of the high concentration myoglobin inhibits the reduction of cyt c_{ox}. Thus, it appears that high concentrations of myoglobin block reduction, presumably due to surface adsorption. Stellacyanin at 0.12 mM, that is even reducible at Pt electrodes, can be reduced with H_2 using the glass/$[(PQ^{2+}\cdot Pt(0)\cdot 2Cl^-)_n]_{surf}$ catalyst. The rate is at least as good as with cyt c_{ox} at the same concentration and conditions, and we observe no complications from surface adsorption.

We have illustrated the principles of a heterogeneous catalyst for the reduction of biological molecules using H_2 as the reductant.[18] Additional applications of the catalyst are presently being elaborated in these laboratories.

Acknowledgment. N.S.L. acknowledges support as a John and Fannie Hertz Fellow, 1977–1981. D.C.B. acknowledges partial support as an M.I.T. NPW Fellow, 1981. Partial support from the United States Department of Energy, Basic Energy Sciences, Division of Chemical Sciences, is acknowledged. We appreciate the generous assistance of Professor Edward I. Solomon and his research group and the use of their purified stellacyanin. Helpful discussions with Professors William H. Orme-Johnson, Alexander Klibanov, and George M. Whitesides are gratefully acknowledged.

(16) Sperm whale myoglobin was obtained from Sigma Chemical Co. as their Type II material and reduction was monitored at pH 7.0 buffered with phosphate buffer in 1.0 M KCl under 1 atm of H_2. The ~450–700-nm region of the optical absorption was monitored as described in ref 13. The oxidized form shows absorption maxima at 503 (ϵ ~9000) and 634 nm (ϵ ~3670), and the reduced form shows a peak at 555 nm (ϵ ~11 700). There are four isosbestic points at 463, 521, 612, and 660 nm just as when $S_2O_4^{2-}$ is used as a reductant. Our measured extinction coefficients are within 5% of those given above from the literature: Ray, D. K.; Gurd, F. R. N. *J. Biol. Chem.* **1967**, *242*, 206. Willick, G. E.; Schonbaum, G. R.; Kay, C. M. *Biochemistry* **1969**, *8*, 3729.

(17) Purified stellacyanin from the lacquer of *Rhus vernicifera* was generously provided by Professor Edward I. Solomon. Reduction of the stellacyanin results in the decline of the visible feature at 604 nm (ϵ 4030). Exposure of reduced material to O_2 in air regenerates the 604-nm feature. The stellacyanin was studied at 0.12 mM in 0.2 M phosphate buffer, pH 7.0. Purity was established by the ratio of 604 to 280-nm absorption, 1–5.6, as in the literature: Reinhammas, B. *Biochem. Biophys. Acta* **1970**, *205*, 35.

(18) An important control experiment using naked, clean, smooth Pt as a heterogeneous catalyst shows that ~50 μM concentrations of cyt c_{ox} are reducible at a rate approaching that of our catalyst but at high concentration; ~1 mM naked Pt does not work whereas our catalyst does work as well as at 50 μM. Myoglobin is not reducible (<5% in 1 h) using naked Pt. Stellacyanin is reducible using the naked Pt as expected from electrochemical experiments using a Pt electrode. However, using Pt alone in any situation may lead to hydrogenation and hydrogenolysis reactions unrelated (and undetected by optical methods) to the redox reactions.

Formation of Monocyclic and Bicyclic Aza-β-lactams and Other Novel Heterocycles from 1-(Diphenylmethylene)-3-oxo-1,2-diazetidinium Inner Salt[1]

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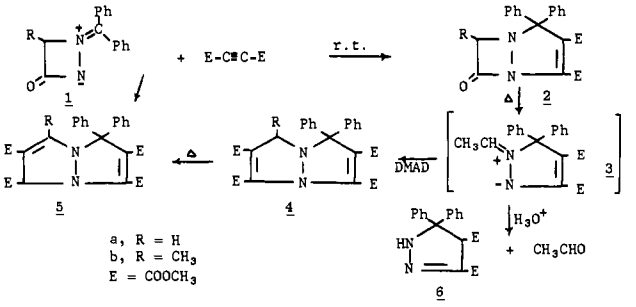
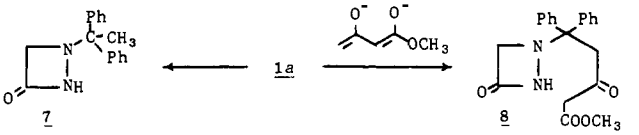
Several years ago we described the intramolecular dehydrohalogenation of the α-chloroacyl hydrazones of diaryl ketones to give 1-(diarylmethylene)-3-oxo-1,2-diazetidinium inner salts (e.g., **1**).[2] We now report some reactions of these readily accessible azomethine ylides which provide novel entries into a variety of heterocyclic systems, including monocyclic and bicyclic aza-β-lactams.[3]

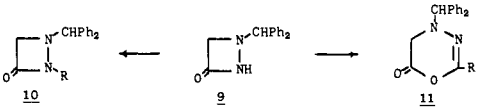
Scheme I



Scheme II



Scheme III



R	mp, °C	Yield, %
a, $COC(CH_3)_3$	112–113	78
b, CH_3	131–132	72
c, CH_2CH_3	75–77	91
d, CH_2Ph	98–100	37
e, $CH(CH_3)_2$	119–121	84
f, CH_2COOH	136–138	41
g, Ph	114	70
h, CH_2CH_2COOH	oil	46

R	mp, °C	Yield, %
a, CH_3	109–112	75
b, Ph	203–204	76
c, OCH_2Ph	113–114	74
d, NHC_6H_4-CH_3-p	158–159	67

Reaction of **1a** with dimethyl acetylenedicarboxylate (DMAD) in methylene chloride at 100 °C gives **4a** (a 2:1 cycloadduct with loss of CO), mp 135.2–136 °C (90%), which isomerizes upon melting to **5a**, mp 117.4–117.5 °C (98%). The course of this transformation was elucidated by examining the reaction of **1b** with DMAD. After 5 days at room temperature, a 1:1 cycloadduct (**2b**) was obtained as yellow crystals, mp 138 °C (56%, IR 1840 cm^{-1}). This compound loses CO upon warming to 70 °C; the ylide **3b** is a possible intermediate, since hydrolysis with dilute hydrochloric acid gives acetaldehyde (isolated as its 2,4-DNP) and 5,5-diphenyl-3,4-bis(carbomethoxy)-Δ^2-pyrazolidine (**6**)[4] (60%), and reaction with additional DMAD gives **5b**, mp 127–128 °C (80%).

Certain organometallic reagents add to the iminium bond of **1a**, providing 1-substituted 1,2-diazetidin-3-ones. Thus, reaction of **1a** with methylmagnesium bromide gives 1-(1,1-diphenylethyl)-1,2-diazetidin-3-one (**7**) as a gum (61%), and addition of the dianion of methyl acetoacetate to **1a** gives **8**, mp 123–125 °C (51%).

We reported previously[5] that selective reduction of the iminium bond in **1a** to give 1-benzhydryl-1,2-diazetidin-3-one (**9**), mp 173–174 °C (99%), could be effected by treatment with a stoichiometric amount of sodium borohydride in methanol. We now report that **9** undergoes a remarkable series of substitution and ring-expansion reactions. Thus, treatment of **9** with pivaloyl chloride in the presence of triethylamine results in the formation of the 2-pivaloyl derivative **10a**. Reaction of **9** with acetic anhydride, however, leads to ring expansion with the exclusive formation of 4-benzhydryl-2-methyl-4,5-dihydro-1,3,4-oxadiaz-

(1) We are indebted for partial support of this work to Eli Lilly and Company and the National Science Foundation (Grant CHE-7918676). Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) (a) Greenwald, R. B.; Taylor, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 5272–5273. (b) Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.*, in press.

(3) Satisfactory microanalytical and/or high-resolution mass spectral data were obtained for all new compounds reported. Yields are not optimized.

(4) van Alphen, J. *Recl. Trav. Chim. Pays-Bays* **1943**, *62*, 210–214.

(5) Greenwald, R. B.; Taylor, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 5273–5274.

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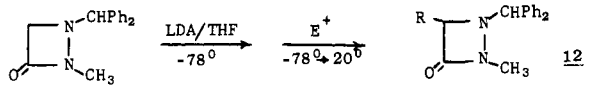
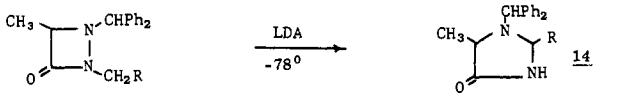
Scheme IV



	R	mp, °C	Yield, %
a,	CH_3	138–140	79
b,	$CHOHCH_3$	146–148	50
c,	CHOHPh	199–199.5	80
d,	$COOC_2H_5$	oil	70

Scheme V



	R	mp, °C	Yield, %
12a (R = H)	a, H	148–149	61
13a (R = CH_3)	b, CH_3	173.5–174	61
13b (R = Ph)	c, Ph	168–170	77

in-6-one (**11a**). Similarly, treatment of **9** with benzoyl chloride or benzyl chloroformate[6] in the presence of 2,6-lutidine gives **11b** and **11c**, respectively. Condensation of **9** with *p*-tolyl isocyanate leads directly to 4-benzhydryl-4,5-dihydro-2-(4-methylanilino)-1,3,4-oxadiazin-6-one (**11d**).

N-2 substituted derivatives (**10b–f**) of **9** are readily obtained either by reaction of the thallium(I) salt of **9** with an excess of the appropriate alkyl halide or preferably by reaction of the corresponding lithium salt of **9** (formed with *n*-butyllithium at −78 °C in anhydrous THF) with 1 equiv of the alkyl halide in the presence of 1 equiv of hexamethylphosphoric triamide. Treatment of the sodium salt of **9** (generated with NaH in DMF at 20 °C) with diphenyliodonium chloride provides the N-2 phenyl derivative **10g**. The Michael adduct **10h** is best prepared by addition of a catalytic amount of NaH to a solution of **9** and methyl acrylate in THF.

1-Benzhydryl-2-methyl-1,2-diazetidin-3-one (**10b**) can be readily substituted at C-4 by deprotonation with LDA in anhydrous THF at −78 °C, followed by addition of 1 equiv of methyl iodide (to give **12a**),[7] acetaldehyde or benzaldehyde (to give **12b** and **12c** respectively),[8] or ethyl chloroformate (to give **12d**). Remarkably, addition of 1 equiv of LDA to a solution of **12a** in anhydrous THF at −78 °C brings about *instantaneous ring expansion* to 1-benzhydryl-5-methylimidazolidin-4-one (**14a**); analogous ring expansions are observed with **13a** and **13b**, giving **14b** and **14c**, respectively. In each case the methylene group adjacent to N-2 is incorporated into the 2-position of the imidazolidinone ring. The extraordinary ease with which this reaction takes place is probably due to formation of a dipole-stabilized anion[10] derived from deprotonation of the methylene group attached to N-2; no deprotonation at C-4 or the benzhydryl methine position appears to take place, since no deuterium incorporation results from a D_2O quench of the reaction mixture. It is not known whether N–N bond cleavage is homolytic or heterolytic, but experiments are in progress to establish this point.

Since hydrolysis of these cyclic animals (e.g., **14**) gives aldehydes derived from the primary alkyl halides employed for N-2 alkylation of the precursor diazetidinone, this sequence of mild reactions holds promise as a general method for effecting the conversion of RCH_2X to RCHO.

(6) This ring expansion can also be carried out by treatment of the lithium salt of **9** with benzyl chloroformate at −78 °C for 2 min.

(7) This compound was prepared independently by sodium borohydride reduction of **1b**, followed by alkylation with methyl iodide.

(8) The aldehyde adducts **12b** and **12c** are formed as diastereomeric mixtures. A single recrystallization of **12b** (shrinks at 140 °C, mp 146–148 °C) failed to separate the diastereomers, while recrystallization of crude **12c** resulted in separation of the major diastereomer, mp 199–199.5 °C, in 80% yield.

(9) Yields of recrystallized analytically pure material. Crude yields appear (IR, TLC) to be quantitative.

(10) See: Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275–316.

3-Oxo-1,2-diazetidinium Tosylate[1]

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We describe in this communication the preparation of the novel small-ring heterocycle 3-oxo-1,2-diazetidinium tosylate (**2**) and our preliminary investigations of its utility for the preparation of several prototype fused aza-β-lactams, pyrazoles, and 4,5-dihydro-1,3,4-oxadiazin-6-ones.[2]

Stirring a solution of 1-(diphenylmethylene)-3-oxo-1,2-diazetidinium inner salt[3] (**1a**) with exactly 1 equiv of *p*-toluenesulfonic acid monohydrate in dry dichloromethane for 1 h at room temperature results in the separation of 3-oxo-1,2-diazetidinium tosylate (**2**), mp 147–149 °C dec (90%; IR 1820 cm^{-1}). Treatment of **2** with aromatic aldehydes in the presence of sodium bicarbonate in DMF or with ketones in the presence of sodium bicarbonate and activated 3-Å molecular sieves effects reconversion to azomethine ylides (**1b–j**). Aromatic aldehydes give only the *Z* isomers **1b–e**, while ketones invariably give mixtures of both possible stereoisomers. The isomers of ylide **1f** were separated by semipreparative HPLC and found to isomerize very slowly upon standing in chloroform at room temperature.

No analogous azomethine ylide is isolated from the reaction of **2** with pivaldehyde; instead, the dimer **3**, mp 260–262 °C (20%), is formed.[4,5] Treatment of ylide **1b** with $BF_3{\cdot}Et_2O$ or *p*-toluenesulfonic acid monohydrate provides a different type of dimer **4**, mp 139–140 °C (19%), which we suggest may be formed as depicted below.

Addition of methylmagnesium bromide to the azomethine ylides **1i,j** gives, after purification by column chromatography, 1-substituted 1,2-diazetidinones (**5a,b**) as colorless gums. Although crystalline 1-substituted 1,2-diazetidinones appear to be indefinitely stable, these noncrystalline samples slowly undergo a virtually quantitative transformation to eight-membered-ring dimers (**6a,b**).

The azomethine ylides **1b–d** react smoothly at 20 °C with 1-pyrrolidinocyclopentene to afford excellent yields of adducts **7**. The potential of this remarkably simple ring annulation for the construction of highly strained aza analogues of the β-lactam antibiotics is under active investigation.

3-Oxo-1,2-diazetidinium tosylate (**2**) can also be employed for the synthesis of heterocycles no longer containing the aza-β-lactam ring. Thus, reaction of **2** with acetylacetone in methanol at room temperature gives the methyl ester of 3,5-dimethylpyrazole-1-acetic acid (**9**), mp 36–37 °C (41%).[6] Ylide **8**, prepared independently by condensation of **2** with acetylacetone in DMF in the presence of sodium bicarbonate, is also smoothly converted to **9** (70%) with

(1) This work was supported in part by grants to Princeton University from Eli Lilly & Company and the National Science Foundation (Grant CHE-7918676). Acknowledgment is also made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) Structural assignments for all new compounds reported are supported by microanalytical and/or mass spectral, IR, and NMR data. We are indebted to Mary Baum of this department for invaluable aid in the determination and interpretation of the ^1H and ^{13}C NMR spectra.

(3) (a) Greenwald, R. B.; Taylor, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 5272–5273. (b) Taylor, E. C.; Haley, N. F.; Clemens, R. J. *J. Am. Chem. Soc.*, in press.

(4) Although dimer **3** has four chiral centers, the simple nature of its ^1H NMR spectrum [($CDCl_3$) δ 5.06 (2 H, d, *J* = 14Hz), 4.23 (2 H, d, *J* = 14Hz), 3.65 (2 H, s), 1.15 (18 H, s)] and ^{13}C NMR spectrum (δ 164.6, 79.0, 63.1, 37.5, 28.1) suggests that only one centrosymmetric diastereoisomer of **3** is formed.

(5) Azomethine imine ylides derived from aliphatic aldehydes are known to dimerize. See: Dorn, H.; Otto, A. *Chem. Ber.* **1968**, *101*, 3287–3301. Grashey, R.; Huisgen, R.; Sun, K. K.; Moriarty, R. M. *J. Org. Chem.* **1965**, *30*, 74–79.

(6) We are indebted to Professor Eldon H. Sund, on leave from Midwestern State University, Wichita Falls, TX, for carrying out this experiment.

(7) Only **10d** was formed under both sets of reaction conditions; no isomerization to **11** was observed.

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