cis- and *trans*-Azetidin-2-ones from Nitrones and Copper Acetylide

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The reaction between nitrones and copper acetylides in pyridine yields *cis*- and *trans*-azetidinones. Deuteriation and isomerisation studies indicate that the *trans*-compound is produced from the initially formed *cis*-isomer and that the amount of *cis*-product may be increased by using non-basic solvents. Lactams with aromatic, aliphatic, and ethoxycarbonyl substituents may be obtained from appropriately substituted acetylenes, and the use of cyclic nitrones leads to bicyclic compounds.

THE stereospecific synthesis of azetidin-2-ones by the cycloaddition reaction of copper phenylacetylide with nitrones has been briefly reported;[1] in this way *cis*-1,3,4-triphenylazetedin-2-one and *cis*-4-(2-chlorophenyl)-1,3-diphenylazetidin-2-one were obtained from *N*-benzylideneaniline *N*-oxide and *N*-(2-chlorobenzylidene)-aniline *N*-oxide. By contrast, cycloaddition of acetylenes to nitrones yields pyrrolinediones or isoxazolidines.[2] We report here some of our own work on the synthesis of *cis*-azetidin-2-ones and some deuteriation and epimerisation studies which explain some of the features of these reactions.

The reaction of copper phenylacetylide with *N*-benzylideneaniline *N*-oxide was performed in dry pyridine, under nitrogen to prevent oxidative coupling of the acetylide;[3] subsequent hydrolysis yielded a mixture of *cis*- (1) and *trans*- (2) 1,3,4-triphenylazetidin-2-one (5 : 3). The *trans*-isomer had a lower m.p. and was significantly more soluble; separation was effected by fractional crystallisation from methanol. The spectroscopic properties of these products were consistent with the assigned structures and the stereochemistry was confirmed by the H-3 and H-4 n.m.r. absorptions (the signals of the *cis*-isomer were at lower field and had the larger coupling constant [4]). The observed products are

[1] M. Kinugasa and S. Hashimoto, *J.C.S. Chem. Comm.*, 1972, 466.

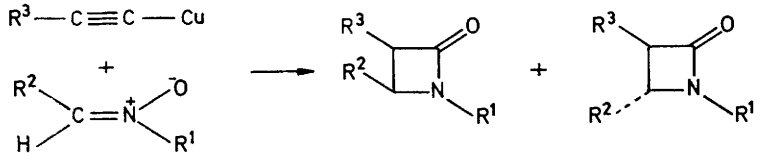
[2] R. Huisgen, *Angew. Chem. Internat. Edn.*, 1963, **2**, 565; R. Huisgen and H. Seidl, *Tetrahedron Letters*, 1963, 2019; P. Beltrame, P. Sartirane, and C. Vintani, *J. Chem. Soc.* (*B*), 1971, 814.

[3] K. Bowden, I. M. Heilbron, E. R. H. Jones, and K. H. Sarjant, *J. Chem. Soc.*, 1947, 1579; J. B. Armitage, C. L. Cook, N. Entwistle, E. R. H. Jones, and M. C.Whiting, *ibid*, 1952, 1998.

[4] K. D. Barrow and T. M. Spotsweed, *Tetrahedron Letters*, 1965, 3325; S. Wolfe and W. S. Lee, *Chem. Comm.*, 1968, 242.

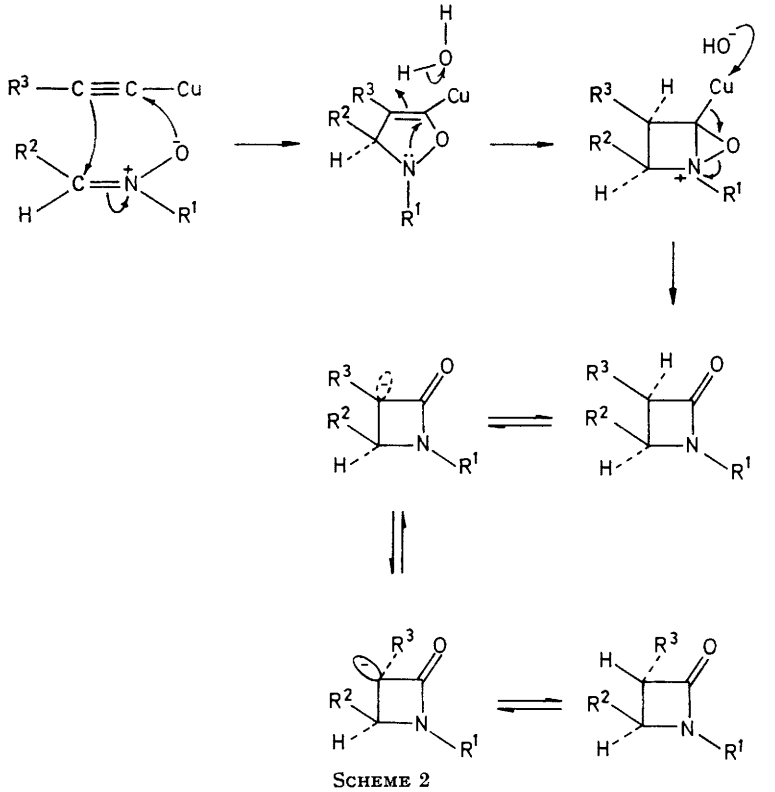
derived from oxygen rearrangement, with the gain of a proton, and the thermodynamically less stable *cis*-product was isolated.

To confirm that the substitution pattern of the azetidin-2-one was directly related to that of the starting materials, showing that other rearrangements did not occur (Scheme 1), the reaction was repeated with a 4-methyl substituent in each of the three phenyl rings in



	R^2, R^3 *cis*				R^2, R^3 *trans*		
	R^1	R^2	R^3		R^1	R^2	R^3
(1)	Ph	Ph	Ph	(2)	Ph	Ph	Ph
(3)	Ph	Ph	4-MeC_6H_4	(4)	Ph	Ph	4-MeC_6H_4
(5)	Ph	4-MeC_6H_4	Ph	(6)	Ph	4-MeC_6H_4	Ph
(7)	Ph	3-MeC_6H_4	Ph	(8)	Ph	3-MeC_6H_4	Ph
(9)	Ph	2-MeC_6H_4	Ph	(10)	Ph	2-MeC_6H_4	Ph
				(11)	Ph	4-MeO·C_6H_4	Ph
				(12)	Ph	4-ClC_6H_4	Ph
(13)	4-MeC_6H_4	Ph	Ph	(14)	4-MeC_6H_4	Ph	Ph
(15)	4-MeC_6H_4	4-ClC_6H_4	Ph	(16)	4-MeC_6H_4	4-ClC_6H_4	Ph
(17)	Ph	Ph	Bu	(18)	Ph	Ph	Bu
(19)	Ph	4-MeO·C_6H_4	Bu				
(20)	Ph	4-MeC_6H_4	CO_2Et	(21)	Ph	4-MeC_6H_4	CO_2Et
				(22)	Ph	4-ClC_6H_4	CO_2Et
(23)	Ph	4-MeC_6H_4	Phth	(24)	Ph	4-MeC_6H_4	Phth
(25)	Ph	4-ClC_6H_4	Phth				
(26)	Ph	4-ClC_6H_4	PhNMe·CH_2	(27)	Ph	4-ClC_6H_4	PhNMe·CH_2
(28)	Ph	4-ClC_6H_4	PhNEt·CH_2	(29)	Ph	4-ClC_6H_4	PhNEt·CH_2
				(30)	Ph	4-$MeOC_6H_4$	PhNEt·CH_2
(31)	Ph	4-ClC_6H_4	Et_2N·CH_2				
(32)	Ph	4-ClC_6H_4	Hmp	(33)	Ph	4-ClC_6H_4	Hmp
(34)	Ph	4-ClC_6H_4	Epa				
(35)	Ph	4-ClC_6H_4	DmpNEt·CH_2				

SCHEME 1 Phth = phthalimidomethyl, Hmp = 4-hydroxy-1-methylpiperidin-4-ylmethyl, Epa = 4-ethoxycarbonylanilinomethyl, Dmp = 4-dimethylaminophenacyl



SCHEME 2

turn. Thus the pairs of azetidinones (3) and (4), (5) and (6), and (13) and (14) were obtained from the corresponding nitrones and acetylides, and their structures were confirmed by mass spectrometry. The mass spectra of these compounds are characterised by anil and keten ions and olefin and isocyanate fragments,[5] and Table 1 records these data for the *trans*-azetidinones (2), (4), (6), (14) and also for one (16) with three different substituents. This fragmentation, which is essentially similar for the corresponding *cis*-isomers, demonstrates the integrity of the substituents. The azetidinones (7)—(12) were obtained in similar cycloaddition reactions, but only *trans*-isomers of 4-(4-methoxyphenyl)- and 4-(4-chlorophenyl)-1,3-diphenylazetidin-2-one were isolated.

That the proton gained in this reaction was incorporated at the azetidinone 3-position and was derived from the solvent was shown by addition of D_2O to the reaction mixture. Thus copper phenylacetylide and

TABLE 1

Mass spectral data (relative intensities in parentheses)

Compd.	$M^{+\cdot}$	$R^3CH{=}C{=}O^{+\cdot}$	$R^2CH{=}NR^{1+\cdot}$	$R^2CH{=}CHR^{3+\cdot}$	$R^1N{=}C{=}O^{+\cdot}$
(2)	299 (3)	118 (—)	181 (26)	180 (100)	119 (—)
(4)	313 (5)	132 (15)	181 (29)	194 (100)	119 (—)
(6)	313 (2)	118 (4)	195 (38)	194 (100)	119 (4)
(14)	313 (4)	118 (8)	195 (100)	180 (57)	133 (—)
(16)	347 (4)	118 (15)	229 (26)	214 (100)	133 (1)

N-(4-methylbenzylidene)aniline *N*-oxide yielded *cis*- and *trans*-3-deuterio-4-(4-methylphenyl)-1,3-diphenylazetidin-2-one (3 : 1). The mass spectra of both isomers showed complete deuterium incorporation at the 3-position: both olefin (*m/e* 196) and keten (*m/e* 120) fragments showed the presence of this isotope. This result was confirmed by ^1H n.m.r.; both isomers showed a singlet for the remaining C-4 proton. *cis*- and *trans*-3-Deuterio-4-(4-chlorophenyl)-1-(4-methylphenyl)-3-phenylazetidin-2-one (1 : 1) and *trans*-4-(4-chlorophenyl)-3-deuterio-1,3-diphenylazetidin-2-one were obtained in similar reactions. The addition of $H_2{}^{18}O$ in this reaction produced no ^{18}O incorporation; it appears that the lactam carbonyl oxygen atom is derived from the nitrone.

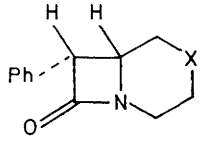
Copper n-butylacetylide, although less reactive than the phenylacetylides, afforded *cis*- (16) and *trans*- (17) 3-n-butyl-1,4-diphenylazetidin-2-one when treated with *N*-benzylideneaniline *N*-oxide. In this case, however, the *cis–trans* ratio was 12 : 1. *cis*-3-n-Butyl-4-(4-methoxyphenyl)-1-phenylazetidin-2-one (11) was obtained in a similar way, and the 3-deuterio-analogue of (19) was also prepared. In contrast copper ethoxycarbonylacetylide was more reactive than the phenylacetylides, and *N*-(4-carbonylmethylbenzylidene) and *N*-(4-chlorobenzylidene)aniline *N*-oxides yielded only *trans*-isomers [(21) and (22)] under the same conditions. It appears that in general the *trans*-isomer is favoured with increasing reaction time, perhaps as a result of base-catalysed isomerisation of initially formed *cis*-compound. The replacement of pyridine by ethanol as solvent enabled the isolation of both *cis*- (20) and *trans*- (21) esters (3 : 1), probably by suppressing the isomerisation. The effect may be illustrated by observing the base-catalysed isomerisation of *cis*-lactams by ^1H n.m.r. spectroscopy. The data indicate that a 3-ester function causes rapid isomerisation, that compounds with phenyl substituents isomerise slowly, and that alkyl substitution suppresses this reaction entirely. The ease of isomerisation, therefore, parallels the production of *trans*-isomer in the cycloaddition reaction and apparently depends upon the ability of the C-3 substituent to stabilise a negative charge. The partial isomerisation of *cis*-1,3,4-triphenylazetidin-2-one in pyridine and methan[^2H]ol showed also that the inversion of the anion may also be a factor controlling the rate of isomerisation. Isolation of the azetidinones after 60% conversion into the *trans*-product yielded both *cis*- and *trans*-isomers with full mono-deuterium incorporation. The deuteriation of the *cis*-compound suggests that reprotonation of the anion before inversion (energy barriers are known in similar systems [6]) occurs at a significant rate.

The incorporation of other substituents such as amino-containing chains is also possible *via* these reactions. However, the copper acetylides are generally too soluble for isolation, but they may be prepared *in situ*. Thus 3-diethylaminopropyne and *N*-(4-chlorobenzylidene)-aniline *N*-oxide in methanol, on addition of ammoniacal copper(I) chloride, yielded exclusively the *cis*-lactam (31). The azetidinones (23)—(30) were also obtained from the corresponding nitrones and acetylenes. The lactam derivatives of benzocaine (34), lignocaine (35), and 4-hydroxy-1-methylpiperidine (32) were also prepared by these methods. A suggested mechanism for the reaction of copper acetylides with nitrones, based upon the above observations, is given in Scheme 2. The stereospecificity is probably a result of protonation from the less hindered face, possibly aided by solvent coordination to copper.

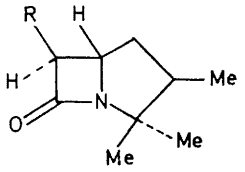
In view of the importance of *cis*-fused bicyclic β-lactams in medicine [7] the extension of this cycloaddition to cyclic nitrones has been examined. Initially, only those nitrones which exist solely in one tautomeric form were chosen.[8] Thus, tetrahydropyridine 1-oxide, prepared *in situ* from 1-hydroxypiperidine and copper phenylacetylide, yielded *cis*-7-phenyl-1-azabicyclo[4.2.0]-octan-8-one (36) as an oil. In a similar manner *cis*-7-

[5] P. G. Bird and W. J. Irwin, *J.C.S. Perkin I*, 1973, 2664.
[6] H. M. Walborsky, F. J. Impastato, and A. C. Young, *J. Amer. Chem. Soc.*, 1964, **86**, 3283.
[7] J. P. Hou and J. W. Poole, *J. Pharm. Sci.*, 1971, **60**, 503.
[8] G. R. Delpierre and M. Lamchen, *Quart. Rev.*, 1965, **19**, 329.

phenyl-4-oxa-1-azabicyclo[4.2.0]octan-2-one (37) was obtained pure from 1-hydroxymorpholine. 4,5,5-Trimethyl-Δ^1-pyrroline 1-oxide was less reactive and the longer reaction time ensured the formation of only *trans*-products (38—40), but again these could not be



(36) X = CH_2
(37) X = O



(38) R = Ph
(39) R = Bu^n
(40) R = EtO_2C

crystallised. The hydroxamic acid 1-hydroxy-4,5,5-trimethylpyrrolidin-2-one was also isolated from these reactions.

EXPERIMENTAL

For instrumentation *etc.* see ref. 9.

General Method for the Preparation of 1,3,4-*Trisubstituted Azetidin-2-ones from Nitrones and Acetylenes.*[10]—*Method A.* The nitrone (0.006 mol) dissolved in dry pyridine (10 cm^3) was added to a solution of the copper acetylide (0.006 mol) suspended in dry pyridine (10 cm^3) under nitrogen. [*Method B* differed only in that the nitrone and acetylene were dissolved in pyridine and a solution of copper(I) chloride (0.5 g) in concentrated ammonia solution (2.5 cm^3) was added.] The mixture was stirred at room temperature for 1 h and then poured into acidified water (70 cm^3). The product was fractionally crystallised from methanol.

Method C. The acetylene (0.01 mol) in methanol (20 cm^3) was added to a stirred solution of the nitrone (0.01 mol) in methanol (20 cm^3) under nitrogen. Copper(I) chloride (0.01 mol) in concentrated ammonia solution (2.5 cm^3) was then added and the mixture was stirred at room temperature for 4 h. The solution was poured into water (50 cm^3) and the product extracted with chloroform.

The azetidin-2-ones prepared by these procedures are recorded in Table 2.

7-Phenyl-1-azabicyclo[4.2.0]*octan-8-one* (36).—1-Hydroxypiperidine [11] (1.0 g) in chloroform (50 cm^3) was shaken with yellow mercury(II) oxide (4.0 g) for 1 h to yield 2,3,4,5-tetrahydropyridine 1-oxide. The filtrate was treated with copper phenylacetylide (1.5 g) and pyridine (1 cm^3) and the mixture was stirred at room temperature for 24 h. The solution was washed with water to yield the *cis*-azetidin-2-one [12] (1.0 g, 40%) as an oil which could not be induced to crystallise even after preparative t.l.c. on silica with benzene (R_F 0.78) (Found: M^+, 201.115 358. Calc. for $C_{13}H_{15}NO$: M, 201.115 669); ν_{CO} 1 735 cm^{-1}; τ 4.54 (1 H, d, J 6 Hz, H-7); *m/e* 201 (M^+).

cis-*7-Phenyl-4-oxa-1-azabicyclo*[4.2.0]*octan-8-one* (37).—4-Hydroxymorpholine (1.0 g) in chloroform (50 cm^3) was shaken with yellow mercury(II) oxide (4.0 g) for 1 h to yield 2,3-dihydro-1,4-oxazine 4-oxide.[11] The filtrate was treated with copper phenylacetylide (1.6 g) and pyridine (1 cm^3), and the mixture was stirred at room temperature for 3 h. Dilution and extraction with ether yielded the crude product (1.4 g, 54%) as an oil which after column chromatography on neutral alumina with ether yielded the *azetidinone* (1.0 g, 40%), m.p. 119° (methanol) (Found: C, 69.0; H, 6.4; N, 6.6. $C_{12}H_{13}NO_2$ requires C, 69.2; H, 6.4; N, 6.9%); ν_{CO} 1 745 cm^{-1}; τ 4.7 (1 H, d, J 6 Hz, H-7); *m/e* 203 (M^+).

2,2,3-Dimethyl-6-phenyl-1-azabicyclo[3.2.0]*heptan-7-one* (38).—4,4,5-Trimethyl-Δ^1-pyrroline 1-oxide [13] (1.3 g) in pyrridine (30 cm^3) was stirred with copper phenylacetylide (1.6 g) at 50 °C for 24 h. The solution was diluted with acidified water and extracted with ether to yield the trans-*azetidin-2-one* (1.1 g, 40%) as an oil which did not crystallise after preparative t.l.c. on silica with benzene–cyclohexane

TABLE 2

Azetidin-2-ones (Scheme 1) from acetylenes and nitrones

M.p. (°C)		Substituents *					Found (%)			Required (%)			τ(*cis*)		τ(*trans*)			
cis	*trans*	R^1	R^2	R^3	Method	Yield %	C	H	N	C	H	N	H-3	H-4	H-3	H-4	ν_{CO}/ cm^{-1}	*cis* : *trans*
185	132—133	Ph	Ph	Ph	A	32	84.1	5.8	4.7	84.3	5.7	4.7	5.0	4.55	5.68	5.0	1 740	5 : 3
251	148—149	Ph	Ph	4-MeC_6H_4	A	50	84.0	6.0	4.6	84.4	6.1	4.5	5.03	4.53	5.68	5.03	1 738	7 : 3
142—143	116—117	Ph	4-MeC_6H_4	Ph	A	40	84.1	6.1	4.6	84.4	6.1	4.5	5.05	4.60	5.75	5.08	1 740	4 : 1
143	129—130	Ph	3-MeC_6H_4	Ph	A	25	84.1	6.2	4.7	84.4	6.1	4.5	5.05	4.62	5.65	5.05	1 740	5 : 4
206	126—127	Ph	2-MeC_6H_4	Ph	A	25	84.1	6.1	4.5	84.4	6.1	4.5	5.07	4.4	5.82	4.77	1 735	10 : 1
	119	Ph	4-MeO·C_6H_4	Ph	A	28	80.6	5.9	4.0	80.2	5.8	4.3			5.75	5.08	1 740	
	140—141	PhC_6H_4	4-ClC_6H_4	Ph	A	45	75.6	4.9	4.0	75.7	4.8	4.2			5.77	5.07	1 740	
176—177	157—158	4-MeC_6H_4	Ph	Ph	A	25	84.1	6.1	4.4	84.4	6.1	4.5	5.05	4.60	5.77	5.1	1 735	3 : 4
180	156—157	4-MeC_6H_4	4-ClC_6H_4	Ph	A	14	75.8	5.5	4.2	76.1	5.2	4.0	5.04	4.62	5.78	5.02	1 740	5 : 4
115—116	70—71	Ph	Ph	Bu	A	66	81.8	7.4	5.1	81.7	7.5	5.0	6.5	4.87	6.5	5.45	1 735	12 : 1
74—75		Ph	4-MeO·C_6H_4	Bu	A	55	77.6	7.3	4.5	77.7	7.4	4.5	6.55	4.9			1 745	
112		4-MeC_6H_4	4-ClC_6H_4	Bu	A	9	73.3	6.8	4.2	73.4	6.7	4.3	6.50	4.95			1 748	
		Ph	4-MeC_6H_4	CO_2Et	A	42												
162—163	150	Ph	4-MeC_6H_4	CO_2Et	C	51	73.7	6.0	4.5	73.8	6.2	4.5	5.59	4.71	4.68	6.05	1 755	3 : 1
	95	Ph	4-ClC_6H_4	CO_2Et	B	50	65.4	4.8	4.1	65.7	4.9	4.3			4.7	5.64	1 740	
196	178—179	Ph	4-MeC_6H_4	Phth	A	31	75.1	5.0	7.1	75.8	5.1	7.1	5.85	4.78		4.9	1 740	9 : 1
203		Ph	4-ClC_6H_4	Phth	A	12	68.9	4.1	6.8	69.2	4.1	6.7	5.9	4.87			1 745	
130	125	Ph	4-ClC_6H_4	$PhNMe·CH_2$	A	52	73.3	5.6	7.5	73.4	5.6	7.5	6.2	4.93		5.2	1 742	1 : 1
72	107	Ph	4-ClC_6H_4	$PhNEt·CH_2$	C	52	73.3	5.6	7.5	73.4	5.6	7.5	6.15	4.83	6.2	5.25	1 740	1 : 5
	115	Ph	4-MeO·C_6H_4	$PhNEt·CH_2$	A	39	78.0	6.8	7.4	77.7	6.7	7.3				5.25	1 735	
130		Ph	4-ClC_6H_4	$Et_2N·CH_2$	C	44	69.4	6.6	8.2	69.0	5.8	8.9	6.10	4.82			1 730	
119—120	177	Ph	4-ClC_6H_4	Hmp	C	50	68.8	6.5	7.6	68.8	6.5	7.3		4.72			1 745	1 : 1
188		Ph	4-ClC_6H_4	Epa	A	75	69.7	5.4	6.2	69.1	5.3	6.5		4.75			1 740	
		Ph	4-ClC_6H_4	$DmpNEt·CH_2$	C	67	70.5	6.6	8.5	70.7	6.3	8.8		4.80			1 740	

* For abbreviations see Scheme 1.

[9] G. Cooper and W. J. Irwin, *J.C.S. Perkin I*, 1976, 75.
[10] L. K. Ding, Ph.D. Thesis, University of Aston in Birmingham, 1976.
[11] J. F. Elsworth and M. Lamchen, *J. Chem. Soc.* (*C*), 1968, 2423.
[12] R. H. Earle, D. T. Hurst, and M. Viney, *J. Chem. Soc.* (*C*), 1969, 2093.
[13] N. J. A. Gutteridge and F. J. McGillan, *J. Chem. Soc.* (*C*), 1970, 642.

(1 : 1) as eluant (R_F 0.13) (Found: C, 77.8; H, 8.1; N, 6.1. $C_{15}H_{19}NO$ requires C, 78.6; H, 8.1; N, 6.4%); ν_{CO} 1 740 cm^{-1}; τ 5.85 (1 H, d, *J* 2.5 Hz, H-6); *m/e* 229 (M^+). Copper butylacetylide and copper ethoxycarbonylacetylide also yielded *trans*-lactams which could not be crystallised.

Deuterium-labelled Azetidin-2-ones.—The copper acetylide (0.01 mol), the nitrone (0.01 mol), and deuterium oxide (1.5 cm^3) were stirred in dry pyridine (20 cm^3) at room temperature for 4 h under nitrogen. Addition of dilute acid and extraction with ether yielded the 3-deuterioazetidin-2-one. These derivatives were identical with the unlabelled analogues except that the ^1H n.m.r. spectra indicated the absence of the H-3 and simplification of the H-4 absorption. The molecular ions and peaks corresponding to olefin and keten fragments also appeared one mass unit higher in the mass spectrum. By this method 4-(4-chlorophenyl)- and 4-(4-methylphenyl)-1,3-diphenyl-, 4-(4-chlorophenyl)-1-(4-methylphenyl)-3-phenyl- and 3-butyl-4-(4-methoxyphenyl)-1-phenyl-3-deuterioazetidin-2-one were obtained. Replacement of the D_2O by $H_2{}^{18}O$ produced no incorporation of ^{18}O into the azetidin-2-ones.

Isomerisation of cis-*Azetidin-2-ones.*—The *cis*-azetidin-2-one (0.000 4 mol) was dissolved in dry pyridine (0.7 cm^3) in a sealed n.m.r. tube and the solution was maintained at 110 °C. The signal from the lactam protons was monitored at various time intervals by successive integral traces over the τ 4.5—6.0 region. The isomerisation was accompanied by the appearance of the high-field absorptions of the *trans*-isomer and the disappearance of the low-field resonance due to the *cis*-compound. First-order rate constants were calculated by using a least-squares procedure: 1,3,4-triphenyl- k 9.61×10^{-3} h^{-1}, 4-(4-methylphenyl)-1,3-diphenyl- k 2.38×10^{-3} h^{-1}. 3-Ethoxycarbonyl-4-(4-methylphenyl)-1-phenyl- (isomerisation complete in 5 min), 3-butyl-1,4-diphenyl- and 3-butyl-4-(4-methoxyphenyl)-1-phenyl- (no isomerisation detected after 24 days), and 4-(4-chlorophenyl)-3-(*N*-methylanilinomethyl):1-phenylazetidin-2-one (no isomerisation detected after 3 days) were examined by this method.

cis-1,3,4-Triphenylazetidin-2-one (0.07 g), dry pyridine (0.4 cm^3), and methan[^2H]ol (0.4 cm^3) were heated together at 100 °C in a sealed n.m.r. tube and the reaction was monitored for 4 days. The mixture of deuterium-labelled *cis*- and *trans*-azetidin-2-ones was fractionated by crystallisation from methanol to yield the *cis*- (0.026 g, 37.1%) and *trans*- (0.042, 60%) isomers. The incorporation of one deuterium atom into these two compounds was shown to be complete by mass spectral data.

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