Functionalized 1-Anilinoazetidin-2-ones by Photochemical Ring Contraction of Pyrazolidinones

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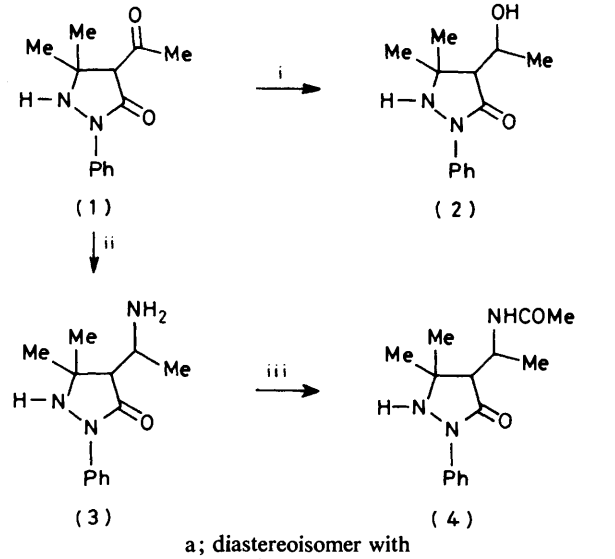
2-Phenylpyrazolidin-3-ones substituted in the 4-position by a side chain containing hydroxy, amino, or acetamido functional groups undergo photochemical ring contraction to the corresponding 1-anilinoazetidin-2-ones. Retention of stereochemistry during the rearrangement was demonstrated by *X*-ray crystallographic analysis for the hydroxy-substituted pyrazolidinone.

Various photochemical methods, chiefly ring-contraction reactions, have been used in the synthesis of a number of β-lactams. Since our early report on the formation of 1-anilinoazetidin-2-ones by the photochemical ring contraction of 2-phenylpyrazolidin-3-ones,[1] the reaction has been extended to 2-acylpyrazolidin-3-ones, which give 1-amidoazetidin-2-ones [2] upon photolysis. Other heterocycles that are converted into β-lactams by photochemical ring contraction are 3-diazopyrrolidine-2,4-diones,[3] 4-azidopyrrolin-2-ones,[4] 3-oxo-1-pyrroline 1-oxides,[5] nitroisoxazolidines,[6] and 4-pyrimidones.[7] Photochemical ring-closure reactions have been used to produce β-lactams from 2-oxoamides,[8] 2-diazoamides,[9] and acrylamides.[10]

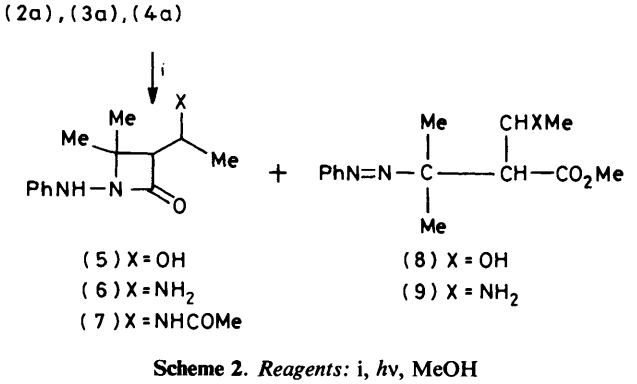
Discovery of β-lactam antibiotics such as the nocardicins,[11] clavulanic acid,[12] and thienamycin,[13] which do not have the structural features of the penicillins and cephalosporins that were previously thought necessary for anti-bacterial activity, has made synthetic approaches to a large variety of β-lactams of greater interest.[14] The products of the photochemical ring contraction of pyrazolidin-3-ones are 1-aminoazetidin-2-ones, not many of which are known,[15] but some of which are reported to have anti-inflammatory activity.[16] We now report on the usefulness of the photochemical ring contraction in creating functionalized 1-aminoazetidin-2-ones.

4-Acetyl-5,5-dimethyl-2-phenylpyrazolidin-3-one (1) [17] is converted by reduction into a mixture of diastereoisomeric alcohols (2), and by reductive amination [18] into the diastereoisomeric amines (3), which are acetylated to the amides (4) (Scheme 1). The diastereoisomers of pyrazolidinones (2), (3), and (4) are separable by fractional crystallization. The higher melting diastereoisomer in each case was photolysed in methanol to the corresponding β-lactam (5), (6), or (7) (Scheme 2). I.r. spectroscopy was used to monitor the decrease in intensity of the absorption band for the carbonyl group of the pyrazolidinone (*ca.* 1 680 cm^{-1}) and the appearance of the characteristic absorption for the β-lactam (*ca.* 1 750 cm^{-1}). The β-lactams appear to be photolabile, with extensive irradiation leading to deterioration of the spectra of the mixtures; therefore photolyses were stopped when only partial conversion of the pyrazolidinones had occurred. Side products of these reactions are small quantities of yellow oils, assigned a phenylazo ester ($\nu_{max.}$ 1 725 cm^{-1}) structure such as (8) (Scheme 2) on the basis of previous experience.[1b] Photolysis of acetylpyrazolidinone (1) under the same conditions gave no β-lactam that could be detected by i.r. spectroscopy.

Lactams (5) and (7) are separable from unchanged pyrazolidinones (2) and (4), respectively, by column chromatography in yields of 75—85% based on unrecovered pyrazolidinone. Aminolactam (6), on the other hand, proved difficult to separate from the aminopyrazolidinone (3).



Scheme 1. *Reagents:* i, $NaBH_4$, MeOH; ii, NH_4OAc, $NaBH_3CN$, MeOH; iii, Ac_2O



Scheme 2. *Reagents:* i, *hν*, MeOH

Repeated chromatography on silica gel gave mixtures that were greatly enriched in lactam according to their i.r. spectra, but which spontaneously deteriorated into amorphous white solids, perhaps products of polymerization reactions [19] triggered by the nucleophilic amino group. Even attempted

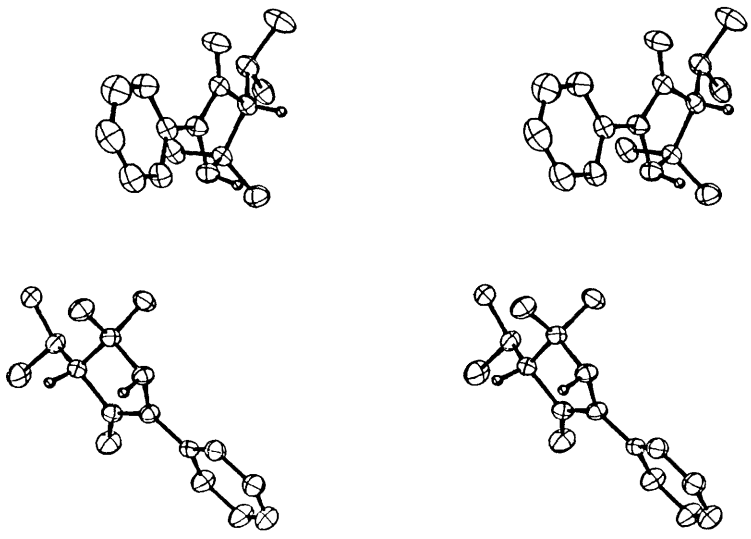


Figure 1. Stereoview showing thermal ellipsoids for the two independent molecules of the pyrazolidinone (2a) in the asymmetric unit

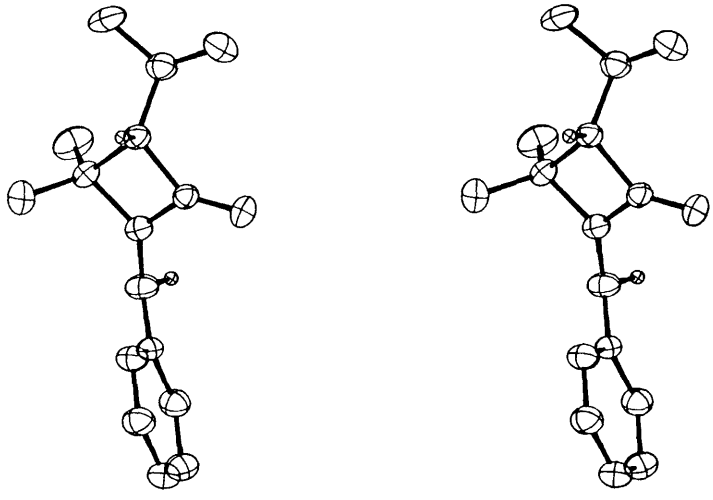


Figure 2. Stereoview showing thermal ellipsoids for the lactam (5)

separation of (3) and (6) by high performance liquid chromatography did not succeed. 1-Aminoazetidin-2-ones have been reported to undergo acid-catalysed ring expansion to pyrazolidinones.[15] Lactam (6), however, proved to be stable under the conditions (reflux with dilute hydrochloric acid for ten minutes), cited [15] as giving this transformation, making it unlikely that the isomerization of (6) to (3) is being catalysed by the columns used.

The structure and, in particular, the stereochemistry of the higher melting diastereoisomeric alcohol (2a) and of the β-lactam (5) obtained upon its photolysis were determined by *X*-ray crystallography. The question of whether the relative stereochemistry of the two chiral centres in compounds (2a) and (5) is changed in the photochemical reaction has bearing on the mechanism of the ring contraction, which may conceivably proceed by Norrish Type I fission of the pyrazolidinone ring, formation of a keten by intramolecular hydrogen abstraction, and reclosure to the lactam. The formation of phenylazoesters, such as (8), as side products points to the possibility of a keten intermediate for the rearrangement. In such a case, stereochemistry would be lost at the chiral ring carbon atom. An alternative mechanism postulates [2a] bridging between the amino nitrogen atom and the carbon atom of the carbonyl group after electron-transfer deactivation of the excited state, with subsequent cleavage of the carbonyl–nitrogen bond of the pyrazolidinone. Such a rearrangement results in preservation of the stereochemistry.

X-Ray crystallographic analysis of the pyrazolidinone (2a) revealed the presence of two independent molecules in the asymmetric unit. Differences between these molecules are negligible. Thermal ellipsoid plots for the pyrazolidinone (2a) and lactam (5) (Figures 1 and 2) and the crystallographic labelling schemes for the two compounds (Figures 3 and 4) are given. Bond lengths and bond angles for non-hydrogen atoms for (2a) are presented in Table 1 and those for (5) in Table 2. The compounds are seen to have the (*R*,*S*) [or (*S*,*R*)] configurations at the chiral centres, indicating that rearrangement has occurred with no loss of stereochemistry. Thus a keten intermediate is not likely for the reaction. This result confirms indications from a low-temperature photolysis experiment [20] in which 5-methyl-2-phenylpyrazolidin-3-one ($\nu_{max.}$ 1 690 cm^{-1}) is converted into the corresponding β-lactam ($\nu_{max.}$ 1 760 cm^{-1}) with no i.r. spectroscopic evidence for the intervention of a keten. Recovery of β-lactam with no incorporation of

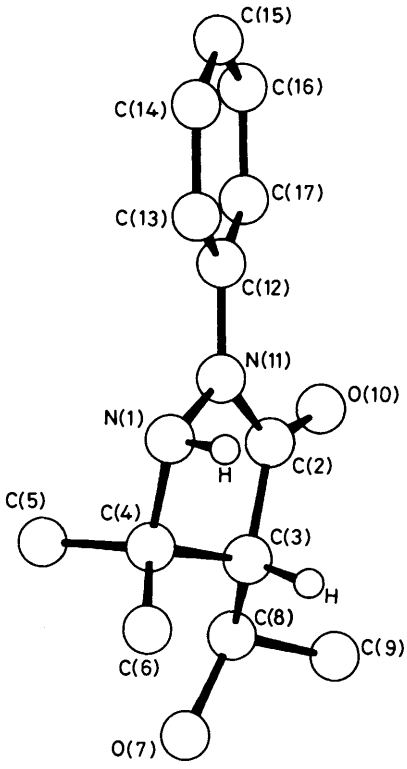


Figure 3. Crystallographic labelling scheme for the pyrazolidinone (2a). There are two independent molecules in the asymmetric unit labelled A and B in the Tables

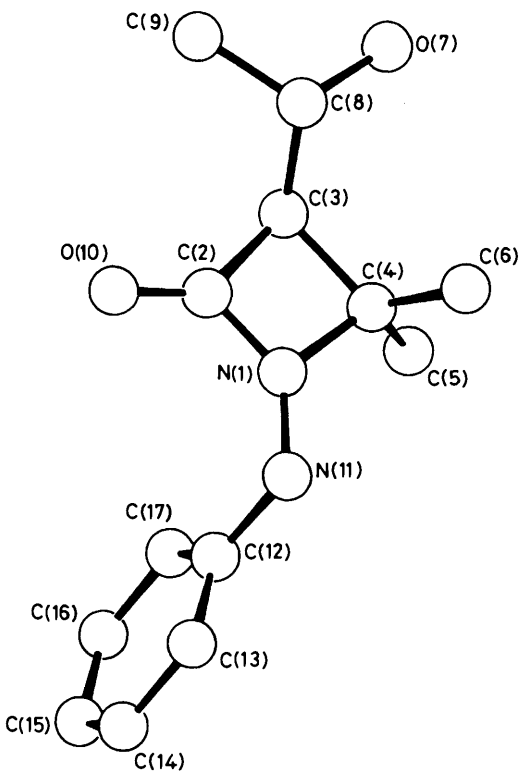


Figure 4. Crystallographic labelling scheme for the lactam (5)

deuterium from photolysis [2a] of a 2-acylpyrazolidinone in deuteriomethanol gives further support for this conclusion.

Pyrazolidinones (2a) and (3a) are the major diastereoisomers produced by reduction and reductive amination, respectively, of acetylpyrazolidinone (1). It seems reasonable to propose that sodium borohydride reduction of the ketone and sodium cyanoborohydride reduction of the imine follow the same stereochemical course. The stereochemical relationship between (2a) and (3a) is confirmed by a comparison of their n.m.r. spectra with those for (2b) and (3b). The coupling constant for the interaction of the hydrogen atom on the ring with the one on the side chain is smaller in (2a) (6.9 Hz) and (3a) (6.1 Hz) than it is in (2b) (8.0 Hz) and (3b) (8.0 Hz). An examination of models shows that in the conformation of the side chain in which intramolecular hydrogen bonding between the hydroxy (or amino group) and the carbonyl group is possible, the dihedral angle between the ring and side-chain hydrogen atoms is *ca.* 30° for (2a) [or (3a)]. In (2b) [or (3b)] a similar conformation of the side chain gives a dihedral angle of *ca.* 150°. The relative magnitudes of the coupling constants for the two sets of compounds are thus in accord with the predictions of the Karplus equation.[21] In addition, the chemical shifts of the protons on the methyl groups on the ring fall into two categories. These protons absorb at δ 1.33, 1.46 for (2a), at δ 1.33, 1.42 for (3a), and at δ 1.34, 1.37 for (4b), which is the amide prepared from (3a). By contrast, the methyl protons absorb at δ 1.21, 1.41 for (2b) and at δ 1.18, 1.39 for (4a). The spectrum of the mixture of amines (3a) and (3b) also exhibits bands at higher field than δ 1.33; an absorption at δ 1.25 is assigned to (3b). The combination of chemical and spectroscopic evidence leads us to conclude that the amino-pyrazolidinone (3a) and acetamidopyrazolidinone (4b) have the same configuration [(*R*,*S*) and (*S*,*R*)] as the pyrazolidinone (2a).

A comparison of the structural parameters of lactam (5) with those of other simple monocyclic β-lactams for which *X*-ray data are available shows that it has the shortest carbon–nitrogen bond, 1.34 Å, of those reported: 1.37 Å is given for an *N*-*p*-chlorophenyl-lactam [22] and 1.40 Å for an *N*-*m*-bromobenzoyl-lactam,[23] the trend reflecting decreasing interaction between the non-bonding electrons on the nitrogen atom with the carbonyl group in the ring. The amide bond in lactam (5) is also shorter than the amide bond in the pyrazolidinone (2a), 1.36 Å, as well as that reported for α-chloro-δ-valerolactam, 1.37 Å.[24] The carbonyl stretching frequency for lactam (5), 1 755 cm^{-1}, is anomalously high compared to that for the *N*-aryl compound,[22] 1 735 cm^{-1}, while that for the *N*-aroyl-lactam,[23] 1 780 cm^{-1}, suggests that the lone pair on the nitrogen atom interacts with two different carbonyl groups. Carbonyl stretching frequencies for monocyclic β-lactams variously substituted on the carbon and nitrogen atoms of the ring have been reported [14a,25] in the range 1 685—1 785 cm^{-1}.

Our present work has shown that functionalization of 2-phenylpyrazolidin-3-ones in ways that do not change the chromophore responsible for the photochemical ring contraction reactions does not interfere with this method of producing β-lactams. The ring contraction does fail for acetylpyrazolidinone (1), in which the proximity of a second carbonyl group to the chromophore apparently channels photochemical reactivity in other, as yet unexplored, directions. Experiments to expand the range of structural variations possible for this reaction are continuing.

Experimental

M.p.s were determined for samples in capillaries with a Thomas-Hoover apparatus and are uncorrected. I.r. spectra were recorded with a Perkin-Elmer 237B spectrophotometer,

Table 1. Bond lengths and bond angles for the non-hydrogen atoms in the pyrazolidinone (2a) with e.s.d.s in parentheses

(a) Bond lengths (Å)

N(1A)–N(11A)	1.445(3)	N(1B)–N(11B)	1.441(3)
N(1A)–C(4A)	1.498(3)	N(1B)–C(4B)	1.492(3)
C(2A)–O(10A)	1.223(3)	C(2B)–O(10B)	1.226(3)
C(2A)–N(11A)	1.362(3)	C(2B)–N(11B)	1.354(3)
C(2A)–C(3A)	1.522(4)	C(2B)–C(3B)	1.517(4)
C(3A)–C(8A)	1.526(4)	C(3B)–C(8B)	1.533(4)
C(3A)–C(4A)	1.536(4)	C(3B)–C(4B)	1.547(4)
C(4A)–C(5A)	1.528(4)	C(4B)–C(6B)	1.512(4)
C(4A)–C(6A)	1.528(4)	C(4B)–C(5B)	1.527(4)
O(7A)–C(8A)	1.437(4)	O(7B)–C(8B)	1.434(4)
C(8A)–C(9A)	1.516(4)	C(8B)–C(9B)	1.510(5)
N(11A)–C(12A)	1.412(3)	N(11B)–C(12B)	1.419(4)
C(12A)–C(13A)	1.392(4)	C(12B)–C(17B)	1.381(4)
C(12A)–C(17A)	1.397(4)	C(12B)–C(13B)	1.383(4)
C(13A)–C(14A)	1.390(4)	C(13B)–C(14B)	1.386(5)
C(14A)–C(15A)	1.376(5)	C(14B)–C(15B)	1.368(6)
C(15A)–C(16A)	1.375(5)	C(15B)–C(16B)	1.376(6)
C(16A)–C(17A)	1.381(5)	C(16B)–C(17B)	1.391(5)

(b) Bond angles (°)

N(11A)–N(1A)–C(4A)	103.3(2)
O(10A)–C(2A)–N(11A)	124.5(3)
O(10A)–C(2A)–C(3A)	127.7(3)
N(11A)–C(2A)–C(3A)	107.8(2)
C(2A)–C(3A)–C(8A)	113.2(2)
C(2A)–C(3A)–C(4A)	102.2(2)
C(8A)–C(3A)–C(4A)	117.3(2)
N(1A)–C(4A)–C(5A)	107.6(2)
N(1A)–C(4A)–C(6A)	107.1(2)
N(1A)–C(4A)–C(3A)	103.4(2)
C(5A)–C(4A)–C(6A)	110.4(3)
C(5A)–C(4A)–C(3A)	113.4(3)
C(6A)–C(4A)–C(3A)	114.3(3)
O(7A)–C(8A)–C(9A)	110.2(3)
O(7A)–C(8A)–C(3A)	108.2(2)
C(9A)–C(8A)–C(3A)	113.8(3)
C(2A)–N(11A)–C(12A)	129.0(2)
C(2A)–N(11A)–N(1A)	112.4(2)
C(12A)–N(11A)–N(1A)	118.2(2)
C(13A)–C(12A)–C(17A)	119.6(3)
C(13A)–C(12A)–N(11A)	119.1(3)
C(17A)–C(12A)–N(11A)	121.3(3)
C(14A)–C(13A)–C(12A)	119.5(3)
C(15A)–C(14A)–C(13A)	121.2(3)
C(16A)–C(15A)–C(14A)	118.7(3)
C(15A)–C(16A)–C(17A)	121.9(4)
C(16A)–C(17A)–C(12A)	119.1(3)
N(11B)–N(1B)–C(4B)	103.6(2)
O(10B)–C(2B)–N(11B)	124.4(3)
O(10B)–C(2B)–C(3B)	127.6(3)
N(11B)–C(2B)–C(3B)	108.0(3)
C(2B)–C(3B)–C(8B)	113.8(2)
C(2B)–C(3B)–C(4B)	101.8(2)
C(8B)–C(3B)–C(4B)	117.1(2)
N(1B)–C(4B)–C(6B)	107.3(2)
N(1B)–C(4B)–C(5B)	107.1(2)
N(1B)–C(4B)–C(3B)	102.9(2)
C(6B)–C(4B)–C(5B)	111.0(3)
C(6B)–C(4B)–C(3B)	115.1(3)
C(5B)–C(4B)–C(3B)	112.7(3)
O(7B)–C(8B)–C(9B)	110.2(3)
O(7B)–C(8B)–C(3B)	108.8(2)
C(9B)–C(8B)–C(3B)	113.7(3)
C(2B)–N(11B)–C(12B)	129.3(3)
C(2B)–N(11B)–N(1B)	112.5(2)
C(12B)–N(11B)–N(1B)	118.0(2)
C(17B)–C(12B)–C(13B)	120.3(3)
C(17B)–C(12B)–N(11B)	121.1(3)
C(13B)–C(12B)–N(11B)	118.6(3)
C(12B)–C(13B)–C(14B)	119.3(4)

Table 1 (*continued*)

(b) Bond angles (°)

C(15B)–C(14B)–C(13B)	121.0(4)
C(14B)–C(15B)–C(16B)	119.4(4)
C(15B)–C(16B)–C(17B)	120.8(4)
C(12B)–C(17B)–C(16B)	119.2(4)

Table 2. Bond lengths and bond angles for non-hydrogen atoms in the lactone (5) with e.s.d.s in parentheses

(a) Bond lengths (Å)

N(1)–C(2)	1.338(5)
N(1)–N(11)	1.397(4)
N(1)–C(4)	1.483(5)
C(2)–O(10)	1.215(4)
C(2)–C(3)	1.536(5)
C(3)–C(8)	1.505(5)
C(3)–C(4)	1.565(5)
C(4)–C(6)	1.518(6)
C(4)–C(5)	1.518(6)
O(7)–C(8)	1.435(5)
C(8)–C(9)	1.503(7)
N(11)–C(12)	1.414(5)
C(12)–C(17)	1.381(5)
C(12)–C(13)	1.384(5)
C(13)–C(14)	1.395(6)
C(14)–C(15)	1.380(6)
C(15)–C(16)	1.367(6)
C(16)–C(17)	1.376(5)

(b) Bond angles (°)

C(2)–N(1)–N(11)	132.0(3)
C(2)–N(1)–C(4)	97.2(3)
N(11)–N(1)–C(4)	129.7(3)
O(10)–C(2)–N(1)	132.7(4)
O(10)–C(2)–C(3)	135.9(4)
N(1)–C(2)–C(3)	91.4(3)
C(8)–C(3)–C(2)	117.5(3)
C(8)–C(3)–C(4)	121.2(3)
C(2)–C(3)–C(4)	86.2(3)
N(1)–C(4)–C(6)	112.0(4)
N(1)–C(4)–C(5)	112.6(3)
N(1)–C(4)–C(3)	85.1(3)
C(6)–C(4)–C(5)	112.2(4)
C(6)–C(4)–C(3)	117.4(4)
C(5)–C(4)–C(3)	114.7(4)
O(7)–C(8)–C(9)	111.2(4)
O(7)–C(8)–C(3)	109.1(3)
C(9)–C(8)–C(3)	111.7(4)
N(1)–N(11)–C(12)	117.1(3)
C(17)–C(12)–C(13)	119.3(4)
C(17)–C(12)–N(11)	123.2(4)
C(13)–C(12)–N(11)	117.5(4)
C(12)–C(13)–C(14)	119.7(4)
C(15)–C(14)–C(13)	120.2(5)
C(16)–C(15)–C(14)	119.5(5)
C(15)–C(16)–C(17)	120.8(5)
C(16)–C(17)–C(12)	120.4(4)

and ^{1}H n.m.r. spectra with a Varian T-60 or a Bruker WM 360 MHz spectrometer, with tetramethylsilane as internal standard. Mass spectra were obtained with an A.E.I. MS 902 spectrometer. Analytical t.l.c. was carried out on Eastman Chromagram Sheets of silica gel and alumina with fluorescent indicator. Solvents were all reagent grade. All evaporations were done with a rotary evaporator under vacuum. Unless otherwise specified, photolyses were done with a Rayonet Photochemical Reactor (Southern New England Ultraviolet Co., Middletown, Connecticut) using 8-W G8T5 254-nm low-pressure mercury lamps (General Electric Company).

Table 3. Crystal data for pyrazolidinone (2a) and lactam (5)

	(2a)	(5)
Molecular formula	$C_{13}H_{18}N_2O_2$	$C_{13}H_{18}N_2O_2$
Space group	$P2_1/a$	$P2_1/n$
a/Å	11.810(3)	6.027(2)
b/Å	10.511(2)	10.501(3)
c/Å	21.696(5)	21.576(7)
β/°	104.90(2)	97.04(3)
V/Å^3	26.02(1)	1 355.2(8)
M	234.3	234.3
Z	8	4
D (calc.)/g ml^{-1}	1.20	1.13
D (obs.)/g ml^{-1}	1.21	1.12
2θ Limit/°	50	55
Reflections, total	5 403	3 821
Reflections, $I > 3\sigma(I)$	2 535	1 101

Table 4. Atomic co-ordinates for the non-hydrogen atoms of the pyrazolidinone (2a) with e.s.d.s in parentheses

	x/a	y/b	z/c
N(1A)	−0.071 8(2)	0.367 4(2)	0.853 0(1)
C(2A)	0.061 3(2)	0.489 3(3)	0.928 0(1)
C(3A)	0.111 5(2)	0.355 4(3)	0.930 8(1)
C(4A)	0.043 3(2)	0.299 1(3)	0.866 7(1)
C(5A)	0.099 2(3)	0.327 9(4)	0.812 0(2)
C(6A)	0.017 2(3)	0.157 0(3)	0.868 9(2)
O(7A)	0.281 0(2)	0.225 6(2)	0.935 9(1)
C(8A)	0.245 0(2)	0.353 0(3)	0.945 8(1)
C(9A)	0.305 3(3)	0.397 2(4)	1.012 7(2)
O(10A)	0.103 5(2)	0.581 4(2)	0.960 2(1)
N(11A)	−0.040 8(2)	0.491 3(2)	0.881 1(1)
C(12A)	−0.122 3(2)	0.591 3(3)	0.862 9(1)
C(13A)	−0.235 0(3)	0.563 5(3)	0.826 5(1)
C(14A)	−0.316 7(3)	0.660 9(4)	0.809 7(2)
C(15A)	−0.288 4(3)	0.784 5(4)	0.828 4(2)
C(16A)	−0.176 0(4)	0.811 0(3)	0.863 0(2)
C(17A)	−0.091 9(3)	0.717 2(3)	0.880 1(2)
N(1B)	0.064 5(2)	0.137 2(2)	0.645 7(1)
C(2B)	0.125 9(2)	0.009 0(3)	0.573 1(1)
C(3B)	0.171 0(2)	0.142 1(3)	0.566 4(1)
C(4B)	0.165 2(2)	0.204 1(3)	0.630 2(1)
C(5B)	0.273 6(3)	0.175 9(4)	0.684 4(2)
C(6B)	0.137 3(3)	0.344 7(4)	0.626 5(2)
O(7B)	0.336 8(2)	0.270 9(2)	0.560 0(1)
C(8B)	0.289 6(3)	0.144 7(3)	0.549 8(1)
C(9B)	0.283 5(4)	0.101 8(5)	0.482 6(2)
O(10B)	0.138 3(2)	−0.086 5(2)	0.543 0(1)
N(11B)	0.068 8(2)	0.011 5(2)	0.619 8(1)
C(12B)	0.009 6(2)	−0.088 1(3)	0.642 8(1)
C(13B)	−0.071 9(3)	−0.056 5(4)	0.676 1(2)
C(14B)	−0.131 4(3)	−0.152 7(5)	0.698 3(2)
C(15B)	−0.109 6(4)	−0.277 9(5)	0.688 6(2)
C(16B)	−0.028 0(4)	−0.308 6(4)	0.655 7(2)
C(17B)	0.032 5(3)	−0.214 1(4)	0.632 6(2)

Throughout ether and anesthesia ether refer to diethyl ether and ethanol-stabilized diethyl ether respectively. Light petroleum refers to that fraction with b.p. 35—60 °C.

4-(1-Hydroxyethyl)-5,5-dimethyl-2-phenylpyrazolidin-3-one (2).—Sodium borohydride (900 mg) was added to a suspension of the acetylpyrazolidinone (1) [17] (3.00 g, prepared from acetone phenylhydrazone and diketen) in methanol (75 ml). After 2.75 h, the solvent was removed on a rotary evaporator, the residue diluted with water, extracted with ether, and the combined ether layers washed once with saturated sodium chloride solution. Removal of the solvent after drying (Na_2SO_4) of the ether layer gave a yellow oil (3.23 g) from which the higher melting diastereoisomer (2.56 g, 85%) was recovered by dissolution in hot light petroleum and isolation of successive crops. Further recrystallization gave the *hydroxyethylpyrazolidinone* (2a), m.p. 129—130 °C (light petroleum–ether), $\nu_{max.}$ ($CHCl_3$), 3 400, 1 680, 1 601, 1 500, 1 375, and 1 300 cm^{-1}; δ ($CDCl_3$) 1.33 (s, 3 H), 1.46 (s, 3 H), 1.51 (d, J 6.4 Hz, 3 H), 1.58 (s, 1 H), 2.55 (d, J 6.9 Hz, 1 H), 4.20 (m, 1 H), 4.36 (br s, 1 H), 7.12 (m, 1 H,) 7.34 (m, 2 H), and 7.82 (m, 2 H) (Found: C, 66.55; H, 7.75; N, 12.0. $C_{13}H_{18}N_2O_2$ requires C, 66.69; H, 7.69; N, 11.96%).

The lower melting diastereoisomer was recovered by triturating the yellow oil from the reduction with light petroleum (20 ml), which was then decanted from the bulk of the product and allowed to crystallize. It was also obtained from the mother-liquors of the original crystallization of the reduction product. *Hydroxyethylpyrazolidinone* (2b), m.p. 65—66 °C (methylcyclohexane–trace of toluene); $\nu_{max.}$ ($HCCl_3$) 3 400, 1 680, 1 601, 1 495, 1 295, 1 100, and 900 cm^{-1}; δ ($CDCl_3$) 1.21 (s, 3 H), 1.33 (d, J 6.2 Hz, 3H), 1.41 (s, 3 H), 1.61 (s, 1 H), 2.46 (d, J 8 Hz, 1 H), 4.10 (m, 1 H), 4.46 (br s, 1 H), 7.13 (m, 1 H), 7.34 (m, 2 H), and 7.82 (m, 2 H) (Found: C, 66.55; H, 7.75; N, 11.9. $C_{13}H_{18}N_2O_2$ requires C, 66.69; H, 7.69; N, 11.96%).

1-Anilino-3-(1-hydroxyethyl)-4,4-dimethylazetidin-2-one (5). —Pyrazolidinone (2a) (1.5 g) in methanol (250 ml) was irradiated through a Vycor filter for 1.75 h by immersing a Hanovia 450-W medium pressure lamp in the mixture. After the solvent had been removed, the mixture was dissolved in benzene and chromatographed on Woelm neutral alumina, grade II (150 g). The column was eluted successively with benzene (300 ml), benzene–ether (4 : 1; 120 ml), benzene–ether (1 : 1; 150 ml), ether (150 ml), anesthesia ether (300 ml), and methanol (150 ml). Benzene and benzene–ether mixtures eluted methyl 2-(1-hydroxyethyl)-3-methyl-3-phenylazobutanoate (8), a yellow oil (100 mg), $\nu_{max.}$ ($CHCl_3$) 1 725 cm^{-1}. Ether (900 ml) eluted pyrazolidinone (2a). The β-lactam (5) [450 mg, 30%, 75% based on unrecovered (2a)] came off the column with anesthesia ether and methanol. Rechromatography on neutral Woelm alumina, grade II, gave the *lactam* (5), m.p. 142—143 °C (light petroleum), *m/e* 234 (parent peak), 190, 134, 108, 93, 92, and 83 (base peak); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 755, 1 603, 1 500, 1 375, and 1 075 cm^{-1}; δ ($CDCl_3$) 1.40 (9 H), 2.4 (br m, 1 H, absent in D_2O), 2.8 (d, 1 H, J 10 Hz), 4.2 (br m, 1 H), 6.4 (s, 1 H, absent in D_2O), 7.2 (m, 5 H) (Found: C, 66.8; H, 7.7; N, 11.9. $C_{13}H_{18}N_2O_2$ requires C, 66.69; H, 7.69; N, 11.96%).

Table 5. Atomic co-ordinates for the non-hydrogen atoms of the lactam (5) with e.s.d.s in parentheses

	x/a	y/b	z/c
N(1)	0.501 5(5)	−0.057 4(3)	0.660 0(2)
C(2)	0.398 0(6)	−0.076 7(4)	0.710 6(2)
C(3)	0.444 1(7)	0.061 0(4)	0.732 5(2)
C(4)	0.578 0(6)	0.074 5(4)	0.675 1(2)
C(5)	0.481 9(11)	0.170 3(5)	0.626 4(3)
C(6)	0.830 7(8)	0.083 1(6)	0.688 2(3)
O(7)	0.610 8(5)	0.212 8(3)	0.807 1(2)
C(8)	0.555 7(8)	0.080 5(4)	0.798 1(2)
C(9)	0.411 8(13)	0.034 5(6)	0.845 8(3)
O(10)	0.301 5(5)	−0.168 0(3)	0.729 2(1)
N(11)	0.560 9(6)	−0.140 3(3)	0.614 1(2)
C(12)	0.385 3(7)	−0.191 2(4)	0.571 9(2)
C(13)	0.428 6(8)	−0.301 7(4)	0.540 5(2)
C(14)	0.262 7(9)	−0.354 2(5)	0.497 2(2)
C(15)	0.057 0(9)	−0.295 5(5)	0.485 2(2)
C(16)	0.016 3(8)	−0.186 4(5)	0.516 5(2)
C(17)	0.178 1(7)	−0.134 3(5)	0.559 6(2)

4-(1-*Aminoethyl*)-5,5-*dimethyl*-2-*phenylpyrazolidin*-3-*one* (3).—Acetylpyrazolidinone (1) (2.06 g) was reduced with sodium cyanoborohydride in the presence of ammonium acetate (6.08 g) in methanol (50 ml) over a period of 3 days. The reducing agent was added in portions (0.70 g, to start, 0.24 g in 5 h, 0.20 g each of the next two days) and the pH of the solution was adjusted to 6 with concentrated hydrochloric acid. The course of the reaction was followed by t.l.c. (SiO_2, $CHCl_3$). Diastereoisomeric alcohols (2) were side products. The diastereoisomeric amines formed were analysed by t.l.c. (SiO_2, $CHCl_3$–MeOH, 9 : 1).

The reaction mixture was acidified to pH 2 with concentrated hydrochloric acid and left overnight to allow HCN to escape. Methanol was removed on the rotary evaporator and the residue was diluted with water and extracted with ether. The aqueous layer was made strongly basic with concentrated sodium hydroxide, extracted with ether (4 × 15 ml), and the combined organic layers were washed with saturated sodium chloride solution and dried (K_2CO_3). Removal of the solvent gave a yellow oil (1.64 g, 80%) that became semicrystalline on cooling in ice.

A crystalline amine (0.17 g; m.p. 76.5—79 °C) was separated from the lower melting diastereoisomer by trituration of the cold mixture first with four successive portions (*ca.* 5 ml) of hexane and then similarly with methylcyclohexane. Evaporation of the combined extractions, and repetition of the trituration gave another portion of crystalline amine (0.26 g; m.p. 75.5—78.5 °C). Repeated crystallization gave the *aminopyrazolidinone* (3a), m.p. 84—84.5 °C (methylcyclohexane with trace of toluene); $\nu_{max.}$ ($CHCl_3$) 3 300, 1 680, 1 590, and 1 480 cm^{-1}; δ ($CDCl_3$) 1.33 (s, 3 H), 1.39 (d, *J* 6.5 Hz, 3 H), 1.42 (s, 3 H), 1.48 (br, 2 H), 2.39 (d, *J* 6.1 Hz, 1 H), 3.32 (m, 1 H), 4.38 (br s, 1 H), 7.10 (m, 1 H), 7.35 (m, 2 H), and 7.85 (m, 2 H) (Found: C, 67.0; H, 8.2; N, 18.1. $C_{13}H_{19}N_3O$ requires C, 66.92; H, 8.21; N, 18.01%). The lower melting amine was not purified further. Superposition of the T-60 n.m.r. spectrum for the crystalline amine on that of the mixture of amines showed the crystalline amine to be the major diastereoisomer (in the ratio 3 : 2) formed in the reductive amination reaction. By observing differences, two bands in the n.m.r. could be assigned to the minor diastereoisomer; δ ($CDCl_3$) 2.30 (d, *J* 8 Hz) and 4.75 (br s, 1 H). Also, the complex absorption for the methyl protons appeared at slightly higher field for this amine, with a band at δ 1.25.

Attempted Preparation of 3-(1-*Aminoethyl*)-1-*anilino*-4,4-*dimethylazetidin*-2-*one* (6).—Aminopyrazolidinone (3a) (100 mg) in methanol (60 ml) was irradiated in a quartz tube. After 8 h (10 lamps in use), the mixture contained *ca.* 50% β-lactam.

Pure β-lactam (6) was never isolated. Careful chromatography on silica gel (750 times the weight of sample) with chloroform–methanol (15 : 1) or using medium-pressure liquid chromatography (Lobar A column, Lithoprep 60, 20 lb in^{-2}, chloroform with 2.5—10% methanol) failed. Lactam-rich fractions were obtained from column chromatography but became unstable and appear to polymerize when approaching purity.

Contrary to reports in the literature [15] that *N*-amino-β-lactams undergo ring expansion in acid, when the β-lactam (7) and pyrazolidinone (3a) (20 mg) were refluxed with 5% aqueous hydrochloric acid for 10 min a mixture, identical by i.r. with the starting mixture, was obtained.

4-(1-*Acetamidoethyl*)-5,5-*dimethyl*-2-*phenylpyrazolidin*-3-*one* (4).—The mixture of diastereoisomeric aminopyrazolidinones (3) (2.0 g) was dissolved in acetic anhydride. When the heat of reaction had abated and t.l.c. (Al_2O_3, ethyl acetate) showed the absence of amine, 10% aqueous sodium hydroxide was added, with stirring until the mixture was basic. The solid that separated was filtered off, washed with water, and recrystallized from ethanol, to give *acetamidopyrazolidinone* (4a) (550 mg), white prisms; m.p. 172—173 °C (methanol); $\nu_{max.}$ ($CHCl_3$) 3 400, 1 665, and 1 510 cm^{-1}; δ ($CDCl_3$) 1.18 (s, 3 H), 1.39 (s, 3 H), 1.41 (d, *J* 7.0 Hz, 3 H), 1.89 (s, 3 H), 2.6 (br s, 1 H), 4.40 (m, 1 H), 4.45 (s, 1 H), 6.43 (m, 1 H), 7.14 (m, 1 H), 7.36 (m, 2 H), and 7.79 (m, 2 H) (Found: C, 65.3; H, 7.6; N, 15.35. $C_{15}H_{21}N_3O_2$ requires C, 65.43; H, 7.69; N, 15.26%).

Fractional crystallization of the mother-liquor from the original crystallization of (4a) gave the other diastereoisomer, acetamidopyrazolidinone (4b), which was formed when the higher melting aminopyrazolidinone (3a) was treated with acetic anhydride, m.p. 143.5—144.5 °C (ethyl acetate); δ ($CDCl_3$) 1.31 (d, *J* 6.7 Hz, 3 H), 1.34 (s, 3 H), 1.37 (s, 3 H), 1.99 (s, 3 H), 2.59 (d, *J* 3.4 Hz, 1 H), 4.33 (s, 1 H), 4.40 (m, 1 H), 6.48 (m, 1 H), 7.14 (m, 1 H), 7.35 (m, 2 H), and 7.82 (m, 2 H).

3-(1-*Acetamidoethyl*)-1-*anilino*-4,4-*dimethylazetidin*-2-*one* (7).—Acetamidopyrazolidinone (4a) (354 mg) was dissolved in methanol (90 ml) and irradiated in a quartz tube (15 lamps) for 20 h. Removal of the solvent gave a semicrystalline residue that was treated with ethyl acetate (10 ml), and amide (4a) (20 mg) was filtered off. The solution was chromatographed on an alumina (Woelm, neutral, grade II, 35 g) column, prepared in ethyl acetate, and eluted with ethyl acetate (20 ml) to recover further amide (4a) (246 mg), mixed with a small amount of yellow oil. Ethyl acetate—5% ethanol (150 ml) eluted the *lactam* (7) (76 mg, 21% overall conversion, 86% based on unrecovered amide), white plates, m.p. 189—190 °C (ethyl acetate), $\nu_{max.}$ 1 750 and 1 670 cm^{-1}; δ ($CDCl_3$) 1.4 (9 H), 2.0 (s, 3 H), 2.7 (m, 1 H), 4.5 (m, 1 H), 6.1 (m, 1 H), 6.3 (s, 1 H), and 7.2 (m, 5 H) (Found: C, 65.6; H, 7.65; N, 15.15. $C_{15}H_{21}N_3O_2$ requires C, 65.43; H, 7.69; N, 15.26%).

Photolysis of 4-*Acetyl*-5,5-*dimethyl*-2-*phenylpyrazolidin*-3-*one* (1).—Acetylpyrazolidinone (1) (250 mg) in methanol (50 ml) was irradiated through Vycor with a Hanovia 450-W medium-pressure mercury arc. Samples of the solution were removed and inspected by i.r. after 2.5, 9, and 15 h of irradiation. The spectra showed deterioration of (1), but no significant band corresponding to β-lactam developed under these conditions, which gives good yields of lactam for pyrazolidinones unsubstituted at C-4 with an acetyl group.[1b]

Crystal Structure Determination of Pyrazolidinone (2a) *and Lactam* (5).—Single crystals of pyrazolidinone (2a) were grown in toluene, while those of lactam (5) were obtained from diethyl ether. The crystals were mounted on a Syntex $P2_1$ automatic diffractometer and the space group determined. Table 3 contains a summary of the conditions for the collection of data and of results. Intensity data were collected using graphite monochromated Mo-K_α radiation, and were reduced by methods previously described.*

The structures were solved by direct methods using the MULTAN crystallographic program.[26] Least-squares refinement using anisotropic thermal parameters for all non-hydrogen atoms behaved normally and a difference map

* Computations were carried out on an Amdahl 470-V8 computer. Computer programs used during the structural analysis were SYNCOR (data reduction by W. Schmonsess), FORDAP (Fourier refinement by A. Zalkin), ORFLS (full-matrix least squares refinement by Busing, Martin, and Levy), ORFFE (distances, angles, and their e.s.d. by Busing, Martin, and Levy), ORTEP (thermal ellipsoid drawings, by S. K. Johnson), HATOMS (hydrogen atom positions, by A. Zalkin), and PLANES (least-squares planes, by D. M. Blow).

revealed all the hydrogen atoms. Refinement to convergence gave $R_1 = 0.050$, $R_2 = 0.055$ for (5) and $R_1 = 0.045$, $R_2 = 0.053$ for (2a), where $R_1 = \Sigma(||F_o| - |F_c||v\Sigma|F_o|)$, $R_2 = [\Sigma s(|F_o| - |F_c|)^2/\Sigma w|F_o|^2]^{\frac{1}{2}}$, and $w = 4F_o^2/\sigma^2(F_o^2)$. The final atomic co-ordinates for (2a) are shown in Table 4, and those for (5) in Table 5. Figure 1 shows a thermal-ellipsoid plot of the molecular structure of pyrazolidinone (2a), while the numbering of the atoms and bond distances and selected angles for the compound are given in Figure 3 and Table 1; those of lactam (5) are shown in Figures 2 and 4 and Table 2. The probability level of the thermal ellipsoids is 50%. Observed and final calculated structure factors and the thermal parameters for (2a) and (5) are available as a Supplementary Publication (SUP No. 23555, 18 pages).*

* For details of the Supplementary Publications see Instructions for Authors (1983), *J. Chem. Soc., Perkin Trans. 1*, 1983, Issue 1.

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