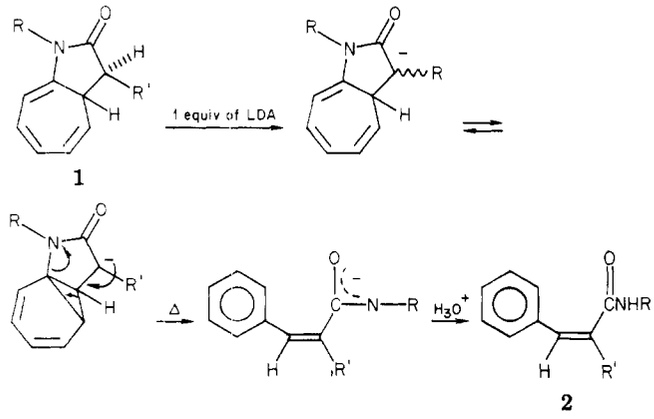
Scheme I



All rearrangement products exhibit a vinylic proton signal at δ 6.57–6.58 except when R′ = phenyl (δ 7.05).

The time and temperature required to effect rearrangement show a dependency on the nature of the group attached to nitrogen. Rearrangement occurs at room temperature when the substituent group is alkyl or mesityl; however, with other aryl substituents on nitrogen, the temperature required to effect complete rearrangement is increased. This may bear some analogy to the π-electron-donor effect on the cycloheptatriene–norcaradiene equilibrium.[6]

The general procedure for rearrangement was as follows. The reaction was carried out in a 50-mL round-bottomed flask equipped with a nitrogen inlet tube, reflux condenser, and a Teflon magnetic stirring bar. The glassware was assembled cold, flame-dried, and allowed to cool under a stream of nitrogen. The ketene–azaheptafulvene cycloadduct (6–8 mmol) was added to the cooled apparatus. DME (15–20 mL, previously dried over sodium ribbon and freshly distilled) was added via syringe and the cycloadduct brought into solution by stirring. This solution was cooled to between −5 and 0 °C with the aid of an ice–salt bath.

Lithium diisopropylamide was prepared in the following manner. To a 50-mL round-bottomed flask equipped with nitrogen inlet tube, rubber stopper, and a Teflon magnetic stirring bar was added 1 equiv of diisopropylamine (previously dried and distilled over sodium ribbon) via syringe. DME (5–10 mL) was added via syringe, and stirring was initiated. The solution was cooled to −5 °C with an ice–salt bath. An equimolar amount of *n*-BuLi/hexane was added via syringe in a dropwise fashion. The solution was then stirred at −5 °C for 45 min.

A double-ended needle was used to transfer the LDA solution dropwise to the original flask containing the cycloadduct. One hour after the addition of LDA, the ice–salt bath was removed, and the reaction mixture was either allowed to warm to room temperature or brought to reflux (depending upon consumption of starting material as monitored by NMR). After quenching with 2% CH_3CO_2H/THF, the reaction mixture was diluted with water (25 mL) and extracted with methylene chloride (2 × 50 mL). The organic extracts were dried ($MgSO_4$), the CH_2Cl_2 was removed in vacuo, and the crude product was purified by column chromatography (silica gel eluted with benzene).

Table I.[a,d] (*Z*)-α-Aryl(or Alkyl)cinnamamides

R	R′ (mp, °C)	% yield[b,c]
$CH_3C_6H_4$	CH_3 (113–114), $C_6H_5CH_2$ (158–160), $(CH_3)_2CH$ (164–166), $(CH_3)_3C$ (170–172), C_6H_5 (189–191.5)	71.0–76.0
$CH_3OC_6H_4$	CH_3 (114–115.5), $C_6H_5CH_2$ (155–157), $(CH_3)_2CH$ (177–179.5), $(CH_3)_3C$ (175–176.5), C_6H_5 (198.5–200)	69.0–86.2
ClC_6H_4	CH_3 (140–141.5), $C_6H_5CH_2$ (173–175), $(CH_3)_2CH$ (169.5–171.5), $(CH_3)_3C$ (174–175.5), C_6H_5 (190–192.5)	70.1–77.0
BrC_6H_4	CH_3 (135–136.5), $C_6H_5CH_2$ (165–167), $(CH_3)_2CH$ (182.5–184), $(CH_3)_3C$ (163–165), C_6H_5 (195–196.5)	68.0–78.0
CH_3	$(CH_3)_3C$ (139–141.5)	86.8
$(CH_3)_3C$	C_6H_5 (152–153.5)	85.7
mesityl	C_6H_5 (179–180.5)	83.7

[a] Reactions carried out in DME. [b] Yields are actual isolated yields. [c] All products were purified by column chromatography. [d] Products were characterized by nuclear, IR, and mass spectroscopic data.

Registry No. 1 (R = $CH_3C_6H_4$; R′ = CH_3), 75234-12-7; 1 (R = $CH_3C_6H_4$; R′ = $C_6H_5CH_2$), 75234-13-8; 1 (R = $CH_3C_6H_4$; R′ = $(CH_3)_2CH$), 75247-64-2; 1 (R = $CH_3C_6H_4$; R′ = $(CH_3)_3C$), 75247-65-3; 1 (R = $CH_3C_6H_4$; R′ = C_6H_5), 62515-90-6; 1 (R = $CH_3OC_6H_4$; R′ = CH_3), 75247-66-4; 1 (R = $CH_3OC_6H_4$; R′ = $C_6H_5CH_2$), 75247-67-5; 1 (R = $CH_3OC_6H_4$; R′ = $(CH_3)_2CH$), 75247-68-6; 1 (R = $CH_3OC_6H_4$; R′ = $(CH_3)_3C$), 75247-69-7; 1 (R = $CH_3OC_6H_4$; R′ = C_6H_5), 62515-89-3; 1 (R = ClC_6H_4; R′ = CH_3), 75247-70-0; 1 (R = ClC_6H_4; R′ = $C_6H_5CH_2$), 75247-71-1; 1 (R = ClC_6H_4; R′ = $(CH_3)_2CH$), 75247-72-2; 1 (R = ClC_6H_4; R′ = $(CH_3)_3C$), 75247-73-3; 1 (R = ClC_6H_4; R′ = C_6H_5), 62515-91-7; 1 (R = Br C_6H_4; R′ = CH_3), 75247-74-4; 1 (R = BrC_6H_4; R′ = $C_6H_5CH_2$), 75247-75-5; 1 (R = BrC_6H_4; R′ = $(CH_3)_2CH$), 75247-76-6; 1 (R = BrC_6H_4; R′ = $(CH_3)_3C$), 75247-77-7; 1 (R = BrC_6H_4; R′ = C_6H_5), 75247-78-8; 1 (R = CH_3; R′ = $(CH_3)_3C$), 75247-79-9; 1 (R = $(CH_3)_3C$; R′ = C_6H_5), 75247-80-2; 1 (R = mesityl; R′ = C_6H_5), 75247-81-3; 2 (R = $CH_3C_6H_4$; R′ = CH_3), 75234-14-9; 2 (R = $CH_3C_6H_4$; R′ = $C_6H_5CH_2$), 75234-15-0; 2 (R = $CH_3C_6H_4$; R′ = $(CH_3)_2CH$), 75234-16-1; 2 (R = $CH_3C_6H_4$; R′ = $(CH_3)_3C$), 75234-17-2; 2 (R = $CH_3C_6H_4$; R′ = C_6H_5), 75234-18-3; 2 (R = $CH_3OC_6H_4$; R′ = CH_3), 75247-82-4; 2 (R = $CH_3OC_6H_4$; R′ = $C_6H_5CH_2$), 75234-15-0; 2 (R = $CH_3OC_6H_4$; R′ = $(CH_3)_2CH$), 75234-19-4; 2 (R = $CH_3OC_6H_4$; R′ = $(CH_3)_3C$), 75234-20-7; 2 (R = $CH_3OC_6H_4$; R′ = C_6H_5), 75247-83-5; 2 (R = ClC_6H_4; R′ = CH_3), 75234-21-8; 2 (R = ClC_6H_4; R′ = $C_6H_5CH_2$), 75234-22-9; 2 (R = ClC_6H_4; R′ = $(CH_3)_2CH$), 75234-23-0; 2 (R = ClC_6H_4; R′ = $(CH_3)_3C$), 75234-24-1; 2 (R = ClC_6H_4; R′ = C_6H_5), 75234-25-2; 2 (R = BrC_6H_4; R′ = CH_3), 75234-26-3; 2 (R = BrC_6H_4; R′ = $C_6H_5CH_2$), 75234-27-4; 2 (R = BrC_6H_4; R′ = $(CH_3)_2CH$), 75247-84-6; 2 (R = BrC_6H_4; R′ = $(CH_3)_3C$), 75247-85-7; 2 (R = BrC_6H_4; R′ = C_6H_5), 75234-28-5; 2 (R = CH_3; R′ = $(CH_3)_3C$), 75234-29-6; 2 (R = $(CH_3)_3C$; R′ = C_6H_5), 75247-86-8; 2 (R = mesityl; R′ = C_6H_5), 75234-30-9.

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Total Synthesis of (−)-Prezizaene and (−)-Prezizanol

Summary: An 18-step total synthesis of the novel zizaane sesquiterpenes, (−)-prezizaene (**1**) and (−)-prezizanol (**2**), from (+)-pulegone is described; the key step of the synthesis is the intramolecular ring expansion of (diazoethyl)hydrindanone **12** to the isomeric methanoperhydroazulenones **13** and **14**.

Sir: The tricyclic sesquiterpene prezizaene was first iso-

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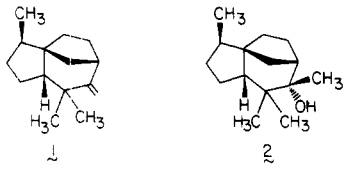
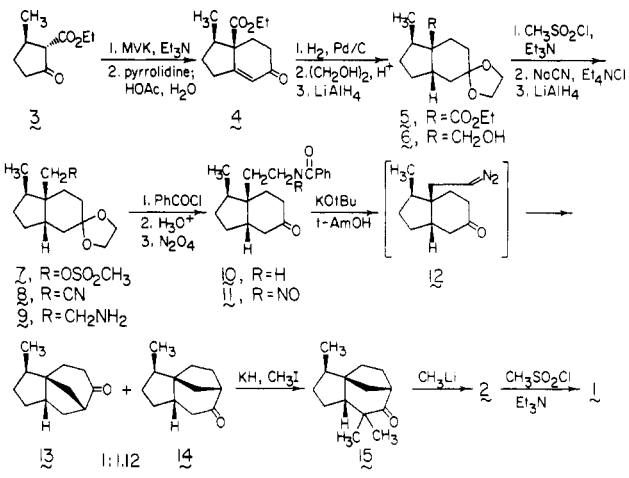
lated as the dextrorotatory isomer by Andersen and Falcone from vetiver oil of Reunion origin (*Vetiveria zizanoides*).[1] The occurrence of (−)-prezizaene (**1**) and (−)-prezizanol (**2**)[2] in a steam volatile fraction from *Eremophilia georgei* was subsequently reported by Carrol, Ghisalberti, and Ralph.[3] The structure of (+)-prezizaene as the enantiomer of **1** was assigned on the basis of spectral data, optical properties, and its acid-catalyzed isomerization to (+)-zizaene.[1,4] We report the first total synthesis of (−)-prezizaene and (−)-prezizanol from (+)-pulegone[5] which serves to confirm the structures of these novel zizaane sesquiterpenes.[6]



The stereospecific construction of the trans-fused ethanohydrindane nucleus was recognized as a crucial problem in the synthesis. We chose to accomplish this indirectly by intramolecular ring expansion of a (diazoethyl)hydrindanone (**12**) having the more accessible cis ring juncture (Scheme I). The preparation of bicyclo[3.2.1]octan-2-one from 4-(2-diazoethyl)cyclohexanone has been reported by Gutsche and co-workers.[7]

β-Keto ester **3**, available in three steps from (+)-pulegone,[8] underwent Michael addition to methyl vinyl ketone (3 equiv, Et_3N, toluene, 25 °C, 7–10 days; 78–93%) and the resulting adduct[9] was cyclized to hydrindenone **4** as a 6:1 mixture of diastereomers via the pyrrolidine dienamine[10] (pyrrolidine, toluene, reflux; H_2O, HOAc, NaOAc, toluene, reflux; 70–80%). The cis stereochemistry was assigned to the major isomer on the assumption that Michael addition would occur preferentially on the cyclopentanone ring opposite to the methyl group. Hydrogenation (5% Pd/C, EtOH, 1 atm, 25 °C) of the isomer mixture gave the hydrindanone ester [86–93%, bp 89–90 °C (0.1 mm); IR (film) 1720, 1710 cm^{-1}] as an 8:1 mixture of two isomers which were presumed to have cis ring junctions.[11] Ketalization (ethylene glycol, *p*-TsOH, toluene, reflux; 90–98%) followed by reduction with lithium aluminum hydride (THF, reflux; 83–87%) provided ketal alcohol **6** which was converted to the crystalline mesylate **7** (mp 85–87 °C; 35–55%) by reaction with methanesulfonyl chloride (CH_2Cl_2, Et_3N, 0 °C). The minor isomer was removed during crystallization and the all cis stereochemistry of the pure mesylate was verified at this point by an X-ray crystallographic structure determination.[12]

Scheme I



Displacement of the hindered mesylate was effected by reaction with 3 equiv of sodium cyanide and 0.2 equiv of tetraethylammonium chloride (Me_2SO, 90 °C, 48 h, then 105 °C, 24 h, 70–77%).[13] Reduction of the resulting nitrile **8** (mp 46–47.5 °C) with lithium aluminum hydride (ether, 25 °C, 30 min; 85–93%) followed by benzoylation (C_6H_5COCl, pyridine, toluene, 70 °C) and hydrolysis (10% HCl, acetone, reflux) afforded keto amide **10** (mp 117–119 °C; 71–80% from **9**). The corresponding *N*-nitroso amide (**11**) was formed by nitrosation with dinitrogen tetroxide (NaOAc, CH_2Cl_2, −30 °C 90–97%)[14] and subjected to reaction with potassium *tert*-butoxide in *tert*-amyl alcohol at 25 °C. The diazoethyl ketone (**12**) presumably generated underwent spontaneous cyclization and rearrangement to a 1:1.12 (GC analysis) mixture of the isomeric ketones **13** [29%; mp 28 °C; $[\alpha]^{25}_D$ −69° (*c* 1.0, $CHCl_3$); IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (d, 3 H, J = 7.5 Hz), 3.02 (br t, 1 H, J = 6 Hz)] and **14** [34%; oil; $[\alpha]^{25}_D$ +115° (*c* 1.0, $CHCl_3$); IR (film) 1710 cm^{-1}; NMR ($CDCl_3$) δ 0.94 (d, 3 H, J = 7.5 Hz), 2.70 (br t, 1 H, J = 7.5 Hz)] which were separated by medium-pressure liquid chromatogra-

(1) N. H. Andersen and M. S. Falcone, *Chem. Ind. (London)*, 62 (1971).

(2) The name 7β-hydroxy-(−)-prezizane has been used for **2**.[3] We have chosen to use (−)-prezizanol since this name is related to (−)-prezizaene in the same manner as zizanoic acid is to zizaene.

(3) P. J. Carrol, E. L. Ghisalberti, and D. E. Ralph, *Phytochemistry*, **15**, 777 (1976).

(4) N. H. Andersen, S. E. Smith, and Y. Ohta, *J. Chem. Soc., Chem. Commun.*, 447 (1973).

(5) (±)-Pulegone has been synthesized from citranellal,[5a] citranellic acid,[5b] and 3-methylcyclohexanone.[5c] Syntheses of (+)-pulegone from citranellal[5a] and citranellic acid[5b] have been reported. The resolution of 3-methylcyclohexanone has been accomplished.[5d] (a) F. Tiemann and R. Schmidt, *Chem. Ber.*, **29**, 903 (1896); *ibid.*, **30**, 22 (1897); (b) W. Kuhn and H. Schinz, *Helv. Chim. Acta*, **36**, 161 (1953); J. C. Bardhan and K. C. Bhattacharyya, *Chem. Ind. (London)*, 800 (1951); (c) C. Black, G. L. Buchanan, and A. W. Jarvie, *J. Chem. Soc.*, 2971 (1956); S. M. Mukherji, R. P. Gandhi, and O. P. Vig, *J. Indian Chem. Soc.*, **33**, 853 (1956); (d) G. Adolphen, E. J. Eisenbraun, G. W. Keen, and P. W. K. Flanagan, *Org. Prep. Proced.*, **2**, 93 (1970), and references cited therein. See also E. J. Eisenbraun, G. H. Adolphen, K. S. Schorno, and R. N. Morris, *J. Org. Chem.*, **36**, 414 (1971).

(6) The formic acid catalyzed cyclization of (+)-β-acoradiene to allocedrol (20%) and the solvolysis of the *p*-bromobenzenesulfonate of allocedrol to (−)-prezizaene (5–15%) have been reported by Tomita and Hirose.[6a] Since β-acordiene[6b] and β-acorenol[6b,c] have been synthesized, a formal synthetic path to (−)-prezizaene may be contrived. However, the two low-yield reactions involving carbonium ion intermediates impart a measure of ambiguity to this formal scheme. (a) B. Tomita and Y. Hirose, *Phytochemistry*, **12**, 1409 (1973); (b) W. Oppolzer, *Helv. Chim. Acta*, **56**, 1812 (1973); (c) I. G. Guest, C. R. Hughes, R. Ramage, and A. Sattar, *J. Chem. Soc., Chem. Commun.*, 526 (1973).

(7) D. M. Bailey, J. E. Bowers, and C. D. Gutsche, *J. Org. Chem.*, **28**, 610 (1963).

(8) (a) J. Wolinsky and D. Chan, *J. Org. Chem.*, **30**, 41 (1965); (b) J. N. Marx and L. R. Norman, *ibid.*, **40**, 1602 (1975).

(9) Satisfactory combustion analyses and compatible IR and NMR spectra were obtained for all new compounds described in this paper. Only key physical and spectral data are actually cited.

(10) C. J. V. Scanio and L. P. Hill, *Synthesis*, 651 (1970).

(11) In the absence of polar substituents on the cyclopentane ring, hydrogenation of hydrindenones of this type affords predominantly the *cis*-hydrindanones. See C. B. C. Boyce and J. S. Whitehurst, *J. Chem. Soc.*, 4547 (1960); W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961); G. Baudin and Y. Pietrasanta, *Tetrahedron*, **29**, 4225 (1973); Y. Inubushi, T. Kikuchi, T. Ibuka, K. Tanaka, I. Suji, and K. Tokane, *Chem. Pharm. Bull. (Tokyo)*, **22**, 349 (1974); Z. G. Hajos and D. R. Parrish, *J. Org. Chem.*, **38**, 3239 (1973); T. C. MacKenzie, *ibid.*, **39**, 629 (1974).

(12) The single-crystal X-ray analysis was carried out by Dr. Eileen Duesler of the X-ray Crystallographic Laboratory, School of Chemical Sciences, University of Illinois. We express our thanks to Dr. Duesler for her able assistance.

(13) In the absence of tetraethylammonium chloride, the yield was 41%. This procedure for formation of tetraethylammonium cyanide in situ is a convenient alternative for cyanide displacement. See G. Simchen and H. Kobler, *Synthesis*, 605 (1975).

(14) E. H. White, *J. Am. Chem. Soc.*, **77**, 6008 (1955).

phy on silica gel.[15] The more polar isomer was identified as the undesired 3a,7-methanoperhydroazulen-6-one (13) by conversion to the α-phenylseleno ketone and selenoxide elimination[16] to the corresponding α,β-unsaturated ketone: NMR ($CDCl_3$) δ 5.84 (dd, 1 H, J = 1.5 and 10 Hz), 6.73 (d, 1 H, J = 10 Hz).

Exhaustive methylation of 14 with potassium hydride and methyl iodide (THF, 25 °C, 1 h; reflux, 4 h)[17] afforded the known norprezizanone 15 (81–93%; oil; $[\alpha]^{25}_D$ +7.6° (c 1.0, $CHCl_3$)), the IR and NMR spectral characteristics of which are in accord with those reported.[3] Reaction of 15 with methyllithium in ether[3] furnished (−)-prezizanol (2) (74–85%; mp 35 °C; $[\alpha]^{25}_D$ −49° (c 1.0, $CHCl_3$)) which exhibited spectra (IR, NMR, and mass spectra), chromatographic mobility (GC and TLC), and specific optical rotation identical with those of an authentic sample of the natural product. Dehydration of (−)-prezizanol to (−)-prezizaene (1) was accomplished with methanesulfonyl chloride and triethylamine (CH_2Cl_2, 0 °C; 62%). The IR and NMR spectra of the synthetic (−)-prezizaene are identical with the corresponding spectra of (+)-prezizaene derived from vetiver oil.

(15) A small amount (~10%) of the vinylhydrindenone was also formed by simple 1,2-hydrogen rearrangement.
(16) H. J. Reich, J. M. Renga, and I. L. Reich, *J. Am. Chem. Soc.*, **97**, 5434 (1975).
(17) A. A. Millard and M. W. Rathke, *J. Org. Chem.*, **43**, 1834 (1978).

Acknowledgment. We thank Professor E. L. Ghisalberti for a generous sample of natural (−)-prezizanol and Professor E. Piers for copies of the IR and NMR spectra of (+)-prezizaene from vetiver oil. This research was supported in part by research grants from the National Science Foundation (No. 07513 and 05287) and the National Institute of General Medical Sciences (GM-13956).

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Additions and Corrections

Vol. 41, 1976

E. G. Breitholle and C. H. Stammer.* Synthesis of Some Dehydrophenylalanine Peptides.

Page 1346. The scheme in the left hand column shows **13** being converted by various reagents into compounds **15**, **16**, **17**, and **18**. **13** should be replaced by **5a**. In the discussion above the scheme starting with "Some further surprising...", **13** should be replaced by **5a** in the remainder of that paragraph. As a consequence of this the four experiments, p 1348, in which **13** is supposedly used to make **15**, **16**, **17**, and **18** are incorrect and **13** should be replaced with **5a**.

Vol. 43, 1978

Stanley J. Cristol,* Robert M. Strom, and Dean P. Stull. Bridged Polycyclic Compounds. 86. Multiple Mechanisms in the Reactions of Some Bridged Alcohols with Triphenylphosphine and Carbon Tetrachloride.

Page 1153, column 2, line 11: **7**-Cl should be **6**-Cl.

Vol. 44, 1979

Friedrich W. Vierhapper and Ernest L. Eliel.* Conformational Analysis. 38. 8-*tert*-Butyl-*trans*-decahydroquinolines: ^{13}C and ^1H Nuclear Magnetic Resonance and Infrared Spectra: The N–H Conformational Equilibrium.

Page 1082, Table I, entry for C–CH_3 for compound **4m**·HCl should read 29.5_8.

Josefina T. Baker and Stylianos Sifniades.* Synthesis and Properties of Pyrrolin-2-ones.

Page 2798. We call attention to a paper by M. Pinza and G. Pifferi, *Il Farmaco, Ed. Sci.*, **33**, 130 (1978), reporting a related synthesis of Δ^3-pyrrolin-2-one.

J. R. Handley,* A. A. Swigar, and R. M. Silverstein. A Route to Keto Acids (or Esters) or to Dicarboxylic Acids (or Esters) from α-Alkylidine Cyclanones.

Page 2954. Corrected Supplementary Material. Compound **5**: NMR ($CDCl_3$) δ 1.47 (3 H, s), 1.64 (3 H, s), 1.76 (3 H, s), 2.38–2.84 (2 H, d of d), 5.10–5.28 (2 H, m), 5.88–6.16 (1 H, m); IR (thin film) 3090 (w), 2980 (w), 2920 (m), 2860 (w), 1790 (s), 1690 (s), 1640 (w), 1410 (w), 1370 (w), 1250 (m), 1185 (m), 1110 (m), 1055 (m), 950 (w), 920 (w) cm^{-1}; mass spectrum, m/e (relative intensity) 39 (17), 41 (33), 42 (24), 43 (15), 44 (38), 53 (12), 55 (18), 67 (20), 68 (32), 69 (20), 70 (100), 71 (10), 81 (15), 95 (25), 96 (10), 109 (37), 123 (12), 124 (14), 151 (4), 166 (40), 167 (4).

Magid Abou-Gharbia and Madeleine M. Joullié.* Cycloadditions of Ketenes with *N*-Fluorenylidenealkylamine and -arylamine Oxides. Synthesis of Spirooxazolidinones and Spiroisoxazolidinones.

Page 2964. Scheme II. Below structures **10** and **9** should read R = alkyl, $R_1 = R_2 = C_6H_5$ (instead of R = alkyl, $R_1 = R_2 = CH_3$).

Jerry A. Hirsch. Conformational Analysis of *N*-Acyl Derivatives of 1-Aza-3-cyclohexanone.

Page 3227. Professor W. A. Szarek has kindly informed me that some of my calculations are in error. Table I should be corrected so that the $\Delta G_c^{\ddagger}$ (kcal/mol) for 1-benzoyl-3-piperidone are 14.11, 13.44, 14.46, 14.23, 14.48, 14.36, 14.34, 13.50, 13.98, 13.73, 13.72, 13.74, 13.60, 13.96, and 13.99, respectively; for 1-acetyl-3-piperidone they are 16.53 and 16.57; for 1-carbomethoxy-3-piperidone they are 14.26, 14.20, and 14.37; for 1-carbomethoxy-3-piperidone they are 14.02, 14.26, 14.28, and 14.31; and for 1-carbobenzoxy-3-piperidone they are 14.14, 14.17, and 14.20. My