Upon completion of the addition, the reaction was allowed to proceed at 6–10 °C for 4 h with stirring; during the entire reaction time the apparent pH of the mixture was monitored and kept constant at pH 7.5–8 (0.5 N KOH, Metrohom E336A pH-stat).[1] Then, the CH_2Cl_2 layer was separated and the aqueous phase extracted with CH_2Cl_2 (40 mL). The combined methylene chloride extracts were dried ($MgSO_4$) and the solvent (and aceton) removed in vacuo, leaving a residue (2.2 g) containing 18-crown-6 and composed mainly of **5b** and 2,6-diepoxy-3,7-dimethyl-octan-1-ol (**5c**)[20] (^1H NMR analysis). The mixture was treated with Ac_2O/Py, affording acetylation of the alcohols; GLC analysis of the mixture of acetates allowed us to determine percent conversion, yield, and product distribution (Table I, fourth entry). Column chromatography (silica gel, petroleum ether–Et_2O) separation of the mixture afforded 0.7 g of 2,6-diepoxy-3,7-dimethyl-octan-1-ol acetate (**5c′**): bp 90–92 °C (0.02 mm); IR (liquid film) 2980, 2940, 1750 (C=O), 1380, 1240, 1125, 1042, 985, 910, 880, 850, 805 cm^{-1}; ^1H NMR (CCl_4, Me_4Si) δ 1.27 (s, 3, C_9H_3), 1.30 (s, 3, $C_{10}H_3$), 1.33 (d, 3 C_8H_3, $J_{6,8}$ = 2.6 Hz), 1.55–1.90 (m, 4, C_4H_2 and C_5H_2), 2.09 (s, 3, $COCH_3$), 2.70 (m, 1, C_6H, $J_{5,6}$ = 5.2 Hz), 3.15 (m, 1, C_2H, X part of ABX system), 4.20 (m, 2, C_1H_2, AB part); ^{13}C NMR (Table II) nicely revealed the sample to be a diastereomeric mixture of enantiomeric couples (2*S*),3(*R*),6(*R*)-, 2(*R*),3(*S*),6(*S*)-**5c′** and 2(*S*),3(*R*),6(*S*)-, 2(*R*),3(*S*),6(*R*)-**5c′**.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 63.46; H, 8.86.

Acknowledgment. Financial support by the Italian National Research Council (CNR, Rome Progetto Finalizatto CFS), the NSF-CNR U.S.–Italy Cooperative Science Program and the NATO Scientific Affairs Committee is gratefully acknowledged. We also thank Professor G. Capozzi (University of Messina, Italy) and Professor O. Sciacovelli (University of Bari) for help in taking and interpreting ^{13}C NMR spectra, R. A. Di Prete (American Hoechst Analytical Research Division) for technical assistance, and Degussa Co. for a gift of Caroat monopersulfate.

Registry No. **2**, 14390-23-9; **2a**, 31821-36-0; **2b**, 31821-35-9; **3**, 6221-49-4; **3a**, 69798-84-1; **3b**, 69853-80-1; **4**, 17320-10-4; **4a**, 50727-96-3; **4b**, 81477-46-5; **5**, 106-24-1; **5a**, 50727-94-1; **5a′**, 50727-95-2; **5b**, 1786-07-8; **5b′**, 37715-31-4; **5c**, 62875-10-9; **5c′** (isomer 1), 81520-62-9; **5c′** (isomer 2), 81520-63-0; potassium caroate, 10058-23-8; acetone, 67-64-1.

(19) Acetone, acting as a catalyst, does not enter the reaction stoichiometry, of course; the reaction rate, however, is proportional to acetone concentration[1,4] and therefore "excess" acetone is used in order to enhance the rate of oxidation.

(20) Prilezhaev, N. *J. Russ. Phys. Chem. Soc.* **1912**, *44*, 581.

Thermal Cycloaddition of 1,3,5-Triazine with Enamines: Regiospecific Pyrimidine Annulation

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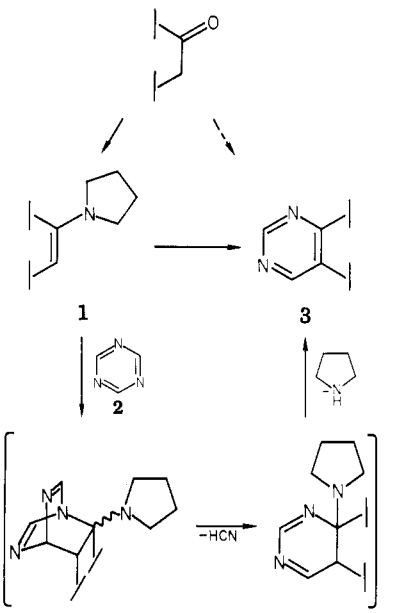
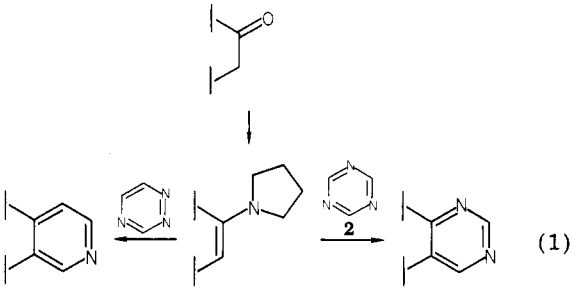
We have recently investigated and described a simple pyridine annulation based on the regiospecific, inverse electron demand cycloaddition reaction of pyrrolidine enamines with 1,2,4-triazine.[2] As a complement to this reaction we became interested in the potential of a related pyrimidine[3] synthesis employing 1,3,5-triazine (**2**)[4] as an electron-deficient diene (eq 1).

Scheme I





(1)

1

A recent study of Neunhoeffer and Bachmann has demonstrated that 1,3,5-triazine (**2**) undergoes a rapid and regiospecific cycloaddition reaction with ynamines, and the subsequent loss of hydrogen cyanide provided a simple pyrimidine synthesis.[5] In addition, Neunhoeffer has shown that a symmetrical enamine, 1-pyrrolidinocyclopentene, participates in a similar cycloaddition reaction with **2** and affords the pyrimidine product **3b** after loss of hydrogen cyanide and pyrrolidine. This demonstrated the potential for 1,3,5-triazine to behave as a dependable, electron-deficient diene and provided the incentive for us to investigate the scope and limitations of its reaction with pyrrolidine enamines 1[3] with the expectation that this process could serve as a useful and *regiospecific* pyrimidine annulation (Scheme I) applicable to our current synthetic studies.

(1) (a) Chicago Community Trust Co./Searle Scholar recipient, 1981–1984. (b) National Institutes of Health Predoctoral Fellow, 1981–1984 (Grant NIH GM 07775).

(2) (a) Boger, D. L.; Panek, J. S. *J. Org. Chem.* **1981**, *46*, 2179. (b) Boger, D. L.; Panek, J. S. *Ibid.* **1982**, *47*, 895.

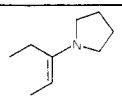
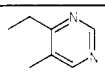
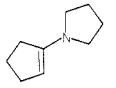
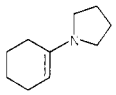
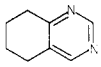
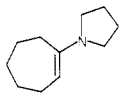
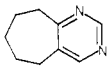
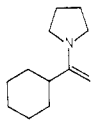
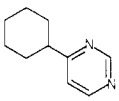
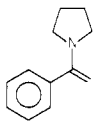
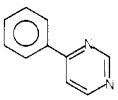
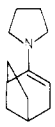
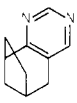
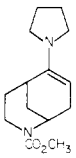
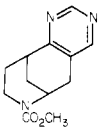
(3) For a summary of conventional pyrimidine synthesis, see: (a) Brown, D. J. "The Chemistry of Heterocyclic Compounds; The Pyrimidines"; Weissberger, A., Ed.; Wiley: New York, 1962; Vol. 16. (b) Amarego, W. L. F. "The Chemistry of Heterocyclic Compounds, Fused Pyrimidines Part I, Quinazolines"; Weissberger, A., Ed.; Wiley: New York, 1967; Vol. 24. (c) Brown, D. J. "The Chemistry of Heterocyclic Compounds, The Pyrimidines"; Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, 1970; Vol. 16, Supplement I.

(4) For a summary of the chemistry of 1,3,5-triazine and its derivatives see: Smolin, E. M.; Rapoport, L. "The Chemistry of Heterocyclic Compounds, *s*-Triazines and Derivatives"; Weissberger, A., Ed.; Wiley: New York, 1959; Vol. 13.

(5) Neunhoeffer, H.; Bachmann, M. *Chem. Ber.* **1975**, *108*, 3877.

0022-3263/82/1947-2673$01.25/0

Table I. Diels-Alder Reaction of 1,3,5-Triazine with Enamines

enamine 1	reaction conditions	product	yield,[a] %
 1a[b]	dioxane, 90 °C (24 h)	 3a	80
 1b	dioxane, 90 °C (5 h) $CHCl_3$, 45 °C (5 h) toluene, 90 °C (5 h)	 3b	72 38 21
 1c	dioxane, 90 °C (48 h)	 3c	47
 1d	dioxane, 90 °C (5 h) dioxane, 90 °C (10 h) dioxane, 90 °C (24 h)	 3d	32 47 76
 1e[c]	dioxane, 90 °C (43 h)	 3e	66
 1f[c]	dioxane, 90 °C (24 h) dioxane, 90 °C (5 h)	 3f	80 23
 1g[b]	dioxane, 90 °C (18 h)	 3g	51[d]
 1h[b]	dioxane, 90 °C (19 h)	 3h	50[d]

[a] Yield of purified product isolated by chromatography (SiO_2). Each pyrimidine exhibited the expected or reported ^1H NMR, IR, and mass spectral chracteristics, and new compounds gave satisfactory C, H, and N analysis (±0.40%) or high-resolution mass spectral data. [b] Prepared by using 4-Å molecular sieves. See: Taguchi, K.; Westheimer, F. H. *J. Org. Chem.* **1971**, *36*, 1570. [c] Prepared with the use of $TiCl_4$. See: White, W. A.; Weingarten, H. *J. Org. Chem.* **1967**, *32*, 213. [d] Yield based on starting ketone.

Table I summarizes the results of this investigation. In each case, pyrimidine formation occurs under unusually mild conditions (45–90 °C), and dioxane was found to be the most effective solvent. No trace of materials derived exclusively from dipolar intermediates could be detected. Complete regiospecificity was observed in cases involving unsymmetrical pyrrolidine enamines: **1a** afforded 4-ethyl-5-methyl-1,3-pyrimidine (**3a**) exclusively, and enamines **1e** and **1f** afforded 4-cyclohexyl- and 4-phenylpyrimidine (**3e,f**), respectively, as the sole reaction products. Our use of this one-step, regiospecific pyrimidine annulation for the preparation of 7-(carbomethoxy)-5,6,7,8,9,10-hexahydro-6,10-methanopyrimido[5,4-*d*]azocine (**3h**), a modified benzomorphan,[6] from enamine **1h** illustrates the ease and effectiveness with which this conversion is capable of being employed.

With modest success, we attempted to reduce this process to a one-flask pyrimidine annulation.[2b] Treatment of a dioxane solution of cyclopentanone with 1,3,5-triazine (**2**, 1.5 equiv) and pyrrolidine (1.0 equiv) in the presence of 4-Å molecular sieves (90 °C, 48 h) afforded 5*H*-6,7-dihydrocyclopentapyrimidine (**3b**) in 36% yield. The instability of 1,3,5-triazine (**2**) toward secondary amines accounts for the low conversion.[4]

Experimental Section

General Procedure for the Diels–Alder Reaction of 1,3,5-Triazine (2) with Enamines. 4-Ethyl-5-methylpyrimidine (3a). A solution of 3-pyrrolidinopent-2-ene (**1a**; 88 mg, 0.63 mmol, 1.20 equiv) in dry dioxane (0.5 mL) was added to 1,3,5-triazine[7] (**2**; 43 mg, 0.53 mmol) under nitrogen (25 °C), and the resulting yellow solution was warmed at 90 °C for 24 h. Chromatography (SiO_2, 9 × 1.25 cm, ether eluant) afforded 51 mg (64 mg theoretical, 80%) of pure **3a** identical in all respects with authentic material:[8] ^1H NMR ($CDCl_3$) 8.86 (1 H, s), 8.29 (1 H, s), 2.68 (2 H, q, J = 7.5 Hz, CH_2Me), 2.18 (1 H, s, Ar CH_3), 1.19 ppm (3 H, t, J = 7.5 Hz, CH_2CH_3); ^{13}C NMR ($CDCl_3$) 169.6, 156.8, 156.7, 128.5, 28.0, 15.3, 11.6; IR (film) ν_{max} 3050, 2985, 2950, 2888, 1575, 1550, 1462, 1394, 1290, 845, 713 cm^{-1}.

5*H*-6,7-Dihydrocyclopenta[*d*]pyrimidine (3b):[5] yield 72% (see Table I); ^1H NMR ($CDCl_3$) 8.96 (1 H, s), 8.51 (1 H, s), 2.92 (4 H, m), 1.74 ppm (2 H, m); IR (film) ν_{max} 2915, 1610, 1530, 1485, 1325 cm^{-1}.

5,6,7,8-Tetrahydroquinazoline (3c):[9] yield 47% (see Table I); ^1H NMR ($CDCl_3$) 8.91 (1 H, s), 8.38 (1 H, s), 2.78 (2 H, m), 2.72 (2 H, m), 2.00–1.61 ppm (4 H, m); IR (film) ν_{max} 2920, 2845, 1605, 1565, 1540, 1432, 1380, 1260, 1095, 815, 714, 698 cm^{-1}.

5*H*-6,7,8,9-Tetrahydrocyclohepta[*d*]pyrimidine (3d):[10] yield 76% (see Table I); ^1H NMR ($CDCl_3$) 8.90 (1 H, s), 8.37 (1 H, s), 2.95 (2 H, m), 2.7 (2 H, m), 1.75 ppm (6 H, m); IR (film) ν_{max} 2960, 2890, 1580, 1560, 1405, 1160, 775, 710 cm^{-1}.

4-Cyclohexylpyrimidine (3e): yield 66% (see Table I); ^1H NMR ($CDCl_3$) 9.11 (1 H, d, J = 1.3 Hz), 8.60 (1 H, d, J = 5.5 Hz), 7.9 (1 H, dd, J = 1.3, 5.5 Hz), 3.10 (1 H, m), 2.05–1.57 ppm (10 H, m); IR (film) ν_{max} 3050, 3022, 2937, 2860, 1575, 1540, 1463, 1445, 1380, 1288, 1000, 962, 810, 760 cm^{-1}; mass spectrum, m/e (relative intensity) 162 (M^+, 11), 161 (14), 147 (6), 134 (8), 133 (44), 121 (17), 119 (18), 108 (16), 107 (base), 106 (10), 94 (49), 80 (11), 52 (17). Anal. Calcd for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.40; H, 9.10; N, 16.98.

4-Phenylpyrimidine (3f):[11a] yield 80% (see Table I); ^1H NMR ($CDCl_3$) 9.25 (1 H, d, J = 1.4 Hz), 8.73 (1 H, d, J = 5.5 Hz), 8.14–8.02 (2 H, m), 7.67 (1 H, dd, J = 1.4, 5.5 Hz), 7.63–7.43 (3 H, m); ^{13}C NMR ($CDCl_3$) 163.9, 159.2, 157.5, 136.6, 131.1, 129.0, 127.2, 117.0 ppm.[11b]

Pyrimidine (3g): yield 51% (see Table I); ^1H NMR ($CDCl_3$) 8.87 (s, 1 H), 8.36 (s, 1 H), 3.25–3.00 (m, 1 H), 2.95–2.35 (m, 2 H), 2.2–1.15 ppm (m, 6 H); IR (film) ν_{max} 2970, 2880, 1580, 1555, 1450, 1395 cm^{-1}; mass spectrum, m/e (relative intensity) 160 (M^+, base), 159 (27), 145 (17), 132 (29), 131 (36). Anal. Calcd for $C_{10}H_{12}N_2$: C, 74.97; H, 7.55; N, 17.48. Found: C, 74.59; H, 7.80; N, 17.10.

7-(Carbomethoxy)-5,6,7,8,9,10-hexahydro-6,10-methanopyrimido[5,4-*d*]azocine (3h): yield 50% (see Table I); ^1H NMR ($CDCl_3$) 8.92 (s, 1 H), 8.37 (s, 1 H), 4.95–4.60 (m, 1 H, C_6 H), 4.05–1.58 (m, 9 H), 3.70 ppm (s, 3 H); IR ($CHCl_3$) ν_{max} 3010, 2965,

(6) For a recent review on benzomorphans, see: Palmer, D. C.; Strauss, M. J. *Chem. Rev.* **1977**, *77*, 1. For recent related studies see: Bosch, J.; Bonjoch, J. *J. Org. Chem.* **1981**, *46*, 1538.
(7) Commercially available from Aldrich Chemical Co.
(8) Authentic **3a** was prepared as described: Koyama, T.; Hirota, T.; Bashou, C.; Satoh, Y.; Watanabe, Y.; Matsumoto, S.; Shinohara, Y.; Ohmoro, S.; Yamato, M. *Chem. Pharm. Bull.* **1975**, *23*, 2158.
(9) Wagner, R. M.; Jutz, C. *Chem. Ber.* **1971**, *104*, 2975.
(10) Breitmaier, E. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 268.
(11) (a) Identical in all respects with commercial material available from Aldrich Chemical Co. (b) "Sadtler Standard Carbon-13 NMR Spectra", 1979; Vol. 36, 7114C.

2885, 1690, 1584, 1562, 1452, 1405, 1380, 1302, 1285, 1225, 1112, 1060 cm^{-1}; mass spectrum, *m/e* (relative intensity) 233 (M^+, 86), 232 (4), 157 (11), 145 (43), 133 (24), 132 (base), 131 (50), 129 (22), 119 (22); high-resolution mass spectrum, *m/e* 233.1168 ($C_{12}H_{15}N_3O_2$ requires 233.1163).

Acknowledgment. This work was assisted financially by a grant from the Anna Fuller Fund, a Biomedical Research Grant (RR 5606), the University of Kansas (General Research Allocation No. 3783-XO-0705), the Chicago Community Trust Co./Searle Scholars Program, and the National Institute of Health (Grant NIH-NIDA DA03153-01). We are grateful to the Research Corp. and the donors of the Petroleum Research Fund,administered by the American Chemical Society, for funds used in the purchase of equipment.

Registry No. **1a**, 13750-57-7; **1b**, 7148-07-4; **1c**, 1125-99-1; **1d**, 14092-11-6; **1e**, 76833-14-2; **1f**, 3433-56-5; **1g**, 41455-22-5; **1h**, 81572-08-9; **2**, 290-87-9; **3a**, 57562-55-7; **3b**, 5661-00-7; **3c**, 5632-33-7; **3d**, 4436-63-9; **3e**, 81572-09-0; **3f**, 3438-48-0; **3g**, 81572-10-3; **3h**, 81572-11-4.

Attempted Cyclization of an Epoxide. Elimination of an Epoxide

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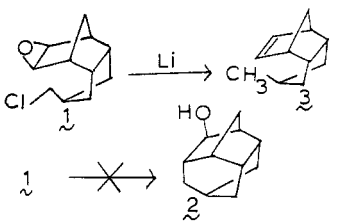
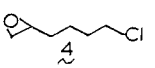
Received July 27, 1981

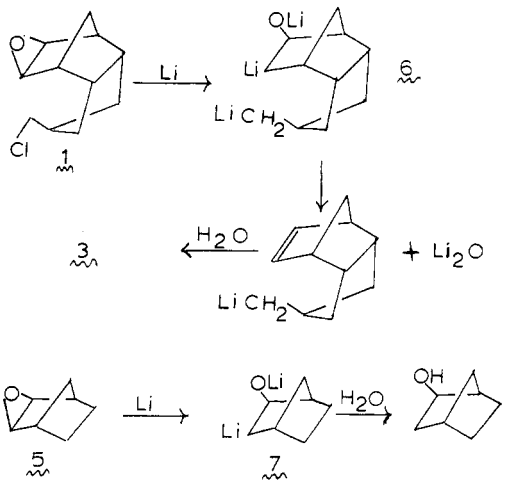
The cyclization of halo epoxides treated with lithium has been reported previously.[1,2] We attempted the transformation of chloro epoxide **1** into tetracyclic alcohol **2** using an analogous procedure. However, tetracyclic alcohol **2** was prepared in only 3% yield (GLC). The major product, found in 60% yield (GLC), was *endo*-4-methyl-*syn*-tricyclo[5.2.1.0^{2,6}]dec-8-ene (**3**).



Perhaps there are steric interactions between the methylene group and the hydrogens of the epoxide ring so that cyclization is slowed. Other reactions then take place. To examine further the geometric requirements for ring closure to occur, we reacted the chloro epoxide derivative of a straight-chain hydrocarbon with lithium. 1,2-Epoxy-6-chlorohexane (**4**) was reacted with lithium in



Scheme I



tetrahydrofuran. GLC examination of the products showed a complex mixture of 15 different compounds. None was present as a major component. There was no cyclohexanol or cyclopentylmethanol produced, which would have been the expected cyclization products. Clearly, for cyclization to occur there are very severe restrictions on the geometry of the chloro epoxide.

We investigated whether the chloromethylene group must be present for reductive epoxide removal to occur. 2,3-Epoxynorbornane (**5**) was treated with lithium to yield 60% *exo*-norborneol and 1% norbornene (GLC). It was recognized that lithium chloride was generated when chloro epoxide **1** was treated with lithium. It had been previously reported that a mixture of magnesium amalgam and magnesium bromide led to reductive eliminations of epoxides.[3] We wanted to see if lithium mixed with lithium chloride was responsible for the elimination occurring in the reaction of **1** with lithium. Consequently, we treated **5** with lithium in tetrahydrofuran containing lithium chloride in a 1:2.5 molar ratio of epoxide to halide. This led to a 64% yield of *exo*-norborneol and 3% of norbornene (GLC). The presence of lithium chloride is not leading to elimination.

For elimination to occur in major amounts, the chloromethyl group must be present. A reasonable mechanism which accounts for the experimental facts is shown in Scheme I. The development of a relatively unstable trianionic intermediate, **6**, where the negative charges repel each other, would trigger an elimination. The major product resulting from the reaction of 2,3-epoxynorbornane with lithium is *exo*-norborneol. In this case dianionic intermediate **7** is produced. Repulsions are less, and the intermediate **7** is sufficiently stable that it does not eliminate and subsequently is protonated to produce an alcohol. Dianionic intermediate **7** is similar to those suggested by Kaiser and co-workers,[4] who studied the reaction of epoxides with alkali metals in liquid ammonia.

The reaction of steroidal epoxides with lithium in ethylamine has been studied.[5] It has been reported for steroidal epoxides that if a hydroxyl group is in the vicinity of the epoxide, substantial reductive elimination takes place. Mechanistic details were not reported in that study. It seems very likely that an elimination occurred for reasons similar to those suggested for halo epoxide **1**. A

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