—CO—CH$_3$



(b) (a)

R = 2,4,6-Me$_3$C$_6$H$_2$ or 2,6-Cl$_2$C$_6$H$_4$

2,6-Cl$_2$C$_6$H$_4$ [b] (b) : (a) Ratio	2,4,6-Me$_3$C$_6$H$_2$ (b) : (a) Ratio	Solvent	E_T [d]
33 : 67	68 : 32	MeOH	55·5
32 : 68	74 : 26	EtOH	51·9
15 : 85	45 : 55 [c]	MeCN	46·0
22 : 78	59 : 41	Me_2CO	42·2
19 : 81	50 : 50	$C_2H_4Cl_2$	41·9
22 : 78	53 : 47	CH_2Cl_2	41·1
26 : 74	70 : 30	AcOEt	38·1
33 : 67	80 : 20	Et_2O	34·6
30 : 70	79 : 21	PhH	34·5
30 : 70	87 : 13	C_6H_{12}	31·2

[a] Reactions carried out at 18 °C, nitrile oxides being in a slight excess (10%). [b] Some 2,6-Cl$_2$C$_6$H$_3$·CN detected and in one case isolated from the reaction mixture. This compound affected the elemental analysis of the adducts (18a and b). [c] Some 3-mesityl-5-methyloxadiazole was also isolated as by-product (cycloaddition of the nitrile oxide to acetonitrile). [d] C. Reichardt and K. Dimroth, *Fortschr. Chem. Forsch.*, 1968, **11**, 1.

* The same phenomenon is still more evident in the case of cyclohexenone, *i.e.* if we compare cycloadducts (5) and (6).

† Indeed the increase in ring size implies a diminished degree of conjugation in the starting cycloalkenone, as indicated by spectroscopic properties (see *e.g.* ref. 32). The i.r.,[33] u.v.,[33] and n.m.r. ($\nu_B - \nu_A$ = 50·5 Hz from tetramethylsilane) data of 4,4-dimethylcyclohex-2-enone are practically coincident with those of cyclohexenone. As far as dipolarophilic reactivity may depend on the ground state polarity of the double bond, the isomeric ratio obtained from the former compound should be very similar to that of the latter (*i.e.* 75 : 25). Actually the bulky dimethyl substituent completely suppresses attack of the sterically more demanding carbon end of the 1,3-dipole on the neighbouring position.

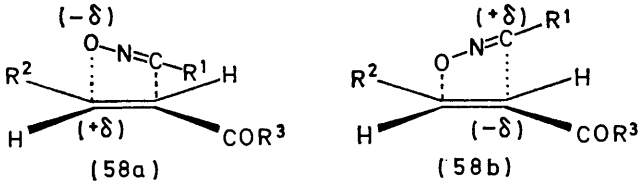
‡ Whereas the acyclic ketones are forced into the *s-trans*-conformation, chalcones and their heteroaromatic analogues predominantly possess *s-cis*-conformations, and benzylideneacetone presents the two forms in comparable amounts.[34]

§ The plot of the logarithms of regioisomeric ratios [(a) : (b)] against the E_T values is fairly linear for the whole range of solvent polarities used. A discontinuity is noticed with ethanol and methanol, for which an interaction between the nitrile oxide and the protic solvent must be taken into account.

¶ The variation of the conformational equilibrium *s-cis* ⇌ *s-trans* with solvent polarity should not influence the isomeric ratio notably, owing to the much higher activation energies involved in the cycloaddition than in the conformational transformations.[35] Furthermore, if we consider only the permanent dipole moments of the reagents, an inspection of all the possible transition states shows that those leading to the 4-acyl isomer are less polar than or of similar polarity to those leading to the 5-acyl isomer.

[32] N. Heap and G. H. Whitham, *J. Chem. Soc.* (*B*), 1966, 164.
[33] J.-M. Conia and A. Le Craz, *Bull. Soc. chim. France*, 1960, 1934.
[34] M. E. Kronenberg and E. Havinga, *Rec. Trav. chim.*, 1965, **84**, 17, 979.
[35] See *e.g.* E. Wyn-Jones and R. A. Pethrick, *Topics Stereochem.*, 1970, **5**, 254.

states (58a) and (58b) are the most favourable from the point of view of charge distribution. Heterocyclic rings, such as 2-furyl or 2-thienyl, or the strongly



(58a) (58b)

electron-releasing 2,4,6-trimethoxyphenyl group in the R^2 position stabilise the positive charge of (58a), whereas the 2,4,6-trimethoxyphenyl group in the R^1 position stabilises (58b), thus accounting for the preponderance of the 4-acyl isomers in these cases. With mesitonitrile oxide in acetonitrile again stabilisation of the route through (58b) is still slightly prevalent, whereas in less polar solvents the picture becomes complicated owing to some other factors, which favour the 5-acyl isomer.*

Further investigations are needed to determine a clearer relationship between regioselectivity and the nature of the substituents. However the present work shows that the formation of two regioisomeric isoxazolines is quite general in the cycloaddition of nitrile oxides to αβ-unsaturated carbonyl compounds, both carboxylic esters [13] and ketones, and that the solvent polarity may notably affect the isomeric ratio.

EXPERIMENTAL

I.r. spectra were obtained for Nujol suspensions or for liquid films on a Perkin Elmer 257 spectrophotometer. The n.m.r. spectra (60 MHz) were recorded at 35° on a Perkin-Elmer R12 spectrometer by Dr. A. Gamba. U.v. spectra were measured by Dr. M. De Bernardi on a Perkin-Elmer 135 instrument for 95% ethanolic solutions. Microanalyses were carried out by Dr. L. Maggi Dacrema. T.l.c. was performed on plates precoated with Silica Gel GF_{254} (Merck). The identity of compounds with authentic materials was always established by mixed m.p. determination and by comparison of i.r. spectra and R_F values (t.l.c.). Preparative columns were prepared with Silica Gel H (Merck).

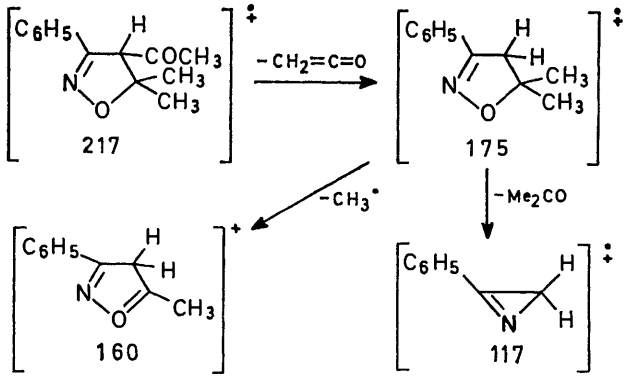
Materials.—The αβ-unsaturated ketones were prepared by literature methods described in a comprehensive review.[36] A few of them were obtained commercially. All compounds had m.p.s or b.p.s in agreement with the literature values. For the synthesis of the nitrile oxides and their precursors, we have applied the most suitable method for each case, as reported in a recent monograph.[37]

Standard Procedures for the Preparation of Isoxazolines (1)—(53).—(i) *Stable nitrile oxides.* Anhydrous ethereal solutions (*ca.* 50—100 mmol l^{-1}) of the stable nitrile oxide and of the αβ-unsaturated ketones were mixed and kept at room temperature for 24 h. The reaction was monitored by t.l.c. After evaporation to dryness, the crude product was analysed by the two methods described below.

(ii) *Nitrile oxides generated* in situ. A stirred ethereal solution of hydroximic acid chloride and αβ-unsaturated ketone (50—100 mmol l^{-1} of each) was treated with the stoicheiometric amount of triethylamine at room temperature. (Excess of triethylamine must be avoided owing to the instability of the isoxazoline ketones towards bases [20,21]). The mixture was left at room temperature for 12 h, then poured into cold water; the organic layer was separated, dried, and evaporated.

In some cases (see Table 1), the reaction was carried out with a large excess of the dipolarophile in order to improve the yield of the cycloadducts. Use of equimolar amounts of the reactants led to the isolation of a large amount of furazan oxide, along with the same ratio of the regioisomeric adducts. The pure regioisomers reported in Table 4 were obtained by working up the crude products from both the procedures (i) and (ii). When one of the two regioisomers was the predominant product of the cycloaddition, it was separated and purified by simple recrystallisation, whereas when the two regioisomers were formed from the reaction in comparable amounts, column-chromatographic separation was used.

4-Acetyl-5,5-dimethyl-3-phenyl-Δ²-isoxazoline.—The reaction of benzonitrile oxide, prepared *in situ* (ii), with a large excess of mesityl oxide afforded, along with some diphenyl furazan *N*-oxide, a 35—40% yield of the *isoxazoline*, m.p. 76° (from petroleum) (Found: C, 72·2; H, 6·9; N, 6·6. $C_{13}H_{15}NO_2$ requires C, 71·9; H, 7·0; N, 6·5%); δ ($CDCl_3$) 1·38 (s, 5-Me), 1·44 (s, 5-Me), 1·98 (s, 4-Me), and 3·7 (s, 4-H) p.p.m.; *m/e* 217 (14%, M^+), 175 (52%, $[M - CH_2CO]^+$), 160 (62%, $[175 - CH_3]^+$), 161 (24%), 118 (21%), 117 (13%, $[175 - CH_3COCH_3]^+$), 103 (10%, $C_6H_5CN^+$), 77 (64%), and 43 (100%) (see Scheme).



SCHEME

Determinations of Isomeric Proportions.—(i) The n.m.r. spectrum of the crude product (isolated as described above) was recorded (*ca.* 10% solution in either CCl_4 or $CDCl_3$). In most cases the n.m.r. spectra of the two regioisomers showed clear separation of signals due to the 4- and 5-protons of the 4-acyl-Δ²-isoxazoline and the 4- and 5-protons of the 5-acyl-Δ²-isoxazoline. Planimetric integration of peak areas gave the isomer proportions. Analysis of synthetic mixtures of 4- and 5-acyl-Δ²-isoxazolines afforded an accuracy of ±5% by this method.

(ii) Column chromatographic separation was applied when n.m.r. quantitative analysis was not reliable owing to the difficulties in assigning the peaks of the spectrum of each one of the two regioisomers. A large number of eluant systems were used: cyclohexane–ethyl acetate,

* Steric effects or even π-interactions cannot be excluded *a priori*.

[36] A. T. Nielsen and W. J. Houlian, *Org. Reactions*, 1968, **16**, 1.
[37] Ch. Grundmann and P. Grünanger, 'The Nitrile Oxides,' Springer-Verlag, Heidelberg, 1971.

benzene–ethyl acetate, methylene chloride–methanol, and benzene–chloroform mixtures in varying proportions.

Hydrolysis of the Acetals (51)—(53).—The acetal (0·5 g) was dissolved in methanol (15 ml) containing hydrochloric acid (36%; 5 ml); the solution was boiled for 2 h, cooled, and evaporated to leave the corresponding ketone (1), (4), or (7) (75—95%).

lines as: 3-*benzyl*-2-*methylquinoxaline*, needles [from light petroleum (b.p. 60—80°)], m.p. 56—57° (Found: C, 82·1; H, 6·2; N, 11·8. $C_{16}H_{14}N_2$ requires C, 82·0; H, 6·0; N, 12·0%); and 2-*methyl*-3-(2,4,6-*trimethylbenzyl*)*quinoxaline*, needles (from ethanol), m.p. 137—138° (Found: C, 82·4; H, 7·5; N, 10·2. $C_{19}H_{20}N_2$ requires C, 82·6; H, 7·3; N, 10.1%).

TABLE 4

Compd.	Solvent	M.p. (*T*/°C)	Found (%) C	H	N	Formula	Required (%) C	H	N	$\lambda_{max.}$/nm (log ε) [e]
(1a) [a]		95—96								268·5 (4·08); 277 (4·05)
(1b)	Cyclohexane [b]	92—93	72·1	5·9	7·0	$C_{12}H_{11}NO_2$	71·6	5·6	7·0	264 (4·11)
(2a)	MeOH [b]	172—173	57·8	4·2	11·3	$C_{12}H_{10}N_2O_4$	58·5	4·1	11·4	
(3a)	Cyclohexane [b]	105—106	67·2	5·8	5·7	$C_{13}H_{13}NO_3$	67·5	5·7	6·1	
(4a)	Light petroleum [c]	78—79	73·9	7·2	5·6	$C_{15}H_{17}NO_2$	74·1	7·0	5·8	
(6a)	Cyclohexane [c]	103	74·7	7·5	5·3	$C_{16}H_{19}NO_2$	74·7	7·4	5·4	
(7a)	MeOH [b]	128—129	74·1	6·8	6·2	$C_{14}H_{15}NO_2$	73·3	6·6	6·1	269 (4·09); 262 (4·06)
(7b)	Cyclohexane [b]	122—124	73·6	6·8	6·2					
(8a)	Cyclohexane [b]	137—138	55·0	4·8	4·7	$C_{14}H_{14}BrNO_2$	54·6	4·6	4·5	
(8b)	EtOH [b]	145—155	54·7	4·5	4·6					
(9a)	MeOH [b]	175—176	61·3	5·3	10·2	$C_{14}H_{14}N_2O_4$	61·3	5·2	10·2	
(9b)	EtOH [b]	166—175	61·5	5·2	10·2					
(10a)	Cyclohexane [b]	133—134	69·4	6·8	5·5	$C_{15}H_{17}NO_3$	69·5	6·6	5·4	
(10b)	EtOH [d]	152—153	69·5	6·6	5·6					
(11a)	MeOH [c]	80	74·3	7·3	5·7	$C_{15}H_{17}NO_2$	74·1	7·1	5·7	
(13a)	MeOH [b]	97—99	76·9	5·7	5·1	$C_{17}H_{15}NO_2$	77·0	5·7	5·3	
(13b)	MeOH [b]	94—95	77·0	5·8	5·1					
(15a)	EtOH [b]	117—118	59·2	4·1	3·8	$C_{17}H_{14}BrNO_2$	59·3	4·1	4·1	
(15b)	EtOH [b]	74—75	59·4	4·3	4·4					
(17a)	EtOH [b]	115—116	65·9	4·7	8·9	$C_{17}H_{14}N_2O_4$	65·8	4·6	9·0	
(17b)	EtOH [c]	133—134	65·7	4·6	8·8					
(21a)	MeOH [c]	113—115	78·2	6·8	4·8	$C_{20}H_{21}NO_2$	78·1	6·9	4·6	
(21b)	EtOH [b]	87—89	78·1	7·0	4·8					
(22a)	EtOH [b]	142—144	63·9	5·2	3·7	$C_{20}H_{19}Cl_2NO_2$	63·8	5·1	3·7	
(26a)	MeOH [b]	137—138	67·7	5·9	4·1	$C_{20}H_{21}NO_5$	67·6	6·0	3·9	
(30a)	EtOH [b]	93—94	77·3	6·2	5·1	$C_{18}H_{17}NO_2$	77·4	6·1	5·0	
(30b)	EtOH [b]	92—93	77·6	5·9	5·2					
(31a)	EtOH [c]	124—125	80·6	5·2	4·6	$C_{22}H_{27}NO_2$	80·7	5·2	4·3	253 (4·41); 255 (4·29); 333 (3·27)
(31b)	EtOH [c]	104	80·9	5·3	4·3					
(32b)	EtOH [c]	123—124	81·3	6·4	4·1	$C_{25}H_{23}NO_2$	81·3	6·3	3·8	248 (4·30)
(36a)	EtOH [b]	146—147	75·8	4·8	4·4	$C_{20}H_{15}NO_3$	75·7	4·8	4·4	280 (4·41)
(36b)	EtOH [b]	137—139	76·1	4·9	4·4	$C_{20}H_{15}NO_3$	75·7	4·8	4·4	276 (4·36)
(37b)	EtOH [c]	118	76·6	5·9	3·9	$C_{23}H_{21}NO_3$	76·8	5·9	3·9	280 (4·25)
(38b)	EtOH [c]	139	71·7	4·6	4·4	$C_{20}H_{15}NO_2S$	72·1	4·5	4·2	269 (4·30)
(39b)	EtOH [b]	118	73·8	5·6	3·8	$C_{23}H_{21}NO_2S$	73·6	5·6	3·7	268 (4·05)
(40a)	EtOH [b]	142	76·7	6·1	4·0	$C_{23}H_{21}NO_3$	76·8	5·9	3·9	245 (4·22)
(41b)	EtOH [b]	115	71·6	4·6	4·1	$C_{20}H_{15}NO_2S$	72·1	4·5	4·2	252 (4·42)
(42a)	EtOH [c]	134	70·1	4·2	4·8	$C_{18}H_{13}NO_4$	70·3	4·3	4·8	276 (4·36)
(43a)	EtOH [b]	155	71·9	5·5	4·0	$C_{21}H_{19}NO_4$	72·2	5·5	4·0	283·5 (4·14)
(44a)	EtOH [b]	132	66·6	4·1	4·3	$C_{18}H_{13}NO_3S$	66·9	4·1	4·3	165 (4·37)
(45a)	EtOH [c]	178	68·6	5·2	4·0	$C_{21}H_{19}NO_3S$	69·1	5·2	3·8	267 (3·98); 297 (3·95)
(46a)	EtOH [b]	157	67·0	4·0	4·4	$C_{18}H_{13}NO_3S$	66·9	4·0	4·3	275·5 (4·39)
(47a)	EtOH [c]	119	63·5	3·9	4·2	$C_{18}H_{13}NO_2S_2$	63·7	3·9	4·1	264·5 (4·39)
(51a)	Cyclohexane [b]	92—93	68·9	5·9	5·8	$C_{14}H_{15}NO_3$	68·6	6·2	5·7	
(52a)	Cyclohexane [c]	117	71·1	7·3	5·0	$C_{17}H_{21}NO_3$	71·1	7·4	4·9	
(53a)	Cyclohexane [b]	89	70·6	7·0	5·2	$C_{16}H_{19}NO_3$	70·3	7·0	5·1	
(53b)	Cyclohexane [b]	94—95	70·4	71·	5·2					

[a] Compound (1a) is known; see ref. 31. [b] Needles. [c] Prisms. [d] Plates. [e] Solutions in 95% EtOH.

Reaction of 5-*Acyl*-Δ^2-*isoxazolines with Triethylamine*.*—The 5-acyl-Δ^2-isoxazolines (7b), (13b), (17b), (21b), (22b), (25b), (28b), (30b), (36b), (37b), (38b), and (39b) were heated under reflux with excess of triethylamine in ethanol solution for 0·5 h with a slight excess of *o*-phenylenediamine, to give the corresponding nitriles and quinoxalines, as described in a previous paper.[24] Products were chromatographed on a column to give the nitriles and the quinoxalines. The yields of nitrile and quinoxaline ranged from 50 to 80%. Spectroscopic and analytical data were consistent with the formulation of hitherto unknown quinoxa-

Reaction of Δ^2-*Isoxazolines* (13a), (13b), *and* (31b) *with* N-*Bromosuccinimide*.—The isoxazoline (3×10^{-3} mol), the stoicheiometric amount of *N*-bromosuccinimide, and a little αα′-azaisobutyronitrile were dissolved in carbon tetrachloride. The solution, which was heated under reflux for 0·5 h, first developed a red colour, then gave off hydrogen bromide. A mixture of products was obtained, the isoxazole being the major component. It was separated

* The behaviour of 5-acyl-Δ^2-isoxazolines towards bases has been thoroughly reinvestigated by two of us and the results will be published in a forthcoming paper.

by column chromatography. *5-Acetyl-3,4-diphenylisoxazole* (44%) gave needles (from ethanol), m.p. 135—136° (Found: C, 77·3; H, 5·0; N, 5·2. $C_{17}H_{13}NO_2$ requires C, 77·5; H, 5·0; N, 5·3%); $\nu_{max.}$ (Nujol) 1700 cm^{-1} (C=O); *4-acetyl-3,5-diphenylisoxazole* (10%) gave needles (from ethanol), m.p. 94—95° (Found: C, 77·4; H, 5·0; N, 5·3. $C_{17}H_{13}NO_2$ requires C, 77·5; H, 5·0; N, 5·3%); $\nu_{max.}$ (Nujol) 1680 cm^{-1} (C=O); 5-benzoyl-3,4-diphenylisoxazole (95%), m.p. 167° (lit.,[38] 167°), was identical with an authentic sample.

The hitherto unknown 4-acetyl 3,5-diphenylisoxazole was prepared by three other routes: (i) 1,3 dipolar cycloaddition of benzonitrile oxide with 4-phenylbut-3-yn-2-one (60%); (ii) dehydrogenation of 4-acetyl-3,5-diphenyl-Δ^2-isoxazoline to the isoxazole by heating under reflux in xylene with a slight excess of chloranil (20%); (iii) reaction of an ethereal solution of benzonitrile oxide [from benzohydroximic acid chloride (5 g, 0·032 mmol) [37]] with ethereal 4-morpholino-4-phenylbut-3-en-2-one at room temp. for 3 h; the usual work-up, followed by column chromatography (ethyl acetate–cyclohexane, 3 : 1), gave 3,5-diphenylfurazan oxide (18%), 4-acetyl-3,5-diphenylisoxazole (26%), and *4-acetyl-5-morpholino-3,5-diphenyl-Δ^2-isoxazoline* (30%), as crystals (from ethanol), m.p. 154—155° (Found: C, 71·9; H, 6·4; N, 8·1. $C_{21}H_{22}N_2O_3$ requires C, 72·0; H, 6·3; N, 8·0%). The last compound when heated above its m.p. gave off morpholine to give the isoxazole (100%).

Methyl 3,5-Diphenylisoxazole-4-carboxylate.—4-Acetyl-3,5-diphenylisoxazole (0·2 g) was dissolved in dioxan–water (5 ml; 1 : 1 v/v). An aqueous solution of iodine and potassium iodide (1 ml; $I_2 : KI : H_2O \equiv 1 : 2 : 10$) and 10% sodium hydroxide (10 ml) were added at once with stirring. The solution was left at room temperature for 3 days, then diluted with water, and extracted three times with ether. The extract was dried (Na_2SO_4) and evaporated to give an unidentified product, m.p. 110—115°, not further investigated.

The aqueous solution was acidified with concentrated hydrochloric acid and the suspension was extracted with ether, dried, and treated with excess of diazomethane to give the title compound (24%), identical with an authentic sample, m.p. 85—86°.[39]

We thank the C.N.R. (Rome) for financial aid.

[2/1016 *Received*, 8*th May*, 1972]

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