Radical 4-*exo* Cyclizations onto *O*-Alkyloxime Acceptors: Towards the Synthesis of Penicillin-Containing Antibiotics

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Dedicated to the memory of *Hanns Fischer* and his outstanding contribution to scientific excellence

The 4-*exo* cyclizations of two types of carbamoyl radicals onto *O*-alkyloxime acceptor groups were studied as potential routes to 3-amino-substituted azetidinones and hence to penicillins. A general synthetic route to 'benzaldehyde oxime oxalate amides' (=2-[(benzylideneamino)oxy]-2-oxoacetamides; see, *e.g.*, **10c**) of 2-{[(benzyloxy)imino]methyl}-substituted thiazolidine-4-carboxylic acid methyl esters **9** was developed (*Scheme 3*). It was shown by EPR spectroscopy that these compounds underwent sensitized photodissociation to the corresponding carbamoyl radicals but that these did not ring close. An analogous open-chain precursor, benzaldehyde *O*-(benzylaminoacetaldehyde-*O*-benzyloxalyl)oxime, **15**, lacking the 5-membered thiazolidine ring, was shown by EPR spectroscopy to release the corresponding carbamoyl radical (*Scheme 4*). The latter underwent 4-*exo* cyclization onto its C=NOBn bond in non-H-atom donor solvents. The rate constant for this cyclization was determined by the steady-state EPR method. Spectroscopic evidence indicated that the reverse ring-opening process was slower than cyclization.

Introduction. – The cyclobutane ring is an important structural motif found in many natural products. The cyclizations of pent-4-enyl and pentadienyl radicals in the 4-*exo* mode (C^{4x}) to give cyclobutylmethyl and cyclobutenylmethyl radicals, respectively, are comparatively slow [1], due to the strain in the 4-membered ring, and the reverse ring-opening processes are about three orders of magnitude faster [2–5]. However, the equilibrium can be shifted in favor of ring-closed species either by rapid trapping of the cyclized radical, or by 2,2-dimethyl substitution, and/or by inclusion of electron-withdrawing substituents at the terminus of the alkene [6][7]. For example, the recently established general stereoselective syntheses of cyclobutanols and cyclobutanones, involving samarium(II) reductions of unsaturated aldehydes [8][9], and titanium(III) reductions of unsaturated epoxides [10][11], owe their success to the rapid trapping tactic.

The 4-membered azetidinone ring system **1** occurs in several families of powerful β-lactam antibiotics. Radical-based cyclizations leading to azetidinones seem to differ from the 4-*exo* norm, because no less than four distinct radical-based disconnections have been investigated [7], although only the three shown in *Scheme 1* have proved successful in synthetic applications.

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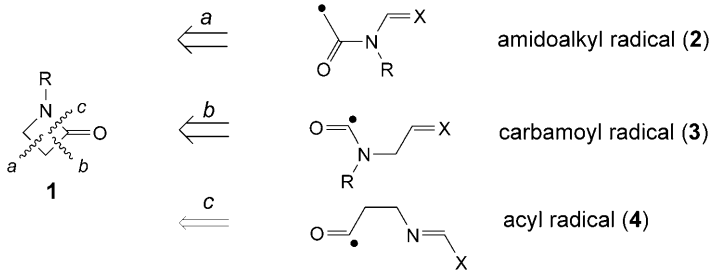
Scheme 1. *Synthetically Useful Radical-Based Disconnections of the Azetidinone Ring*



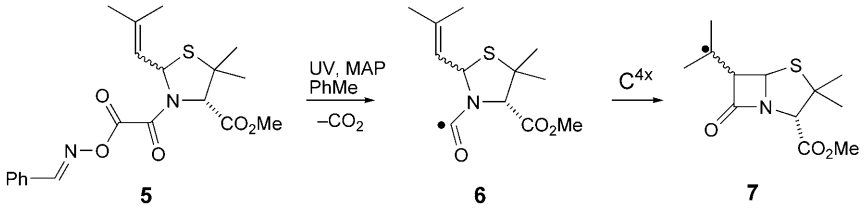
Disconnection *a* in *Scheme 1* implies a C^{4x} closure of an amidoalkyl (α-carbamoyl) radical **2** onto an enamide acceptor. This approach has been employed in numerous successful β-lactam syntheses [6]. Disconnection *c* connotes C^{4x} ring closure of an acyl radical **4** onto an imine acceptor. *Ryu* and co-workers have prepared suitable acyl radicals and made successful syntheses by carbonylations of azaenynes [12][13]. Disconnection *b* implies C^{4x} closure of a carbamoyl-type radical (aminoacyl radical) **3** onto an unsaturated acceptor group.

Quite a range of β-lactams have been made by methodologies following disconnection *b*. *Pattenden* and co-workers made carbamoyl(salophen)cobalt complexes and showed that on photolysis carbamoyl radicals were released and underwent C^{4x} cyclizations [14][15] (salophen = 2,2′-[1,2-phenylenebis(nitrilomethylidyne]bis[phenol]). We have recently developed several 'clean', metal-free routes to carbamoyl radicals. Cyclohexadiene-based reagents have proved useful as precursors of C- and heteroatom-centered radicals [16][17]. Cyclohexadienecarboxamides released carbamoyl radicals, and those with allyl and cinnamyl side chains afforded azetidinones in moderate yields [18–20]. 'Oxime oxalate amides' (= 2-[(alkylideneamino)oxy]-2-oxoacetamides) $R^1C(R^2)=N-O-C(O)-C(O)-N(R^3)R^4$ are easily prepared from an oxime, oxalyl chloride, and an *N*-alkenylamine, and they also function as novel, clean sources of carbamoyl radicals [21]. The best conditions for preparations of lactams involved photolyses of dilute 'oxime oxalate amide' solutions in toluene, with a 2–3-fold excess of 4-methoxyacetophenone (= 1-(4-methoxyphenyl)ethanone; MAP). In these photosensitized reactions, sufficient energy was transferred to the 'oxime oxalate amide' to break the weak N–O bond and release the phenyliminyl radical $PhCH=N^{\cdot}$ (R^1 = Ph, R^2 = H) together with a carbamoyl radical ($R^4N(R^3)-C(O)^{\cdot}$). The phenyliminyl radicals simply abstracted an H-atom from the toluene solvent, and the resulting imine was hydrolyzed to benzaldehyde during workup. By means of this methodology, several β-lactams were prepared, including a bicyclic example [22].

An attempt was made to access penicillin derivatives by this route. Thiazolidine-containing 'oxime oxalate amide' **5** was prepared and photolyzed in the presence of MAP in toluene (*Scheme 2*). EPR Spectroscopy showed unequivocally that the carbamoyl radical **6** was generated. GC/MS Evidence suggested the penicillin derived from radical **7** had formed, but the yield was low and none could be isolated [22].

Cyclizations onto *O*-alkyloxime functional groups >C=NOR are regiospecific to the C-atom [23] and can be significantly faster than with analogous alkene acceptors [24]. Moreover, useful N-functionality remains available for further synthetic elabora-

Scheme 2. *Putative Synthesis of a Penicillin Derivative from Thiazolidine-Containing 'Oxime Oxalate Amide'* **5**



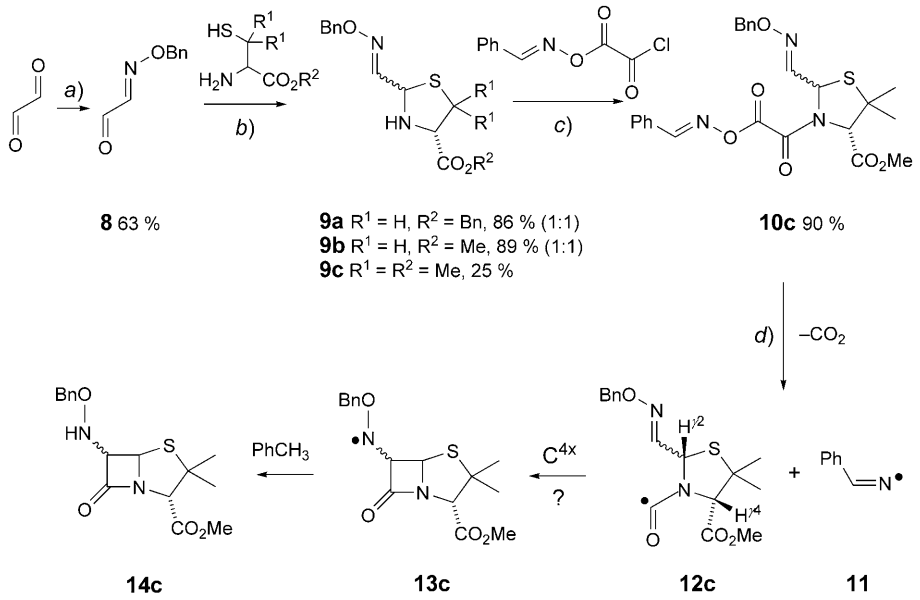
tion. We thought, therefore, that C^{4x} ring closures onto suitable *O*-alkyloximes to give (oxoazetidinyl)aminyl radicals, and hence 3-amino-β-lactams, could show advantages over previous methods. Accordingly, we prepared two types of 'oxime oxalate amide' containing *O*-benzyloxime side chains and investigated their photodissociations. Part of this research has been published in a preliminary communication [25].

Results and Discussion. – A synthetic route to thiazolidines incorporating *O*-alkyloxime side chains at the 2-position was first devised. Glyoxal oxime **8** was prepared by condensation of *O*-benzylhydroxylamine hydrochloride with glyoxal (=ethanedial) according to the method of *Zimmermann* and co-workers [26]. The {[(benzyloxy)imino]methyl}thiazolidines **9** were prepared by addition of cysteine (R^1=H) or penicillamine (R^1=Me) esters (or their HCl salts) to a solution of oxime **8** in EtOH, followed by stirring at room temperature for 24 h (*Scheme 3*). Thiazolidines **9a–c** were all obtained as inseparable 1:1 mixtures of isomers, and **9c** was unstable and had to be used immediately. The thiazolidine **9c** was converted to the corresponding 'oxime oxalate amide' **10c** through reaction with benzaldehyde *O*-(chlorooxalyl)oxime (=2-[(benzylideneamino)oxy]-2-oxoacetyl chloride). Precursor **10c** was obtained as a colorless oil, and its ^{1}H-NMR spectrum showed it to be a mixture of isomers.

By analogy with other 'oxime oxalate amides', it was expected that photosensitized dissociation of **10c** would occur at the weak N–O bond followed by rapid CO_2 loss to release a phenyliminyl radical **11** and carbamoyl radical **12c** (*Scheme 3*). Potentially, radical **12c** could undergo C^{4x} ring closure to afford 'penicillano-aminyl' radical **13c** that should abstract an H-atom from the toluene solvent and hence yield the penicillin derivative **14c**, with N-functionality conveniently placed at the 3-position.

The photodecomposition of **10c** was first examined by EPR spectroscopy. A solution containing **10c** (0.05 g, 0.1 mmol) and MAP (1 equiv.) in (*tert*-butyl)benzene (0.2 ml) was placed in a quartz tube and deaerated by bubbling N_2. The tube was transferred to the resonant cavity of a 9-GHz EPR spectrometer and photolyzed with unfiltered light from a 500-W Hg arc. The spectrum shown in *Fig. 1,a* was obtained at 220 K. The two sets of N-triplets at low and high field are clearly due to the phenyliminyl radical **11**, and the EPR parameters (g=2.0034, a(1H)=7.97 mT, a(N)=0.98 mT) were essentially identical to those in the literature [27]. The g-factor and N hyperfine splitting (hfs) of the second radical (*Fig. 1,a*, centre) were very similar to those of other carbamoyl radicals [21][22] which indicated that the spectrum was due to radical **12c**. The spectrum also displays a small long-range d hfs from one or other of the nonequivalent γ-H-atoms. A density-functional-theory (DFT) computation (UB3LYP/6-31G*) [28]

Scheme 3. *Preparation of an* O*-Alkyloxime-Substituted 'Oxime Oxalate Amide' and Its Proposed Photochemical Transformation*



a) $BnONH_2 \cdot HCl$, NaOH, r.t., 16 h. *b*) Et_3N, r.t., 24 h. *c*) Pyridine, CH_2Cl_2, 3 h. *d*) UV, 4-methoxyacetophenone (MAP), PhMe.

on model radical **12d** (*Fig. 2*) gave hfs in good agreement with the experimental data. The computed hfs for $H^{\gamma 4}$ (see *Scheme 3*) was considerably larger than the computed hfs for $H^{\gamma 2}$ (*Table 1*). This explains the origin of the *d* hfs and accordingly, we have assigned the experimental hfs to $H^{\gamma 4}$. These spectroscopic results indicated that 'oxime ester amide' **10c** underwent ready homolysis of its weak N–O bonds and that loss of CO_2 from the initial acyloxyl radicals was rapid. At higher temperatures, the EPR spectra weakened, as expected, eventually leaving no sign of carbamoyl **12c** (*Fig. 1*,*b*). However, no trace of the ring-closed penicillano-aminyl radical **13c** was observable.

Table 1. *EPR Parameters for Thiazolidinylcarbamoyl Radicals in* ^{t}*BuPh solution*

Radical	Temp./K or method	*g*-Factor	*a*(N)/mT	*a*($H^{\gamma 2}$)/mT	*a*($H^{\gamma 4}$)/mT
12c	220	2.0014	2.22		0.10
12a	220	2.0017	2.22		0.15
12d	DFT[a])		2.20	−0.06	−0.16

[a]) UB3LYP/6-311++G(d,p)//UB3LYP/6-31G*

Attempts to carry out preparative-scale photolyses in toluene as a suitable H-donor were hampered by the comparatively rapid degradation of the precursor **10c**. ^{1}H-NMR Analyses showed that solutions of **10c** rapidly developed by-products when kept at or

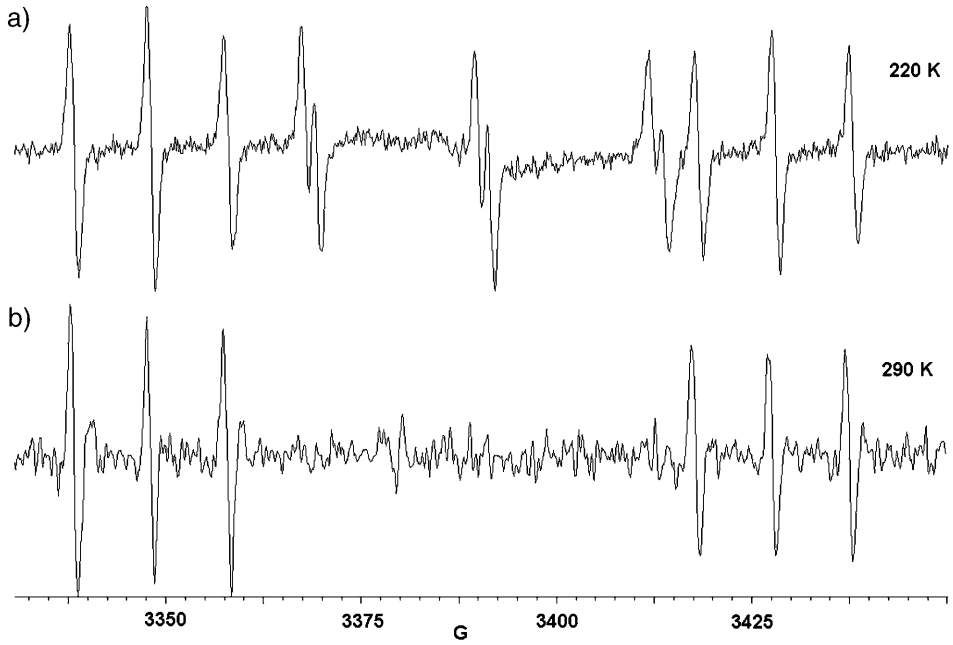


Fig. 1. *EPR Spectra obtained on photolysis of* ^{t}*BuPh solutions of* **10c** *containing MAP at* a*) 220 K and* b*) 290 K*

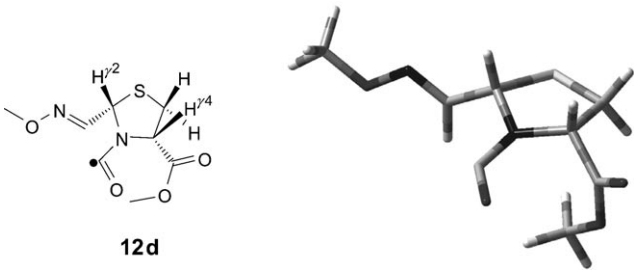


Fig 2. *DFT-Computed structure of model radical* **12d** (UB3LYP/6-31G*)

above *ca.* 270 K. A photosensitized reaction with **10c** and 2 equiv. of MAP in toluene was carried out at room temperature, but the NMR spectrum showed no trace of **14c**, and a GC/MS of the whole product mixture showed a complex spread of individually minor components. Disappointingly, therefore, no evidence of C^{4x} ring closure of thiazolidinylcarbamoyl radicals onto the oxime ether acceptor could be obtained. The lack of cyclization could be due to precursor degradation, or to the extra strain imposed on the C^{4x} process by the presence of the adjacent 5-membered ring, or to an interaction of the carbamoyl radical centre with the neighboring ester group. The structure of model thiazolidine-containing carbamoyl **12d**, computed at the UB3LYP/6-31G* level (*Fig. 2*), showed an all-*trans* arrangement of the *O*-alkyloxime chain with the carbamoyl C=O well placed for ring closure. However, the ester group approaches the car-

bamoyl rather closely and adopts a conformation in which the two C=O groups are nearly parallel; supporting the idea of an interaction.

To probe for C^{4x} ring closure onto a precursor without an adjacent 5-membered ring, the open-chain 'oxime oxalate amide' **15** was prepared as described previously [25]. The EPR spectrum obtained on photolysis of **15** and MAP in (*tert*-butyl)benzene at 280 K is shown in *Fig. 3,b* (see also *Scheme 4*). The signals of the phenyliminyl radical are clearly visible in the wings of the spectrum. Another species characterized by

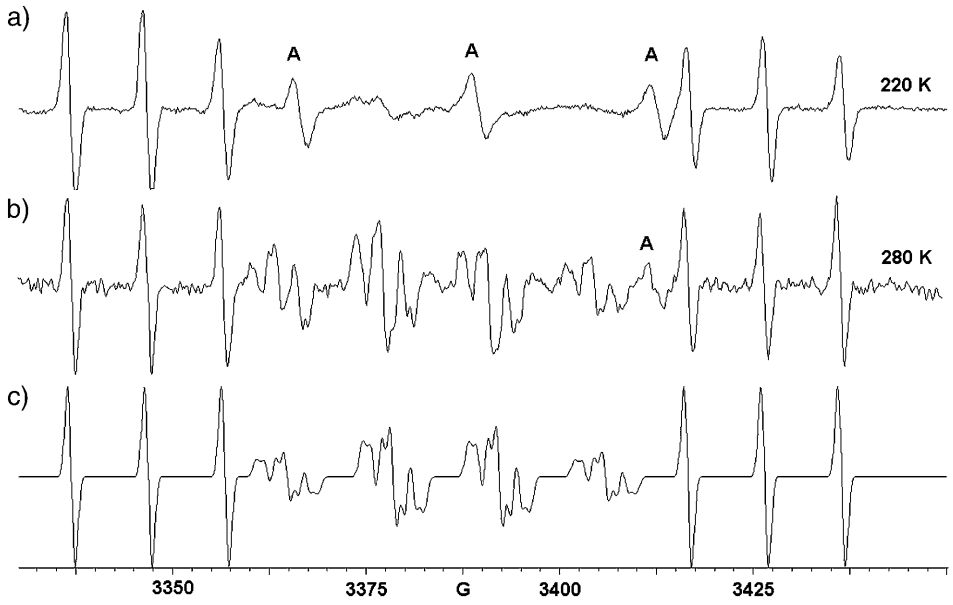
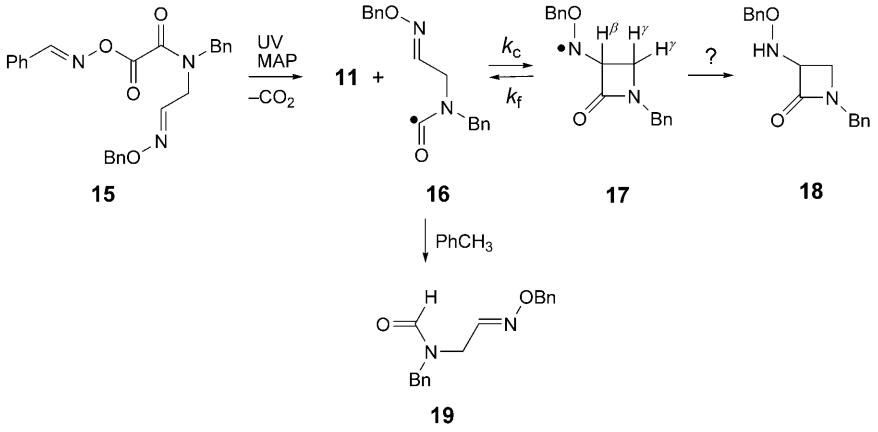


Fig. 3. *Isotropic EPR spectra obtained during UV photolysis of a* ^{t}*BuPh solution of* **15** *and MAP:* a) *experimental spectrum at 220 K,* b) *experimental spectrum at 280 K, and* c) *computer simulation*

Scheme 4. *Ring Closure* (C^{4x}) *onto an* O-*Alkyloxime Acceptor*

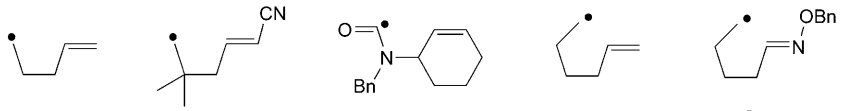


four *m* is also present at 280 K and was satisfactorily simulated (*Fig. 3,b*) with the following parameters: $g = 2.0049$, $a(N) = 1.37$, $a(1H^{\beta}) = 1.37$, $a(2H^{\gamma}) = 0.25$, $a(2H) = 0.1$ mT at 280 K). The *g*-factor is typical of an alkoxyaminyl radical, and the other hfs are as expected for (oxoazetidinyl)aminyl radical **17**. This assignment was supported by a DFT computation (UB3LYP/EPR-iii//UB3LYP/6-31G*) which gave hfs in reasonable agreement *viz.*: $a(N) = 1.16$, $a(1H^{\beta}) = 1.85$, $a(2H^{\gamma}) = 0.15$, $a(2H) = -0.03$ mT. A third radical (marked A in *Fig. 3*) was also present and dominated spectra taken at lower temperatures (*Fig. 3,a*). The EPR parameters, *i.e.*, $g = 2.0018$, $a(N) = 2.32$ mT, showed this to be the carbamoyl radical **16** (the other peaks from **16** are overlapped by the spectrum of **17** in *Fig. 3,b*). The spectroscopic evidence strongly supports the conclusion that C^{4x} ring closure of the open-chain carbamoyl radical **16** does indeed rapidly take place onto the *O*-benzyloxime acceptor; even at temperatures well below room temperature.

Competition from the reverse ring fission process (k_f) needs to be considered in assessing the kinetics. When ring opening is included, the kinetic expression of *Eqn. 1* is easily derived, where $2k_t$ is the diffusion-controlled rate constant for termination reactions of **16** and **17** [29][30]. The concentrations of **16** and **17** were determined by double integration of their EPR spectra and comparison with the spectrum of a known concentration of DPPH run under identical conditions [4]. Experiments were carried out with MAP concentrations ranging from 0.1 to 5 equiv. so as to vary the ratio [**16**]/[**17**]. It was found that, to within experimental error, the results were not sensitive to this ratio, and hence the second term on the right of *Eqn. 1* is small, meaning that k_f is significantly less than k_c. Under these conditions, k_c values were derived in the temperature range 205–280 K from the simplified form of *Eqn. 1* giving *Arrhenius* parameters of $\log(A_c/s^{-1}) = 9.6$ and $E_a = 30$ kJ mol^{-1}.

$$[\mathbf{17}] + [\mathbf{17}]^2/[\mathbf{16}] = k_c/2k_t - k_f/2k_t([\mathbf{17}]/[\mathbf{16}]) \quad (1)$$

The rate constants for ring closure, and the reverse where available, are compared in *Table 2* with data for some related species. The rate constant for C^{4x} ring closure of carbamoyl **16** onto the C=NOBn acceptor is four orders of magnitude greater than the rate constant for the archetype pent-4-enyl (**20**) C^{4x} cyclization. Furthermore, it is also faster than cyclization of pent-4-enyl radical **21**, even though this is favored by dimethyl substitution and produces a resonance-stabilized product radical. This is in good agreement with the deduction from preparative work that azetidinone rings form more easily than cyclobutyl-type rings in radical reactions. Ring opening is of the same order of magnitude for both types of ring, and the main difference is the faster cyclization giving azetidinones.



20 **21** **22** **23** **24**

As anticipated, the 4-*exo* cyclization of **16** has a smaller rate constant than the 5-*exo* cyclizations of the hex-5-enyl radical **23**. Interestingly, carbamoyl 4-*exo* cyclizations

Table 2. *Rate Constants for C^{4x} and C^{5x} Ring Closures at 300 K*

Radical	k_c/s^{-1}	k_f/s^{-1}	Ref.
20	1	10^3	[1–4]
21	$2\cdot10^{4a}$)		[31]
16	$3\cdot10^4$	*ca.* 10^3	this work
22	$5\cdot10^4$		[25]
23	$2\cdot10^5$		[32]
24	$4\cdot10^{7b}$)		[33]

[a]) At 323 K. [b]) At 353 K.

were found to be less reversible than 4-*exo* cyclizations of amidoalkyls for which there is much evidence that azetidinone formation is reversible [34]. The spectroscopic evidence clearly indicated that 4-*exo* closure of the open-chain carbamoyl radical **16** was faster than 4-*exo* ring closure of carbamoyls **6** or **12c** with adjacent thiazolidine rings. The 4-*exo* cyclization onto a >C=NOR bond was expected to be faster than onto a C=C bond. The error limits are large on the kinetic data for carbamoyl radicals **16** and **22** so that, although *Table 2* shows a marginally greater k_c for the latter, the two are indistinguishable within the error limits. The two specific examples are stereoelectronically dissimilar so that a general conclusion about the kinetics of 4-*exo* ring closures onto the two types of acceptors cannot be made.

Attempts were made to devise a suitable methodology for the preparative use of *O*-alkyloxime containing 'oxime oxalate amides'. A solution of the 'oxime oxalate amide' **15** in toluene containing MAP was photolyzed by light from a 400-W UV lamp for 5 h at room temperature. The solvent was removed and the resulting yellow oil was analyzed by ^{1}H-NMR spectroscopy. The H–C(3) of the azetidinone ring usually appear between δ 3.0 and 4.0 ppm. This region of the spectrum was clear suggesting that the β-lactam **18** was not formed. The peaks corresponding to the benzaldehyde oxime H-atom had disappeared and were replaced by a *s* at δ 10.2 corresponding to benzaldehyde (derived from radical **11**). This suggested that the photodissociation had actually occurred in accordance with *Scheme 4* but that the cyclized product had not formed. The remaining peaks were closely related to those of the amine precursor to **15**. In addition, the presence of a new series of peaks at δ 8.2 suggested that the major product was the formamide **19** resulting from direct H-abstraction by the carbamoyl radical. Formation of **19** was unexpected since the EPR study had demonstrated that cyclization occurred readily at low temperatures in the non-H-donating solvent (*tert*-butyl)benzene. It is probable that cyclization of **16** could not compete with the H-atom abstraction from the toluene solvent. The reaction was repeated at a higher temperature, but once again, only the formamide was observed. The photolysis was repeated in the non-H-donating solvent trifluorotoluene (=(trifluoromethyl)benzene), and also in THF and in trichlorobromomethane, but the expected azetidinone NMR peaks were not observed, and a complex mixture resulted in each case.

Experimental Part

General. Column Chromatography (CC): *ICN* silica gel (63–200, 60 Å); FC = flash CC. IR spectra: in nujol or neat; *Perkin-Elmer RX-I*-FT-IR spectrometer; in cm^{-1}. ^1H (300 MHz)- and ^{13}C (75 MHz)-NMR Spectra: $CDCl_3$ soln.; δ in ppm rel. to $SiMe_4$ (= 0 ppm) as an internal standard, *J* in Hz; *Varian-Gemini-2000* and *Bruker Avance-300* spectrometers. EI-MS and high-resolution (HR) MS: 70 eV ionization, or chemical ionization (CI) with isobutane as target gas; *VG-Autospec* spectrometer; in *m*/*z* (rel. %).

EPR Spectra. EPR spectra were obtained with a *Bruker EMX-10/12* spectrometer operating at 9.5 GHz with 100 kHz modulation. Solns. of freshly purified 'oxime oxalate amide' (*ca.* 0.1–0.2M) and 4-methoxyacetophenone (MAP; usually 1 mol-equiv.) in (*tert*-butyl)benzene were placed in 4-mm (o.d.) quartz tubes and deaerated by bubbling N_2 gas for 20 min. Samples were irradiated in the resonant cavity by unfiltered light from a 500-W super-pressure Hg arc. In all cases where spectra were obtained, hfs were assigned with the aid of computer simulations by the *Bruker* SimFonia software package. For concentration measurements, signals were double-integrated with the *Bruker* WinEPR software, and radical concentrations were calculated by reference to a known concentration of DPPH (2,2-diphenyl-1-(2,4,6-trinitrophenyl)hydrazyl), as described previously. In kinetic experiments, to minimize sample-depletion effects, 'single-shot' runs were carried out where samples were irradiated for only one spectrum (< 5 min) before a fresh sample was introduced.

Glyoxal Mono-O-*benzyloxime* (= *Ethanedial Mono*-O-*(phenylmethyl)oxime*; **8**). *O*-Benzylhydroxylamine hydrochloride (800 mg, 5 mmol) was dissolved in H_2O (50 ml) neutralized with NaOH (3 mol-equiv.). To this was added glyoxal (7.5 g of a 40% soln. in H_2O). The mixture was left at r.t. for 16 h after which time it was extracted with CH_2Cl_2 (4 × 25 ml). The org. phase was dried ($MgSO_4$), the solvent evaporated, and the crude yellow oil purified by bulb-to-bulb distillation at 60–62° at 0.2 Torr: **8** (515 mg, 63%) ([26]: 63%). Colorless oil. ^1H-NMR: 5.33 (*s*, CH_2); 7.34–7.80 (*m*, 5 arom. H); 7.56 (*d*, *J* = 8, CH=N); 9.59, (*d*, *J* = 8, CH=O).

2-{[(Benzyloxy)imino]methyl}-1,3-thiazolidine-4-carboxylic Acid Benzyl Ester (**9a**). To a soln. of the benzyl ester of L-cysteine (2.11 g, 10 mmol) in EtOH (50 ml) at 0° was added **8** (1.63 g, 10 mmol). The mixture was stirred at r.t. for 24 h. After this time, the solvent was removed and the crude colorless oil subjected to CC (AcOEt/hexane). The product was further purified by recrystallization from AcOEt/hexane: **9a** as a 1:1 mixture of isomers (3.06 g, 86%). Colorless needles. M.p. 78–80°. IR (NaCl): 1741 (C=O). ^1H-NMR: 2.94 (*dd*, *J* = 7, 10, 1/2 H, CH_2(5)); 3.02 (*dd*, *J* = 7, 9, 1/2 H, CH_2(5)); 3.29 (*dd*, *J* = 7, 10, 1/2 H, CH_2(5)); 3.37 (*dd*, *J* = 7, 10, 1/2 H, CH_2(5)); 3.95 (*dd*, *J* = 7, 9, 1/2 H, H–C(4)); 4.11 (*t*, *J* = 6, 1/2 H, H–C(4)); 5.05, 5.09 (2*s*, 2 H, OCH_2); 5.12 (*d*, *J* = 6, 1/2 H, HC=N); 5.20, 5.22 (2*s*, 2 H, OCH_2); 5.30 (*d*, *J* = 6, 1/2 H, HC=N); 7.30–7.37 (*m*, 10 arom. H); 7.33 (1/2 H, NCHS, under arom. H); 7.48 (*d*, *J* = 6, 1/2 H, NCHS). ^{13}C-NMR ($CDCl_3$): 37.9, 38.8 (C(5)); 64.9, 65.7, 66.1, 66.5 (C(4), C(2)); 76.6, 76.9 (OCH_2); 128.3, 128.4, 128.5, 128.7, 128.8, 128.9, 129.1, 135.5 (arom. C); 147.4, 149.1, 149.4, 152.3 (C=O, C=N). Anal. calc. for $C_{19}H_{20}N_2O_2$: C 64.0, H 5.66, N 7.86; found: C 64.1, H 5.45, N 7.79.

2-{[(Benzyloxy)imino]methyl}-1,3-thiazolidine-4-carboxylic Acid Methyl Ester (**9b**). To a stirred soln. of L-cysteine methyl ester hydrochloride (3.42 g, 20 mmol) in EtOH (25 ml) at −10° was added a soln. of Et_3N (2.02 g, 20 mmol) in EtOH (5 ml). The mixture was stirred at −10° for 10 min (until the precipitate of $Et_3N \cdot HCl$ started to appear). To this was added a soln. of **8** (3.26 g, 20 mmol) in EtOH (5 ml). The mixture was stirred between −10 and 5° for 1 h and then at r.t. for 24 h. After this time, the mixture was filtered and the solvent evaporated. The crude product was purified by CC (AcOEt/hexane): pure **9b** as a 1:1 mixture of isomers (4.98 g, 89%). Colorless oil. IR (NaCl): 1753 (C=O), 1635 (C=N). ^1H-NMR: 2.95 (*dd*, *J* = 7, 10, 1/2 H, CH_2(5)); 3.03 (*dd*, *J* = 6, 10, 1/2 H, CH_2(5)); 3.24 (*dd*, *J* = 7, 10 1/2 H, CH_2(5)); 3.28 (*dd*, *J* = 6, 10, 1 H, CH_2(5)); 3.78, 3.80 (*s*, 3 H, MeO); 3.92 (*dd*, *J* = 6, 9, 1/2 H, H–C(4)); 4.10 (*t*, *J* = 7, 1/2 H, H–C(4)); 5.06, 5.10 (2*s*, 2 H, OCH_2); 5.13 (*d*, *J* = 6, 1/2 H, HC=N); 5.31 (*d*, *J* = 7, 1/2 H, HC=N); 7.30–7.40 (*m*, 5 arom. H); 7.38 (1/2 H, NCHS, under arom.); 7.49 (*d*, *J* = 6, 1/2 H, NCHS). ^{13}C-NMR: 37.8, 38.7 (C(5)); 53.1 (MeO); 64.8, 65.2, 66.0, 66.4 (C(4), C(2)); 76.6, 76.9 (OCH_2); 128.5, 128.7, 128.8, 128.9 (arom. C); 147.4, 149.1, 149.2, 152.3 (C=O, C=N). CI-MS: 281 (45, $[M^+H]^+$), 108 (46), 91 (100). HR-MS: 281.0960 ($C_{13}H_{17}N_2O_3S^+$, $[M^+H]^+$; calc. 281.0961).

2-{[(Benzyloxy)imino]methyl}-5,5-dimethyl-1,3-thiazolidine-4-carboxylic Acid Methyl Ester (**9c**). As described for **9b**, with the methyl ester hydrochloride of L-penicillamine (=3-mercapto-L-valine; 3.03 g, 18.6 mmol), EtOH (70 ml), Et_3N (1.90 g) in EtOH (5 ml), and **8** (3.03 g, 18.6 mmol) in EtOH (5 ml): pure **9c** (1.43 g, 25%). Colorless oil. ^{1}H-NMR: 1.21 (*s*, 3 H, Me); 1.63 (*s*, 3 H, Me); 3.72 (*s*, 1 H, NCH); 3.79 (*s*, 3 H, MeO); 5.10 (*s*, 2 H, OCH_2); 5.21 (*d*, *J* = 6, 1 H, HC=N); 7.33–7.37 (*m*, 5 arom. H); 7.46 (*d*, *J* = 6, 1 H, NCHS); no further characterization was carried out because **9c** was unstable.

Benzaldehyde O-*(Chlorooxalyl)oxime* (=*Oxo{[(phenylmethylene)amino]oxy}acetyl Chloride*) [35]. A soln. of benzaldehyde oxime (1.21 g, 10 mmol) in Et_2O (10 ml) was added dropwise to a cold (−40°) soln. of oxalyl chloride (=ethanedioyl dichloride; 1.90 g, 15 mmol) in Et_2O (10 ml). After stirring for 1 h at −20°, the solvent was evaporated at −10°/13 Torr to leave a colorless temperature-sensitive powder which was dried under vacuum for 2 h to remove residual Et_2O: title oxime (2.01 g, 96%) ([35]: 97%). IR (NaCl): 1791 (C=O). ^{1}H-NMR: 7.2–7.49 (*m*, 5 arom. H); 8.55 (*s*, CH). ^{13}C-NMR: 128.2, 128.8, 129.2, 132.9 (arom. C); 159.4, 160.4 (C=N, C=O). MS: 211 (20, M^+).

3-{2-[(Benzylideneamino)oxy]-2-oxoacetyl}-2-{[(Benzyloxy)imino]methyl}-5,5-dimethyl-1,3-thiazolidine-4-carboxylic Acid Methyl Ester (**10c**). To a stirred soln. of benzaldehyde *O*-(chlorooxalyl)oxime (1.0 g, 5 mmol) in CH_2Cl_2 (20 ml) at 0° was added a soln. of Et_3N (400 mg, 5 mmol) in CH_2Cl_2 (5 ml) followed by a soln. of **9c** (1.43 g, 5 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at 0° for 10 min and then at r.t. for 3 h. After this time, a small quantity of pentane was added to promote formation of the pyridine hydrochloride salt. The mixture was filtered, the solvent evaporated, and the residue purified by FC: **10c** (1.97 g, 92%). Colorless oil. ^{1}H-NMR: 1.47 (*s*, 3 H, Me); 1.58 (*s*, 3 H, Me); 3.78 (*s*, 3/2 H, MeO); 3.81 (*s*, 3/2 H, MeO); 4.73 (*s*, 1/2 H, H–C(4)); 4.82 (*s*, 1/2 H, H–C(4)); 4.97 (*s*, 1 H, OCH_2); 5.13 (*s*, 1 H, OCH_2); 5.95 (*d*, *J* = 7, 1/2 H, HC=N); 6.00 (*d*, *J* = 7, 1/2 H, HC=N); 7.17–7.73 (*m*, 10 arom. H); 8.26 (*s*, 1 H, HC=NO); additional peaks were observed on standing at −20°. Further characterization was not carried out due to product degradation.

2-Oxo-N-*{2-[(phenylmethoxy)imino]ethyl}*-N-*(phenylmethyl)-2-{[(phenylmethylene)amino]oxy}acetamide* (**15**) was prepared as described previously [25].

EPR Study of **15**. The ESR samples were prepared by taking 70 mg of the starting 'oxime oxalate amide' **15**, 1 mol-equiv. of MAP, and dissolving them in (*tert*-butyl)benzene (3.5 ml). The soln. was stirred until homogeneous, and this allowed the preparation of seven identical samples, each of 500 µl. The degassed sample was placed in the EPR resonant cavity, and the cavity was cooled to 220 K. Once thermal equilibrium was reached, the sample was photolyzed with light from a 500-W UV lamp, and the EPR spectrum was recorded. The cavity temp. was then increased by 10 K to 230 K, and a fresh sample was placed in the resonant cavity. This was also photolyzed and the spectrum recorded. The procedure was repeated, increasing temp. in increments of 10 K until 280 K.

Preparative-Scale Photolysis of **15**. A soln. of **15** (800 mg, 1.9 mmol) in toluene (400 ml) and in the presence of MAP (840 mg, 5.7 mmol) was photolyzed by light from a 400-W UV lamp for 5 h at r.t. After this time, the solvent was evaporated, and a sample was analyzed by ^{1}H-NMR. The photolysis was repeated at 80°.

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