Reaction of Some Azetidin-2-ones with Secondary Amines

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The reaction of some azetidin-2-ones with secondary amines gave 3-arylaminopropionamide derivatives in high yield. When a 2-chloro-substituent was present, these compounds reacted further to form aziridinecarboxamides.

THE amide bond of azetidin-2-ones is susceptible to nucleophilic attack, resulting in ring opening or molecular rearrangement in some cases. However, the reaction of azetidin-2-ones with nitrogen nucleophiles has received little attention.[1,2]

We have now studied the behaviour of such azetidinones towards secondary amines as internal[3] and external nucleophiles. The action of secondary amines results in ring opening and provides a practicable route to various 3-arylaminopropionamides [(1) ⟶ (2)] as summarised in Table 1.

In the case of 3-cyano-1,4-diphenyl-3-t-butylazetidin-2-one (1; Ar = Ph, R^1 = Bu^t, R^2 = CN), no reaction was observed even after prolonged reflux (24 h) in piperidine.

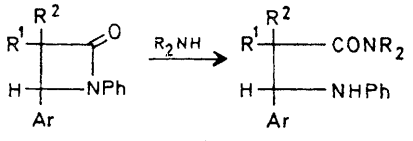
An extension of this reaction occurred with *trans*-4-aryl-3-chloro-1-phenylazetidin-2-ones (1b) at reflux

[1] H. T. Clark, J. R. Johnson, and R. Robinson, 'The Chemistry of Penicillin,' Princeton University Press, 1949.

[2] J. C. Sheehan and A. K. Bose, *J. Amer. Chem. Soc.*, 1951, **73**, 1761; J. C. Sheehan and J. J. Ryan, *ibid.*, p. 1204; C. Metzger, *Chem. Ber.*, 1971, **104**, 59.

[3] R. L. Bentley and H. Suschitzky, unpublished work.

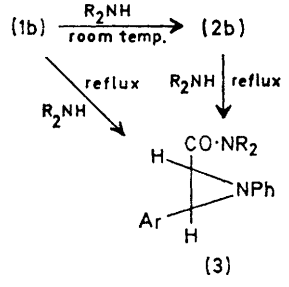
temperature, resulting in elimination of chlorine with ring closure to give *trans*-3-aryl-1-phenylaziridine-2-carboxamides (3), as given in Table 2. The intermediate



(1) a; R^1=H, R^2=N_3 (2)
b; R^1=Cl, R^2=H
c; R^1=H, R^2=OPh

R_2NH = piperidine or pyrrolidine

propionamides (2b) were isolated when the reaction mixture was left at room temperature for 1 day. These propionamides could then be made to cyclise under the reaction conditions. This appears to be the first



(3)

R_2NH=piperidine, pyrrolidine, or morpholine

example of a monocyclic azetidin-2-one undergoing ring contraction. A previous claim of a related conversion [4] was subsequently proved to be incorrect.[5]

The aziridines thus prepared underwent instantaneous hydrolysis in dilute ammonia or sodium hydrogen carbonate solution or on chromatography, producing 2-anilinoacetamides and the corresponding aldehydes (isolated as the 2,4-dinitrophenylhydrazone) in good yield.

The azetidin-2-ones (1) could not be made to react with various carbon and phosphorus nucleophiles.

[4] J. W. J. Taylor, J. S. Owen, and D. Whittaker, *J. Chem. Soc.*, 1938, 206.
[5] C. H. Hassall and A. R. Lippmann, *J. Chem. Soc.*, 1953, 1059.
[6] A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, 1967, **23**, 4769.

EXPERIMENTAL

I.r. spectra were recorded for Nujol mulls with a Perkin-Elmer 257 instrument, ^1H n.m.r. spectra for solutions in deuteriochloroform with a Varian A60 or HA100 instrument (tetramethylsilane as internal reference), and mass spectra with an A.E.I. MS12 instrument.

Preparation of Azetidinones.—*cis*-4-Aryl-3-azido-1-phenylazetidin-2-ones (1a) were prepared from the reaction of azidoacetyl chloride with the appropriate Schiff's base in the presence of triethylamine.[6] The 4-(2-*thienyl*) *derivative* had m.p. 125—126° (Found: C, 57.6; H, 3.9; N, 20.9. $C_{13}H_{10}N_4OS$ requires C, 57.8; H, 3.7; N, 20.7%), $\nu_{max.}$ 2 110 (N_3) and 1 760 cm^{-1} (C=O), τ 2.5—3.0 (8 H, m, aromatic), 4.39 (1 H, d, H-4), and 4.99 (1 H, d, $J_{3,4}$ 6.0 Hz, H-3). *cis*-3-Phenoxy-1,4-diphenylazetidin-2-one (1c; Ar = Ph) was prepared by a known method.[7] *trans*-4-Aryl-3-chloro-1-phenylazetidin-2-ones (1b) were prepared by a literature method.[8] The 4-(4-*methoxyphenyl*) *derivative* (74%) had m.p. 95—96° (Found: C, 66.8; H, 4.8; N, 4.9. $C_{16}H_{14}ClNO_2$ requires C, 66.8; H, 4.9; N, 4.9%), $\nu_{max.}$ 1 760 cm^{-1} (C=O), τ 2.5—3.2 (9 H, m, aromatic), 5.02 (1 H, d, H-4), 5.36 (1 H, d, $J_{3,4}$ 2.0 Hz, H-3), and 6.25 (3 H, s, OMe). The 4-(2-*thienyl*) *derivative* (57%) had m.p. 107° (Found: C, 59.1; H, 3.8; N, 5.2. $C_{13}H_{10}ClNOS$ requires C, 59.2; H, 3.8; N, 5.3%), $\nu_{max.}$ 1 760 cm^{-1} (C=O), τ 2.5—3.0 (8 H, m, aromatic), 4.68 (1 H, d, H-4), and 5.29 (1 H, d, $J_{3,4}$ 2.0 Hz, H-3). 3-*Cyano*-1,4-*diphenyl*-3-*t*-*butylazetidin*-2-*one*, prepared from the appropriate keten [9] quantitatively, had m.p. 207° (Found: C, 78.8; H, 6.6; N, 9.1. $C_{20}H_{20}N_2O$ requires C, 78.9; H, 6.6; N, 9.2%).

Preparation of 3-*Arylaminopropionamide Derivatives* (2).—The appropriate azetidinone was dissolved in dry amine (25 ml) and kept at room temperature. When all the starting material had been consumed (t.l.c.), the excess of amine was removed under reduced pressure, and trituration of the resulting oil with sodium-dried light petroleum (b.p. 60—80°) gave the corresponding 3-*arylaminopropionamide* which was then recrystallised (Table 1).

TABLE 1

3-Arylaminopropionamides (2) *

						Found (%)				Required (%)			$\nu_{max.}$/cm^{-1}	
Ar	R^1	R^2	NR_2	Yield (%)	M.p. (°C)	C	H	N	Formula	C	H	N	NH	
2-Thienyl	Cl	H	$C_5H_{10}N$	Quant.	168	61.8	6.2	8.2	$C_{18}H_{21}ClN_2OS$	62.0	6.1	8.0	3 320	1 630
Ph	Cl	H	$C_5H_{10}N$	Quant.	188	69.8	6.7	8.0	$C_{20}H_{23}ClN_2O$	70.0	6.8	8.2	3 360	1 630
Ph	Cl	H	C_4H_8N	Quant.	170	69.2	6.3	8.3	$C_{19}H_{21}ClN_2O$	69.4	6.4	8.5	3 340	1 630
Ph	H	N_3	$C_5H_{10}N$	50	153—154	68.9	6.8	20.0	$C_{20}H_{23}N_5O$	68.7	6.6	20.1	3 340	1 640
2-Thienyl	H	N_3	$C_5H_{10}N$	47	156—157	60.5	6.0	19.4	$C_{18}H_{21}N_5OS$	60.8	6.0	19.7	3 340	1 640
Ph	H	OPh	$C_5H_{10}N$	Quant.	104	77.7	6.9	6.9	$C_{26}H_{28}N_2O_2$	78.0	7.1	7.0	3 340	1 630

* The 3-H n.m.r. signal appeared in the range τ 4.7—5.0 as a quartet ($J_{2,3}$ 5.9, $J_{NH,3}$ 3.4 Hz), which was simplified to a doublet on addition of D_2O.

Preparation of Aziridines (3).—The *trans*-4-aryl-3-chloro-1-phenylazetidin-2-one (1.0 g) was refluxed in dry amine (20 ml), and when all the starting material had been consumed (t.l.c.) the mixture was allowed to cool. The precipitated amine hydrochloride was filtered off and the excess of amine was removed under reduced pressure to give a viscous oil. Trituration with sodium-dried light petroleum (b.p. 60—80°) gave the *aziridine*, which was then

[7] A. K. Bose, Y. H. Chiang, and M. S. Manhas, *Tetrahedron Letters*, 1972, 4091.
[8] F. Duran and L. Ghosez, *Tetrahedron Letters*, 1970, 245.
[9] H. W. Moore and W. Weyler, *J. Amer. Chem. Soc.*, 1970, **92**, 4132.

recrystallised from a suitable dry solvent (Table 2). On boiling *trans*-3-chloro-1,4-diphenylazetidin-2-one (1.0 g) in dry benzene (25 ml) with dry piperidine (0.7 g) for 5 days, piperidine hydrochloride was precipitated. After cooling, filtration, and evaporation, the piperidide of *trans*-2,3-diphenylaziridine-2-carboxylic acid (1.1 g, 92%) was isolated, identical with the sample already obtained. Refluxing the piperidine of 3-anilino-2-chloro-3-phenylpropionic acid (1.0 g) in dry piperidine (20 ml) for 0.75 h gave a precipitate of piperidine hydrochloride and, after work-up as before, the piperidide of *trans*-1,3-diphenylaziridine-2-carboxylic acid (0.8 g, 86%) was isolated.

Aziridine Cleavage.—The piperidide of *trans*-1,3-diphenylaziridine-2-carboxylic acid (1.0 g) was dissolved in ethanol (10 ml) and dilute ammonia solution (10 ml) was added at room temperature to give immediately a precipitate of the piperidide of 2-anilinoacetic acid (0.6 g, 85%), m.p. 102° (lit.,[10] 102—103°). On concentrating the mother liquors and addition of 2,4-dinitrophenylhydrazine solution, benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 237°, was isolated.

TABLE 2

Aziridines (3) *

Ar	NR_2	Yield (%)	M.p. (°C)	Found (%) C	H	N	Formula	Required (%) C	H	N	ν_{CO}/cm^{-1}
Ph	$C_5H_{10}N$	Quant.	148	78.8	9.4	9.3	$C_{20}H_{22}N_2O$	78.4	7.2	9.1	1 640
Ph	C_4H_8N	90	164	78.4	6.6	9.4	$C_{19}H_{20}N_{20}$	78.1	6.9	9.6	1 650
Ph	$[CH_2]_2{\cdot}O{\cdot}[CH_2]_2{\cdot}N$	20	132	73.7	6.3	8.9	$C_{19}H_{20}N_2O_2$	74.0	6.5	9.1	1 650
p-MeO·C_6H_4	$C_5H_{10}N$	62	120	74.6	7.1	8.0	$C_{21}H_{24}N_2O_2$	75.0	7.2	8.3	1 640
p-MeO·C_6H_4	C_4H_8N	37	116—117	74.7	6.8	8.5	$C_{20}H_{22}N_2O_2$	74.5	6.9	8.7	1 650

* The 3-H n.m.r. signal appeared at τ 5.9—6.1 as a doublet, J_{trans} 2—3 Hz.

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[10] 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965.