1225, 1200, 1150, 1120, 1080, 1030, 860, 755, 700, 675, 630 cm^{-1}; NMR ($CDCl_3$) δ 0.32 (s, 9 H), 3.05 (s, 6 H), 7.45 (q, 4 H); mass spectrum, m/e 221 ($M^{+\cdot}$), 220, 207, 206, 178, 177, 149, 102. Anal. Calcd for $C_{12}H_{19}NOSi$: C, 65.09; H, 8.67; N, 6.34. Found: C, 64.91; H, 8.69.

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Registry No. **2**, 82-58-6; **7a**, 82645-11-2; **7b**, 120-72-9; **7c**, 17983-42-5; **7d**, 83188-11-8; **7e**, 83188-12-9; **7f**, 83188-13-0; **7g**, 83188-14-1; **7h**, 92012-86-7; **7i**, 92012-87-8; **7j**, 92012-88-9; **7k**, 576-15-8; **8b**, 92012-89-0; **12**, 92012-90-3; **13**, 92012-91-4; **14**, 70290-55-0; **15**, 87497-88-9; **16a**, 92012-92-5; **16b**, 92012-93-6; **16c**, 92012-94-7; **16d**, 92012-95-8; **16e**, 92012-96-9; **16f**, 92012-97-0; **16g**, 92012-98-1; **16h**, 92012-99-2; **16i**, 92013-00-8; **17a**, 92013-01-9; **17b**, 92013-02-0; **18**, 40641-03-0; **19a**, 92013-03-1; **19b**, 92013-04-2; **21a**, 37945-46-3; **21b**, 3744-82-9; **22a**, 92013-05-3; **22b**, 92013-06-4; **22c**, 92013-07-5; **23**, 92013-08-6; **24a**, 18301-46-7; **24b**, 92013-09-7; **25**, 65094-40-8; **26**, 34906-65-5; Me_3SiCl, 75-77-4; AcCl, 75-36-5; $CH_3C(=NOH)CO_2Et$, 20591-87-1; $CH_2=NMe_2^+Cl^-$, 30354-18-8; $CH_2(CO_2Et)_2$, 105-53-3; Bu_3P, 998-40-3; $O_2NCH_2CO_2Et$, 626-35-7; Bu_3SnH, 688-73-3; $Me_2C(CN)N=NC(CN)Me_2$, 78-67-1; $CH_2=CHCO_2Et$, 140-88-5; $O_2NCH_2CO_2Me$, 2483-57-0; $Cl(CH_2)_2COCl$, 625-36-5; $CH_2=CHCOCl$, 814-68-6; $ClCH_2COCl$, 79-04-9; $(CF_3CO)_2O$, 407-25-0; TsCl, 98-59-9; $(EtO)_2P(O)Cl$, 814-49-3; $C_6H_5CONMe_2$, 611-74-5; pyridine, 110-86-1; 2,6-dimethylpyridine, 108-48-5; quinoline, 91-22-5.

Synthesis and Reactions of Some 1-Substituted 1,2-Diazetidinones

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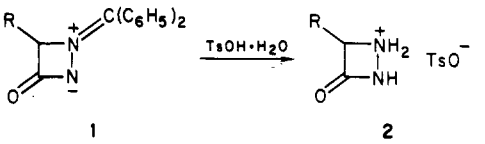
A number of 1,2-diazetidin-3-ones variously substituted at N-1 have been prepared by sodium borohydride reduction of, or addition of methylmagnesium bromide to, 3-oxo-1,2-diazetidinium inner salts (formed by condensation of 3-oxo-1,2-diazetidinium tosylate with carbonyl compounds). 1-Cinnamyl-1,2-diazetidin-3-ones, silylated at N-2, underwent base-promoted alkylation and aldol reactions at C-4. Some unusual dimerization and fragmentation reactions of these aza-β-lactam derivatives have been observed.

We have recently described a convenient, high-yield synthesis of the novel four-membered heterocycle 3-oxo-1,2-diazetidinium tosylate (**2**) by hydrolysis of 1,1-diphenylmethylene-3-oxo-1,2-diazetidinium inner salt **1** (available in two steps from benzophenone hydrazone) with *p*-toluenesulfonic acid monohydrate (Scheme I).[1] With the ultimate objective of introducing substituents into the diazetidinone ring system capable of eventual intramolecular cyclization to give bridgehead aza analogues of the β-lactam antibiotics, we have initiated a program aimed at functionalization of **2** at N-1, N-2, and C-4. We have already described our unexpected results[2] when one of the normal strategies for the synthesis of carbapenems from monocyclic β-lactams, the intramolecular carbene insertion reaction,[3] was applied to the aza-β-lactam system. Other strategies based on intramolecular Wittig,[4] Horner–Emmons,[5] aldol,[6] or Dieckmann cyclizations[7] would require as precursors a side-chain aldehyde. In order to apply the latter three procedures to the preparation of bicyclic 1,2-diazetidin-3-ones (aza-β-lactams), we have prepared a number of 1,2-diazetidin-3-ones with latent aldehyde substituents at position 1. We also report our initial results

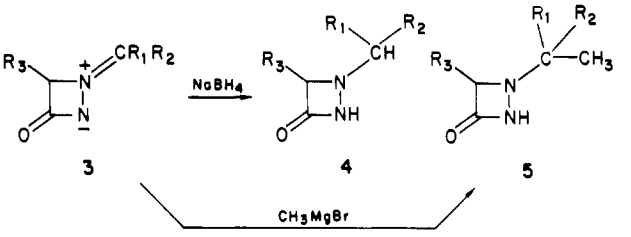
Scheme I[a]



1 2

[a] a, R = H; b, R = CH_3; c, R = C_2H_5.

Table I. Synthesis of 1-Substituted 1,2-Diazetidin-3-ones



3 4 5

starting material	R_1	R_2	R_3	yield, % 4	5
3a	C_6H_4Cl-4	H	H	78	
3b	$CH=CHC_6H_5$	H	H	82	
3c	$CH=CHC_6H_5$	H	CH_3	95	
3d	$CH=CHC_6H_5$	H	CH_2CH_3	95	
3e	$CH_2C_6H_5$	CH_3	H	72	44
3f	$CH_2CH(OCH_3)_2$	CH_3	H	81	73
3g	$CH(OCH_3)_2$	CH_3	H		12
3h			H		36
3i	$CH=CHC_6H_5$	CH_3	H		70
3j	$CH=CHC_6H_5$	CH_3	CH_3		81

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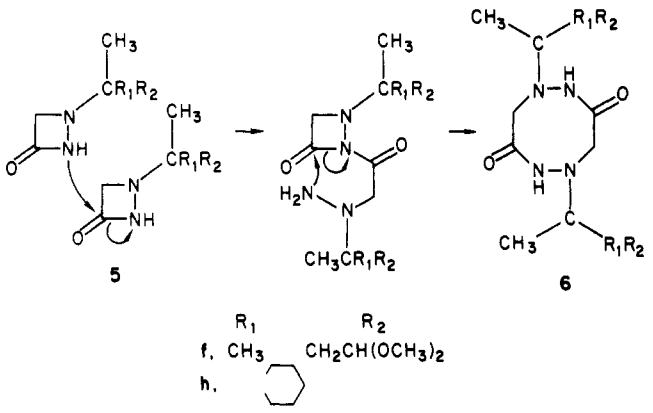
0022-3263/84/1949-4415$01.50/0

Table II. Alkylation of 1-Cinnamyl-1,2-diazetidin-3-one (4b)

base	electrophile	product (yield, %)
$LiN(SiMe_3)_2$	CH_3CH_2I	**4d** (45)
LDA	CH_3CH_2I	**4d** (33)
$LiN(SiMe_3)_2$	CH_3I	**4c** (31)
LDA	CH_3COCH_3	**7b** (17)
LDA	CH_3CHO	**7a** (7)

Scheme II

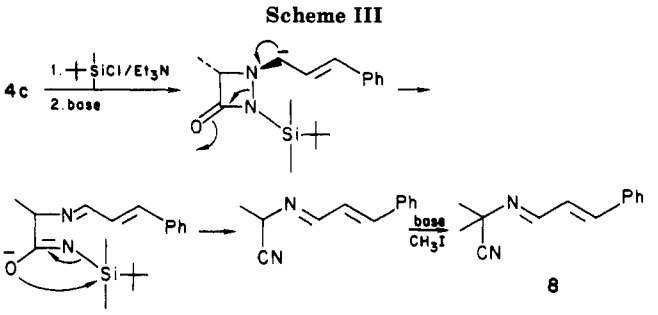


with the direct introduction of substituents at C-4.

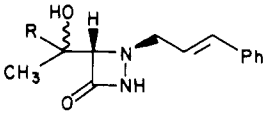
Attempts to alkylate **2** (R = H) with a variety of alkyl halides resulted only in extensive polymerization, apparently as a result of the instability of 1,2-diazetidin-3-one in the absence of an effective electrophilic trapping agent.[8] We therefore investigated an alternate strategy for selective N-1 alkylation via the intermediacy of the readily accessible 3-oxo-1,2-diazetidinium inner salts **3**, available as previously described by the condensation of **2** with carbonyl compounds.[9] Thus, reduction of the 3-oxo-1,2-diazetidinium inner salts **3a–f** with sodium borohydride in methanol gave the 1-substituted 1,2-diazetidin-3-ones **4a–f** in high yield (see Table I). In the case of ylides **3e,f** which are derived from unsymmetrical ketones, reduction necessarily generated a chiral center as a consequence of hindered inversion at N-1.[10] A mixture of invertomers was thus produced as can be seen in the ^1H NMR spectrum of **4e** (see Experimental Section). It should be noted that reduction of **3c,d**, which already contain a chiral center at C-4, does not give a mixture of invertomers, presumably because the equilibrium between the two invertomers exclusively favors the trans isomer.

A second series of 1-substituted 1,2-diazetidin-3-ones free from the above complication was prepared by the reaction of the ylides **3e–j** with methylmagnesium bromide (see Table I). Addition takes place exclusively to the iminium bond, undoubtedly because the amide grouping is protected as its magnesium salt. Although crystalline 1-substituted 1,2-diazetidin-3-ones prepared in this manner (e.g., **5e,i**) appeared to be indefinitely stable, those products which were isolated as gums underwent an irreversible transformation upon standing. For example, both **5f** and **5h** slowly changed over a period of 2 weeks from the orginally isolated gums into crystalline materials which could be isolated by trituration with ether. A molecular weight determination showed them to be dimers which no longer possessed an intact 1,2-diazetidin-3-one ring (the highest carbonyl absorption bands were at 1662 cm^{-1}). We suggest that these crystalline dimers are 1,5-disubstituted 1,2,5,6-tetraazacyclooctane-3,7-diones (**6f,h**), which are probably formed as outlined in Scheme II. An analogous formation of an eight-membered ring via a six-membered intermediate is precedented in β-lactam chemistry by Wasserman's synthesis of homaline.[11]

Scheme III



By these straightforward reactions a series of 1,2-diazetidine-3-ones, suitably functionalized at N-1 for eventual elaboration into aldehyde precursors for the preparation of bicyclic derivatives, has been prepared. 1-Cinnamyl-4-ethyl-1,2-diazetidin-3-one (**4d**) is a particularly important derivative since it possesses the requisite substitution pattern for eventual elaboration into the aza analogue of PS-5.[12] The precursor ylide **3b**, however, was available only in very low overall yield from benzophenone hydrazone (see Experimental Section). As a consequence, we have briefly examined an alternative approach to **4d** by alkylation of the readily accessible 1-cinnamyl-1,2-diazetidin-3-one (**4b**). Generation of an anion at C-3 of silylated β-lactams, followed by treatment with an appropriate electrophilic reagent, has been widely used for the preparation of a variety of useful β-lactam intermediates.[13] Application of this approach to **4b** indeed gave the 4-ethyl derivatives **4d**; reaction of the intermediate anion with methyl iodide, acetaldehyde, and acetone gave **4c**, **7a**, and **7b**, respectively. Since the acetaldehyde aldol product **7a**



7a, R = H
b, R = CH_3

(which was obtained as a diastereomeric mixture) has considerable potential for eventual elaboration into an aza analogue of thienamycin, we are now investigating stereoselective procedures for its preparation.

Attempted alkylation of 1-cinnamyl-4-methyl-1,2-diazetidin-3-one (**4c**) led to destruction of the diazetidinone ring and the formation of the nitrile **8**. A reasonable reaction pathway for this unexpected fragmentation is outlined in Scheme III.

These studies have provided a number of functionalized

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(14) The *E*/*Z* ratio was readily determined by integration of the NMR spectrum; see ref 9.

1,2-diazetidin-3-ones whose further elaboration into bicyclic aza-β-lactams will be reported independently.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 467 spectrophotometer, and NMR spectra were recorded on Perkin-Elmer R-32 (90 MHz) or JEOL Model FX 90Q spectrometers. Mass spectra were determined on an AEI MS-9 instrument. Elemental analyses were carried out by Eli Lilly & Co., Indianapolis, IN.

Benzophenone (α-Chlorobutanoyl)hydrazone. A solution of α-chlorobutyryl chloride (53 mL, 0.52 mol) in dichloromethane (50 mL) was added dropwise to a stirred solution of benzophenone hydrazone (92 g, 0.47 mol) and pyridine (42 mL, 0.52 mol) in dichloromethane (400 mL) at 0 °C. After stirring for a further 3 h, the organic layer was washed with saturated ammonium chloride solution and dried ($MgSO_4$), and the solvent was evaporated in vacuo. Recrystallization of the residue from ethanol gave 110 g (83%) of the product: mp 101–103 °C; IR (Nujol) 3160, 1678 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.45 and 8.38 (each br s, total 1 H), 7.80–7.15 (m, 10 H), 5.36 and 4.32 (t and dd, respectively, total 1 H), 2.30–1.85 (m, 2 H), 1.12 and 1.00 (each t, total 3 H, J = 7 Hz).

Anal. Calcd for $C_{17}H_{17}ClN_2O$: C, 67.88; H, 5.70; N, 9.31; Cl, 11.79. Found: C, 68.14; H, 5.75; N, 9.17; Cl, 11.91.

1-(Diphenylmethylene)-4-ethyl-3-oxo-1,2-diazetidinium Inner Salt (1c). A solution of benzophenone (α-chlorobutanoyl)hydrazone (14.2 g, 47 mmol) in THF (120 mL) was added to a stirred suspension of sodium hydride (2.4 g, 50 mmol, 50% dispersion in oil) in THF (20 mL), and the mixture was heated under reflux for 4 h. After cooling to 25 °C, the organic layer was washed with ammonium chloride solution and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. The residue was triturated twice with ether/petroleum ether (100 mL, 1:1), and the gummy solid was recrystallized from toluene/heptane (30 mL, 3:1) to give 1.6 g (13%) of the product: mp 148–149 °C; IR (Nujol) 1760, 1575, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (m, 2 H), 7.65–7.20 (m, 8 H), 5.91 (m, 1 H), 1.70–1.10 (m, 2 H), 0.90 (t, 3 H, J = 7 Hz).

Anal. Calcd for $C_{17}H_{16}N_2O$: C, 77.25; H, 6.10; N, 10.60. Found: C, 77.28; H, 6.37; N, 10.43.

4-Ethyl-3-oxo-1,2-diazetidinium Tosylate (2c). A solution of 1-(diphenylmethylene)-4-ethyl-3-oxo-1,2-diazetidinium inner salt (2.64 g, 10 mmol) and p-toluenesulfonic acid (1.90 g, 10 mmol) in dichloromethane (75 mL) was stirred for 45 min. The precipitate was filtered and washed with ether to give 0.97 g (36%) of the product: mp 180 °C dec; IR (Nujol) 1825 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.49 and 7.12 (each d, 2 H, J = 8 Hz), 5.27 (t, 1 H, J = 7 Hz), 2.29 (s, 3 H), 1.97 (quintet, 2 H, J = 7 Hz), 1.00 (t, 3 H, J = 7 Hz).

Anal. Calcd for $C_{11}H_{16}N_2O_4S$: C, 48.52; H, 5.92; N, 10.29; S, 11.77. Found: C, 48.66; H, 5.97; N, 10.04; S, 11.74.

(Z)-1-Cinnamylidene-4-ethyl-3-oxo-1,2-diazetidinium Inner Salt (3d). Cinnamaldehyde (0.397 g, 3 mmol) in DMF (1 mL) was added to a stirred solution of 4-ethyl-3-oxo-1,2-diazetidinium tosylate (0.816 g, 3 mmol) in DMF (4 mL) at 0 °C. After 5 min, sodium bicarbonate (0.6 g, 7 mmol) was added and after a further 1 h, the mixture was added to water (100 mL). The solid which precipitated was collected, dried, and recrystallized from toluene to give 0.34 g (53%) of **3d**: mp 189–191 °C; IR (Nujol) 1755, 1745, 1604, 1590, 1573 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.60–7.00 (m, 8 H), 5.60 (t, 1 H, J = 6 Hz), 2.12 (quintet, 2 H, J = 6 Hz), 1.14 (t, 3 H, J = 6 Hz).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.67; H, 6.33; N, 12.83.

1-(4-Phenyl-2-but-3-enylidene)-4-methyl-3-oxo-1,2-diazetidinium Inner Salt (3j). Benzalacetone (18.8 g, 124 mmol) was added to a vigorously stirred solution of 4-methyl-3-oxo-1,2-diazetidinium tosylate (31.0 g, 120 mmol) in dry DMF (150 mL) at 0 °C. After stirring for 1.5 h, sodium bicarbonate (25 g, 0.3 mmol) was added, and after a further 2 h, water (1 1) was added. The mixture was extracted several times with dichloromethane and the organic phase was then dried ($MgSO_4$). The solvent was removed in vacuo, and trituration of the residue with ether gave 21.0 g (82%) of **3j**: E/Z ratio 70:30;[14] mp 110–130 °C; IR (Nujol) 1755, 1610, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ Z form 7.40 (m, 7 H), 5.64 (q, 1 H, J = 7 Hz), 2.29 (s, 3 H), 1.74 (d, 3 H, J = 7 Hz); E form 7.40 (m, 5 H), 7.08 and 6.65 (each d, 1 H, J = 16 Hz), 5.64 (q, 1 H, J = 7 Hz), 2.42 (s, 3 H), 1.78 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{13}H_{14}N_2O$: C, 72.87; H, 6.59; N, 13.07. Found: C, 72.59; H, 6.77; N, 12.84.

Reduction of 3-Oxo-1,2-diazetidinium Inner Salts. General Procedure. To a stirred mixture of the 3-oxo-1,2-diazetidinium inner salt (1 mmol) in methanol (5 mL) at 0 °C was added sodium borohydride (0.1 g) in portions at such a rate that the temperature remained below 15 °C. After stirring for a further 3 min, acetone (1 mL) and saturated ammonium chloride solution (20 mL) were added. Extraction with ether or dichloromethane, followed by drying of the extract over $MgSO_4$ and evaporation in vacuo, afforded the product which was recrystallized or purified by column chromatography.

1-(4-Chlorobenzyl)-1,2-diazetidin-3-one (4a): mp 120–122 °C (dichloromethane/hexane), 78% yield; IR (Nujol) 3120, 3040, 1788, 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27 (br s, 4 H, 4 Ar H), 4.35 and 3.86 (each d, 1 H, J = 16 Hz, total NCH_2CO), 3.79 (m, 2 H, NCH_2Ar); ^{13}C NMR ($CDCl_3$) δ 167.5, 134.6, 134.0, 130.4, 128.8, 68.2, 65.4.

Anal. Calcd for $C_9H_9ClN_2$: C, 54.97; H, 4.61; N, 14.25; Cl, 18.03. Found: C, 55.16; H, 4.67; N, 14.08; Cl, 18.16.

1-Cinnamyl-1,2-diazetidin-3-one (4b): mp 75–79 °C (purified by chromatography on silica with ether as solvent), 82% yield; IR (Nujol) 3200, 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.41 (m, 5 H, 5 Ar H), 6.67 (d, 1 H, J = 16 Hz, C=CH), 6.23 (dt, 1 H, J = 16, 6 Hz, C=CH), 4.45 and 3.88 (each d, 1 H, J = 14 Hz, total NCH_2CO), 3.55 (d, 2 H, J = 6 Hz, NCH_2); LRMS (70 eV), m/e (relative intensity) 188 (observed M^+, 2), 145 (101), 117 (100), 115 (20), 91 (10); HRMS calcd for $C_{11}H_{12}N_2O$ 188.0949, found 188.0947 ± 0.0018.

1-Cinnamyl-4-methyl-1,2-diazetidin-3-one (4c). Method A: mp 73–75 °C (purified by chromatography on silica with ether as solvent), 95% yield; IR (Nujol) 3165, 1756 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (m, 5 H), 6.62 (d, 1 H, J = 16 Hz), 6.19 (dt, 1 H, J = 16, 6 Hz), 3.95 (q, 1 H, J = 7 Hz), 3.52 (m, 2 H), 1.44 (s, 3 H).

Anal. Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.90; N, 13.85. Found: C, 70.99; H, 6.86; N, 13.58.

1-Cinnamyl-4-ethyl-1,2-diazetidin-3-one (4d). Method A: gum (purified by chromatography on silica with ether as solvent), 95% yield; IR (neat) 3200, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34 (s, 5 H), 6.61 (d, 1 H, J = 16 Hz), 6.20 (dt, 1 H, J = 16, 6 Hz), 3.82 (t, 1 H, J = 6 Hz), 3.50 (d, 2 H, J = 6 Hz), 1.80 (quintet, 2 H, J = 6 Hz), 1.02 (t, 3 H, J = 6 Hz); LRMS, m/e (relative intensity) 216 (obsd M^+, 3), 188 (1), 173 (5), 144 (8), 117 (100); HRMS calcd for $C_{13}H_{16}N_2O$ 216.1263, found 216.1256 ± 0.002.

1-(1-Phenyl-2-propyl)-1,2-diazetidin-3-one (4e): gum (purified by column chromatography with ether/petroleum ether (bp 30–60 °C) (3:7) as solvent, 72% yield; ^1H NMR ($CDCl_3$) δ 7.24 (m, 10 H, 10 Ar H), 4.35, 4.27, 3.83, and 3.76 (each d, 1 H, J = 15.5 Hz, total 2 NCH_2CO), 3.0–2.4 (m, 6 H, 2 $PhCH_2CH$), 1.05 and 0.94 (each d, 3 H, J = 6 Hz, total 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 168.1, 168.0, 138.3, 138.1, 129.4, 128.5, 126.5, 67.4, 66.7, 66.5, 41.1, 40.0, 18.4, 17.3; LRMS (70 eV), m/e (relative intensity) 190 (observed M^+, 3), 119 (3), 118 (15), 99 (80), 91 (100); HRMS calcd for $C_{11}H_{14}N_2O$ 190.1106, found 190.1111 ± 0.0019.

1-(4,4-Dimethoxy-2-butyl)-1,2-diazetidin-3-one (4f): gum (purified by column chromatography on silica with ether as solvent), 81% yield; ^1H NMR ($CDCl_3$) δ 4.50 (m, 2 H, 2 $CH(OCH_3)_2$), 4.35, 4.35, 3.88, and 3.80 (each d, 1 H, J = 15 Hz, total 2 NCH_2CO), 3.34, 3.33, 3.32, and 3.31 (each s, 3 H, total 4 OCH_3), 2.60 (br m, 2 H, 2 NCH), 1.70 (br m, 4 H, 2 CH_2), 1.13 and 1.06 (each d, 3 H, J = 7 Hz, total 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 168.0, 167.8, 102.3, 102.1, 66.7, 66.4, 61.4, 61.1, 53.3, 53.1, 52.8, 52.0, 37.2, 36.5, 17.5, 16.4; LRMS (70 eV), m/e (relative intensity) 188 (observed M^+, 0.5), 173 (0.5), 171 (0.5), 157 (1.5), 156 (2), 130 (5), 114 (25), 97 (90), 89 (100), 75 (50); HRMS calcd for $C_8H_{16}N_2O_3$ 188.1161, found 188.1157 ± 0.0018.

Reaction of 3-Oxo-1,2-diazetidinium Inner Salts with Methylmagnesium Bromide. General Procedure. The 3-oxo-1,2-diazetidinium inner salt (5 mmol) was added either as a powder or in THF solution to a stirred solution of methyl-

magnesium bromide (7 mL, 3.0 M in ether) in THF (20 mL) at 0 °C under nitrogen. After stirring for a further 1 h, saturated ammonium chloride solution was added, and the mixture was extracted 3 times with ether or dichloromethane. Extraction of the organic phase with saturated sodium bicarbonate solution, followed by drying over $MgSO_4$ and evaporation in vacuo, afforded the product which was then recrystallized or purified by column chromatography.

1-(2-Methyl-1-phenyl-2-propyl)-1,2-diazetidin-3-one (5e): mp 94–95 °C (purified by column chromatography on silica gel with ether/petroleum ether (bp 30–60 °C) (3:7) as solvent), 44% yield; IR (Nujol) 3200, 1760, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.24 (m, 5 H, 5 Ar H), 4.06 (s, 2 H, NCH_2CO), 2.65 (s, 2 H, $PhCH_2$), 1.03 and 1.01 (each s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.5, 137.5, 130.5, 128.1, 126.5, 61.0, 59.9, 45.2, 20.5, 20.4.

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.80; H, 7.88; N, 13.68.

1-(4,4-Dimethoxy-2-methyl-2-butyl)-1,2-diazetidin-3-one (5f): gum (purified by column chromatography on silica with ether as solvent), 73% yield; IR (neat) 3450, 3200, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.53 (t, 1 H, J = 4 Hz, $CH(OCH_3)_2$), 4.00 (s, 2 H, NCH_2CO), 3.29 and 3.27 (each s, 3 H, OCH_3), 1.65 (d, 2 H, J = 4 Hz, CH_2CH), 1.05 (s, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 168.3, 101.8, 60.4, 57.4, 53.0, 52.1, 42.3, 21.9, 19.9; LRMS (70 eV), m/e (relative intensity) 202 (observed M^+, 2), 111 (50), 75 (100); HRMS calcd for $C_9H_{18}N_2O_3$ 202.1317, found 202.1326 ± 0.0010.

1-(1,1-Dimethoxy-2-methyl-2-propyl)-1,2-diazetidin-3-one (5g): gum (purified by column chromatography on silica with ether as solvent), 12% yield; IR (neat) 3200, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.10 (s, 2 H, NCH_2O), 4.02 (s, 1 H, $CH(OCH_3)_2$), 3.53 (s, 6 H, 2 OCH_3), 1.03 (s, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 167.3, 112.0, 62.4, 61.6, 58.7, 57.8, 17.8, 14.7; LRMS (70 eV), m/e (relative intensity) 188 (observed M^+, 10), 113 (100), 75 (10); HRMS calcd for $C_8H_{16}N_2O_3$ 188.1161, found 188.1169 ± 0.0009.

1-(1-Methylcyclohexyl)-1,2-diazetidin-3-one (5h): gum (purified by column chromatography on silica with ether/petroleum ether (bp 30–60 °C) (1:1) as solvent), 36% yield; IR (neat) 3400, 3200, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.08 (s, 2 H, NCH_2CO), 1.7–1.2 (m, 10 H, 5 CH_2), 1.03 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.9, 59.7, 58.2, 33.6, 33.2, 25.7, 22.0, 16.8; LRMS (70 eV), m/e (relative intensity) 168 (observed M^+, 5), 97 (100), 86 (50), 84 (80); HRMS calcd for $C_9H_{16}N_2O$ 168.1262, found 168.1266 ± 0.0008.

1-(3-Methyl-1-phenyl-3-but-1-enyl)-1,2-diazetidin-3-one (5i): mp 106–107 °C (from ethyl acetate/heptane), 70% yield; IR (Nujol) 3160, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45 (m, 5 H, 5 Ar H), 6.64 and 6.38 (each d, 1 H, J = 16 Hz, C=CH), 4.09 (br s, 2 H, NCH_2CO), 1.29 (s, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 168.3, 136.6, 131.2, 131.0, 128.6, 127.8, 126.5, 61.9, 60.2, 23.7, 22.0.

Anal. Calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 72.16; H, 7.41; N, 12.81.

1-(3-Methyl-1-phenyl-3-but-1-enyl)-4-methyl-1,2-diazetidin-3-one (5j): gum 81% yield; IR (neat) 3200, 1760 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (m, 5 H), 6.56 and 6.35 (each d, 1 H, J = 16 Hz), 4.10 (q, 1 H, J = 6 Hz), 1.40 (d, 3 H, J = 6 Hz), 1.29 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 171.9, 136.7, 131.6, 130.9, 128.6, 127.7, 126.4, 68.9, 60.1, 24.2, 22.4, 15.4; LRMS, m/e (relative intensity) 230 (observed M^+, 2), 187 (5), 145 (100), 129 (20), 117 (15), 91 (35); HRMS calcd for $C_{14}H_{18}N_2O$ 230.1419, found 230.1417 ± 0.002.

1,5-Bis(4,4-dimethoxy-2-methyl-2-butyl)-1,2,5,6-tetraazacyclooctane-3,7-dione (6f). After 2 weeks of standing at room temperature, compound **5f** dimerized. Trituration with ether then gave the product: mp 149–151 °C; IR (Nujol) 3180, 3080, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.62 (br s, 1 H, NH), 4.66 (t, 1 H, J = 6 Hz, $CHCH_2$), 3.96 and 3.47 (each d, 1 H, J = 16 Hz, total NCH_2CO), 3.31 and 3.29 (each s, 3 H, OCH_3), 1.83 and 1.77 (each d, 1 H, J = 6 Hz, total $CHCH_2$), 1.17 (s, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 173.5, 101.3, 58.5, 55.7, 52.4, 51.6, 40.8, 23.8, 23.2; HRMS calcd for $C_{18}H_{36}N_4O_6$ 404.2635, found 404.2622 ± 0.004.

1,5-Bis(1-methylcyclohexyl)-1,2,5,6-tetraazacyclooctane-3,7-dione (6h). After 2 weeks of standing at room temperature, compound **5h** dimerized. Trituration with ether then gave the product: mp 310–315 °C; IR (Nujol) 3165, 3075, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18 (br s, 1 H, NH), 3.97 and 3.43 (each d, 1 H, J = 15 Hz, total NCH_2CO), 1.8–1.2 (m, 10 H, 5 CH_2), 1.03 (s, 3 H, CH_3); LRMS (70 eV), m/e (relative intensity) 336 (observed M^+, 15), 292 (8), 240 (5), 210 (10), 196 (20), 169 (20), 144 (10), 126 (30), 116 (30), 99 (50), 97 (100), 73 (25), 55 (100); HRMS calcd for $C_{18}H_{32}N_4O_2$ 336.2526, found 336.2529 ± 0.003.

General Procedure for C-4 Alkylation of 1-Cinnamyl-1,2-diazetidin-3-one (4b). A solution of **4b** (1 equiv), triethylamine (1.1 equiv) and *tert*-butyldimethylsilyl chloride (1.1 equiv) in dry benzene was stirred overnight at 20 °C. The mixture was then filtered and the solvent was evaporated in vacuo to give the silylated 1,2-diazetidin-3-one as a pale yellow liquid. A solution of the silylated 1,2-diazetidin-3-one in THF was added dropwise to a stirred solution of LDA (or $LiN(SiMe_3)_2$) in THF at −78 °C under N_2. The resulting solution was stirred for 1 h, the electrophile (1.1 equiv) was added, and the reaction mixture was stirred for the specified period (see the individual cases). Saturated ammonium chloride solution was then added and the mixture was extracted with ether. The combined extracts were dried ($MgSO_4$) and cooled to 0 °C, and then tetrabutylammonium fluoride (1.1 equiv, 1 M in THF) was added. After being stirred for 1 min, the mixture was washed with saturated ammonium chloride solution and dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Chromatography on silica with ether/petroleum ether gave the pure products. The aldol products **7a** and **7b** had the same R_f values as the starting material **4b**. In order to obtain pure **7a** and **7b**, therefore, it was necessary to chromatograph the silylated products before treatment with tetrabutylammonium fluoride.

1-Cinnamyl-4-methyl-1,2-diazetidin-3-one (4c). Method B. $LiN(SiMe_3)_2$ was used as base; after addition of methyl iodide, the mixture was stirred for 1 h and warmed to 20 °C: 31% yield, mp 73–75 °C. The product was identical with **4c** prepared by method A.

1-Cinnamyl-4-ethyl-1,2-diazetidin-3-one (4d). Method B. $LiN(SiMe_3)_2$ was used as base; after addition of ethyl iodide, the mixture was stirred for a further 1 h at −78 °C; 45% yield. The product was identical with **4d** prepared by method A.

1-Cinnamyl-4-(1-hydroxy-1-ethyl)-1,2-diazetidin-3-one (7a). LDA was used as base; after addition of acetaldehyde, the mixture was stirred for 30 min at −78 °C; 7% yield; IR (neat) 3435, 3215, 1736 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (m, 5 H, Ar H), 6.58 (d, 1 H, J = 16 Hz, C=CH), 6.16 (dt, 1 H, J = 16.6 Hz, C=CH), 4.02 (m, 1 H, $CHOH$), 3.85 (m, 1 H, C_4-H), 3.52 (m, 2 H, NCH_2), 1.25 (m, 3 H, CH_3); LRMS, m/e (relative intensity) 189 (M^+ − HNCO, 30), 146 (65), 117 (100), 116 (85), 115 (80); HRMS calcd for $C_{12}H_{15}NO$ 189.1154, found 189.1147 ± 0.0019.

1-Cinnamyl-4-(1-hydroxy-1-methyl-1-ethyl)-1,2-diazetidin-3-one (7b). LDA was used as base; after addition of acetone, the mixture was stirred for 30 min at −78 °C: 17% yield; mp 107–109 °C; IR (Nujol) 3495, 3170, 1755 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30 (m, 5 H, Ar H), 6.59 (d, 2 H, J = 16 Hz, C=CH), 6.20 (dt, 1 H, J = 16.6 Hz, C=CH), 3.80 (s, 1 H, C_4-H), 3.55 (m, 2 H, NCH_2), 2.52 (br s, 1 H, NH), 1.34 and 1.27 (each s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 168.3 (s), 136.3 (s), 134.8 (d), 128.5 (d), 127.9 (d), 126.4 (d), 123.9 (d), 86.6 (d), 69.5 (s), 63.5 (t), 27.2 (q), 24.3 (q); LRMS, m/e (relative intensity) 203 (M^+ − HNCO, 15), 185 (50), 117 (100), 116 (40), 115 (80).

Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.29; H, 7.37; N, 11.37. Found: C, 67.98; H, 7.45; N, 11.15.

Cinnamaldehyde Imine of 2-Amino-2-cyanopropane (8). The attempted methylation of **4c** was carried out by using similar reaction conditions as described above for the alkylation of **4b**. LDA was used as base; after addition of methyl iodide, the mixture was stirred for 12 h at −78 °C, and the reaction was then worked up as described above for C-4 alkylations of **4b**: 38% yield. IR (neat) 2230, 1675, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.34 (d, 1 H, J = 8 Hz), 7.45 (m, 5 H), 7.17 (d, 1 H, J = 16 Hz), 6.84 (dd, 1 H, J = 16, 8 Hz), 1.62 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 160.6 (d), 144.1 (d), 135.1 (s), 129.5 (d), 128.7 (d), 127.3 (d), 126.7 (d), 120.5 (s), 58.8 (s), 29.0 (q); LRMS, m/e (relative intensity) 198 (M^+, 20), 183 (5), 130 (100), 115 (50); HRMS calcd for $C_{13}H_{14}N_2$ 198.1157, found 198.1150 ± 0.002.

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Registry No. **1c**, 92184-69-5; **2b**, 79289-51-3; **2c**, 92184-71-9; **3a**, 92184-49-1; **3b**, 92184-50-4; **3c**, 92184-51-5; **3d**, 92184-52-6; **3e**,

92184-53-7; **3f**, 92184-54-8; **3g**, 92184-55-9; **3h**, 80351-01-5; **3i**, 92184-56-0; **3j**, 92184-57-1; **4a**, 89773-80-8; **4b**, 79559-06-1; **4c**, 92184-58-2; **4d**, 92184-59-3; **4e**, 92184-60-6; **4f**, 92184-61-7; **5e**, 92184-62-8; **5f**, 80351-04-8; **5g**, 92184-63-9; **5h**, 80351-05-9; **5i**, 89773-81-9; **5j**, 92184-64-0; **6f**, 80351-06-0; **6h**, 80351-07-1; (*R**,*R**)-**7a**, 92184-72-0; (*R**,*S**)-**7a**, 92184-65-1; **7b**, 92184-66-2; **8**, 92184-67-3; $ClCOCHClCH_2CH_3$, 7623-11-2; $(C_6H_5)_2C{=}NNH_2$, 5350-57-2; $(C_6H_5)_2C{=}NNHCOCHClCH_2CH_3$, 92184-68-4; $C_6H_5CH{=}CHCHO$, 104-55-2; $C_6H_5CH{=}CHCOCH_3$, 122-57-6; CH_3I, 74-88-4; CH_3CH_2I, 75-03-6; CH_3CHO, 75-07-0; $(CH_3)_2CO$, 67-64-1.

Synthesis of [1]Benzopyrano[3,4-*d*]isoxazol-4-ones from 2-Substituted Chromone-3-carboxylic Esters. A Reinvestigation of the Reaction of 3-Acyl-4-hydroxycoumarins with Hydroxylamine. Synthesis of 4-(2-Hydroxybenzoyl)isoxazol-5-ones

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A convenient method for the synthesis of ethyl 2-substituted chromone-3-carboxylates by the condensation of *o*-acetoxyaroyl chlorides with β-keto esters is described. These chromones are converted into the corresponding 4*H*-[1]benzopyrano[3,4-*d*]isoxazol-4-ones (**7**) by treatment with hydroxylamine. The previously reported synthesis of the fused isoxazole **7b** from 3-acetyl-4-hydroxycoumarin with the same reagent is shown to be in error. Instead of the reported compound **7b**, the products obtained appear to be a mixture of 4-(2-hydroxybenzoyl)-3-methylisoxazol-5(4*H*)-one (**11a**) as the main product and 4-methyl-3*H*-[1]benzopyrano[4,3-*c*]isoxazol-3-one (**12a**). Chemical evidence is presented in support of their structures. The **11a**:**12a** ratio can be affected by varying the reaction conditions. By using a 1/1.2/2 molar ratio of 3-acyl-4-hydroxycoumarins (**9**), hydroxylamine hydrochloride, and potassium acetate, respectively, a series of compounds **11** was obtained in good yields.

The use of chromone derivatives to synthesize heterocyclic systems via a ring opening and ring closure sequence with appropriate nucleophiles is well-known.[1-6] There have been however only few applications using 4-oxo-4*H*-[1]benzopyran-3-carboxylic acids (**1**) or their esters (**2**).[7-9] Recently, we reported their conversion to 4-oxo-1*H*-[1]benzopyrano[4,3-*c*]pyrazoles with phenylhydrazine.[10,11] Reaction of chromone-3-carboxylic acid (**1a**) with hydroxylamine hydrochloride, in refluxing petroleum ether, has been described as yielding the oxazepine (**3**) via a Beckmann rearrangement (Scheme I).[12]

However, structure **3** was not established with certainty and remained open to question, since we noted the lack of molecular ion $C_{10}H_7NO_4$ (205.2) and a surprising fragmentation pattern in the mass spectrum: *m/e* 161 ($M - CO_2$), 134, 121, 105, 93. It seemed more logical to us that the nucleophile nitrogen would attack at the C-2 position of the chromone rather than at the C-4. We therefore synthesized a series of ethyl 4-oxo-4*H*-[1]benzopyran-3-carboxylate derivatives (**2**) with a view to obtaining fused isoxazole derivatives by reacting with hydroxylamine. We also prepared the known acids **1a**,**b** in order to see whether the 3-ethoxycarbonyl or 3-carboxy substituent have an influence on the structure of the reaction products.

Scheme I

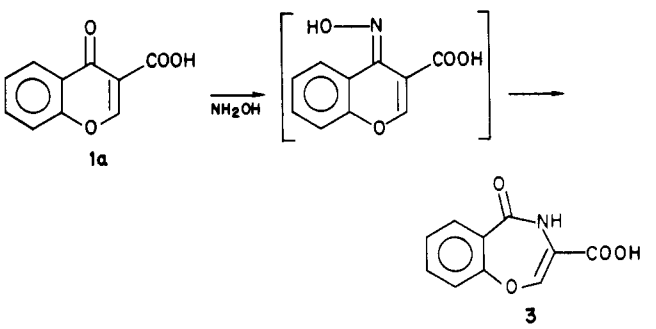

Table I. Ethyl 4-Oxo-4*H*-[1]benzopyran-3-carboxylates 2

compd	% yield	mp, °C (solvent), or bp (mmHg)	mol form or lit. mp, °C
2b	84	68 (EtOAc)	63–65[15,16]
2c	75	157–167 (0.1)	oil[16]
2d	66	86–87 (EtOAc/hexane 3:7)	88–91[16]
2e	60	102–103 (EtOH)	$C_{13}H_{11}ClO_4$
2f	60	93–94 (EtOAc/hexane 1:9)	$C_{14}H_{14}O_4$

A. Reaction of Hydroxylamine with Chromone-3-carboxylic Acids (1). Treatment of **1a**,**b** with hydroxylamine gave the isoxazoles (**4a**,**b**). The reaction proceeded by nucleophilic attack at the C-2 position of the chromone followed by decarboxylation and isoxazole cyclization

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