required in the final deoxygenation to yield cyclopropenes and cyclobutenes.

In conclusion, the intramolecular reductive coupling of diketones with $TiCl_3$–$LiAlH_4$ is an effective and convenient method for the preparation of moderate amounts of strained, normal, medium and large carbocyclic alkenes.

Experimental Section

3,3-Dimethyl-1,2-diphenylcyclopropene (2). $LiAlH_4$ (MCB) (0.6 g, 16 mmol) was added to 5.7 g (37 mmol) of fresh $TiCl_3$ (Alfra-Ventron) in ~250 mL of dry THF under N_2. The black mixture was heated under reflux for 15 min. Dimethyldibenzoylmethane (1) (2.0 g, 8 mmol) in dry THF (under N_2) was added dropwise over a period of 30 to 60 min. The mixture was heated under reflux for 6 days.[12] The cool reaction mixture was poured into petroleum ether followed by addition of water. The organic layer was separated, washed, and dried. Removal of solvent under reduced pressure yielded 1.5 g of crude product which was purified by column chromatography (alumina/petroleum ether–CH_2Cl_2) to yield 0.8 g of **2** (46%). The oily sample of **2** slowly crystallized upon standing at 4 °C: mp 34–37 °C (lit.[6] mp 43.5–44.0 °C); ^1H NMR ($CDCl_3$) δ 1.50 (s, 6 H) and 7.2–7.7 (m, 10 H); mass spectrum, parent peak 220 (47% of base peak at 205) and a P + 1 of 18.7% consistent with $C_{17}H_{16}$. The UV spectrum was in good agreement with the reported spectrum.[6] The IR spectrum (CCl_4) was identical with that of an authentic sample.[12] Anal. Calcd: C, 92.68; H, 7.32 Found: C, 92.63; H, 7.31.

The procedure described for the preparation of **2** is representative for the cycloalkenes listed in Table I. All compounds gave UV spectra consistent with the structures and showed only one peak on the gas chromatograph (2 m 5% SE 20 column, temperature range 200–240 °C).

3,3-Diethyl-1,2-diphenylcyclopropene (4): ^1H NMR ($CDCl_3$) δ 0.92 (t, 6 H), 2.1 (q, 4 H), 7.1–7.6 (m, 10 H); mass spectrum, parent peak 248 (10% of base peak at 219), P + 1 of 20.8%, peak at 233 (3% of base) consistent with $C_{19}H_{20}$. Anal. Calcd: C, 91.88; H, 8.12. Found: C, 91.80; H, 8.06.

1,2-Diphenylcyclopentene (6): ^1H NMR ($CDCl_3$) δ 2.1 (m, 2 H), 2.9 (t, 4 H), 7.19 (s, 10 H); mass spectrum, base and parent 220. The UV spectrum was in good agreement with the reported spectrum.[14] The ^{13}C NMR spectra (^1H coupled and decoupled) were in excellent agreement with the reported spectra.[15]

1,2-Diphenylcyclooctene (8): mp 74–76 °C (lit.[16] mp 77.5); ^1H NMR ($CDCl_3$) δ 1.5–1.9 (b, 8 H), 2.5–2.9 (b, 4 H), 7.13 (s, 10 H); mass spectrum, parent 262 with P + 1 of 22.2% consistent with $C_{20}H_{22}$. The UV spectrum was in agreement with the published value.[14] Calcd: C, 91.55; H, 9.45. Found: C, 91.29; H, 8.52.

1,2-Diphenylcyclononene (10): mp 42–45 °C; ^1H NMR ($CDCl_3$) δ 1.67 (bs, 10 H), 2.5–2.9 (b, 4 H), 7.13 (s, 10 H); mass spectrum, parent 276 consistent with $C_{21}H_{24}$. Anal. Calcd: C, 91.25; H, 8.75. Found: C, 91.37; H, 8.60.

1,2-Diphenylcyclodecene (12): mp 91–93 °C; ^1H NMR ($CDCl_3$) δ 1.62 (bs, 12 H), 2.5–2.9 (b, 4 H), 7.08 (s, 10 H); mass spectrum, parent 290 with P + 1 of 24.4% consistent with $C_{22}H_{26}$. Anal. Calcd: C, 90.98; H, 9.02. Found: C, 90.88; H, 9.02.

1,2-Diphenylcyclododecene (14): mp 82–84 °C; ^1H NMR ($CDCl_3$) 1.5 (bs, 14 H), 2.3–2.8 (b, 4 H), 7.04 (bs, 10 H); mass spectrum, parent 318 with P + 1 of ~26% consistent with $C_{24}H_{30}$. The ^{13}C NMR ($CDCl_3$, ^1H decoupled) showed a ten-line spectrum consistent with the structure. The stereochemistry was tentatively assigned as cis on the basis of the UV spectrum which was similar to that of **8**. Anal. Calcd: C, 90.51; H, 9.49. Found: C, 90.34; H, 9.58.

The dibenzoylalkanes shown in Table I were prepared in ~50% yield by the Friedel–Crafts acylation[17] of dry benzene ($AlCl_3$ catalyst) with the corresponding diacid chlorides. All the products were recrystallized from methanol and dried. The IR and NMR spectra were consistent with the proposed structures: **1**, mp 95–97 °C;[18] **3**, mp 104–105 °C (lit.[19] mp 104 °C); **5**, mp 60–62 °C (lit.[20] mp 63 °C); **7**, mp 87–89 °C (lit.[21] mp 85 °C); **9**, mp 46–48 °C (lit.[22] mp 44 °C); **11**, mp 90–92 °C (lit.[23] mp 94–96 °C); **13**, mp 94–96 °C (lit.[24] mp 98–99 °C). Contrary to early reports,[18b,19] **1** and **3** have been prepared in moderate yields.[18a] The yields of **1** and **3** were found to be erratic under the present set of conditions and fell in the range of 20–55%.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research and to the Georgia State University Research Fund. The mass spectra were taken at the Georgia Institute of Technology, on an instrument supported in part by NSF.

Registry No.—$TiCl_3$, 7705-07-09; $LiAlH_4$, 16853-85-3.

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(4) No cyclopropenes were isolated from either reaction. A few percent of 1,2,4,5-tetraphenylbenzene was isolated from the attempted reductive coupling of dibenzoylmethane. Tetraphenylbenzene is the formal dehydrogenation product of a dimer of 1,2-diphenylcyclopropene. [See R. Breslow and P. Dowd, *J. Am. Chem. Soc.*, **85**, 2729 (1963), for the dimerization of triphenylcyclopropene and subsequent dehydrogenation to hexaphenylbenzene.] It is not clear if tetraphenylbenzene is the product of unusual reactions of the 1,3-diketone or side reactions of the unstable cyclopropene.
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(12) Note: care must be taken to avoid solvent loss during the prolonged heating period under N_2 or substantial product loss will result. Substitution of 1,2-dimethoxyethane for THF as the solvent decreased the reaction time to 2 days with little or no effect on the yields.
(13) We thank Professor D. R. Arnold of the University of Western Ontario, Canada, for the gracious donation of an authentic sample of 3,3-dimethyl-1,2-diphenylcyclopropene.
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On the Epimerization of 6α-Bromopenicillanic Acid and the Preparation of 6β-Bromopenicillanic Acid

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The epimerization of penicillanic acid derivatives at C-6 (see **1**) has been of considerable interest for some years now, both to organic chemists and to biologists, since only compounds possessing the 6β configuration are biologically active as "penicillins". It has been demonstrated (these points have been recently reviewed by Stoodley[1]) that both the bulk of the 6 substituent and its electronic properties are important to this process, the former dictating the position of the equilibrium and the latter the rate of its achievement. The 6α epimer

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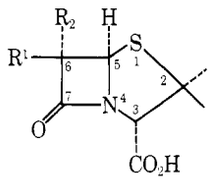
is apparently always the thermodynamically favored species, presumably because of unfavorable steric interactions of 6β substituents with the thiazolidine sulfur cis to them and with the 2β-methyl group. Indeed, in certain cases where very bulky 6 substituents are present, e.g., phthalimidopenicillin[2] and hetacillin,[3] the equilibrium amounts of 6β epimers are not detectable by the usual NMR methods, i.e., presumably ≤1%.

Another well-known case is that of the 6-halopenicillanic acids. The 6-bromo and 6-chloro compounds have been prepared by treatment of 6β-aminopenicillanic acid in the appropriate hydrogen halide solution with sodium nitrite and as prepared both have the 6α configuration, **1a**[5] and **1b**.[6] The former compound has also been obtained, again in the 6α configuration, by partial hydrogenation of 6,6-dibromopenicillanic acid, **1c**.[7]



1a, R_1 = H; R_2 = Br
b, R_1 = H; R_2 = Cl
c, R_1 = R_2 = Br
d, R_1 = Br; R_2 = H

Although certain derivatives have been reported,[8,9] all previous attempts to detect or isolate the parent 6β-halopenicillanic acids have failed.[7,10] Despite this all available data[1] would suggest that 6-halopenicillanic acids should epimerize with moderate ease and probably even in aqueous solution. This is apparently true. Clayton et al.[6] report that although **1a** is recovered unchanged on prolonged exposure to dilute sodium hydroxide, exchange of the 6α-hydrogen with solvent occurs. This suggests equilibration of **1a** with an undetectably (by NMR) small concentration of 6β-bromopenicillanic acid, **1d**.

We report here the preparation of **1d** (as a mixture with **1a**) and present evidence for the existence of a substantial (ca. 12%) amount of **1d** in equilibrium with **1a** in aqueous solution.

The NMR spectrum of a 30 mM solution of **1a** in 20 mM sodium pyrophosphate in H_2O at pH 9.1 (aliquots were freeze–dried and spectra taken in ^2H_2O) maintained at 30 °C changed slowly with time. The initial spectrum was as expected from those reported for **1b**[10] and for **1a** methyl ester:[7] τ (^2H_2O, p^{2}H ca. 9) 8.52 (3 H, s, CH_3), 8.42 (3 H, s, CH_3), 5.71 (1 H, s, 3-H), 4.90 (1 H, d, J = 1.5 Hz, 6-H), and 4.55 (1 H, d, J = 1.5 Hz, 5-H). The magnitude of the coupling constant here, 1.5 Hz, is characteristic of that for a trans configuration between vicinal hydrogens in the β-lactam ring of a penam system.[11] Under the above conditions the following new peaks appear uniformly with time in a first-order manner ($t_{1/2}$ ca. 12 h): τ 8.50 (3 H, s), 8.37 (3 H, s), 5.76 (1 H, s), and 4.44 and 4.39 (2 H, AB quartet, J = 3.7 Hz). Integration indicates that a final (10 half-lives) conversion of 12 ± 2% of **1a** to product has occurred. This product spectrum is readily interpretable as arising from the hitherto unknown **1d**. The coupling constant is as expected for cis β-lactam protons[11] and the chemical shift differences between these resonances and those of **1a** are analogous to those between α- and β-benzylpenicillin.[12] The spectrum is certainly not consistent with those of other likely possibilities, the rearrangement product, 6-bromo-2,3,4,5-tetrahydro-2,2-dimethyl-7-oxo-1,4-thiazepine-3-carboxylic acid,[13] the penicilloate hydrolysis product,[5] or 3,6-dicarboxy-2,2-dimethyl-2,3-dihydro-1,4-thiazine, the rearrangement product of the penicilloate.[5] Reactions producing these species would not likely stop at 12% reaction either, of course.

Incubation of either **1a** or the equilibrium mixture from above in ^2H_2O (p^{2}H ca. 9) for several days at 30 °C yielded spectra essentially identical to the final spectrum above except that the 6-H resonance of the starting material had disappeared and the 5-H resonance had collapsed to a single hydrogen singlet at τ 4.55 and that the AB quartet of the product had collapsed to a single hydrogen singlet at τ 4.40. These observations are consistent with exchange at the C-6 position of **1a** concomitant with epimerization yielding 6-^{2}H-**1d**.

Hydrogenation of **1c** over 10% Pd/C in phosphate buffer at pH 7.5 yielded a product mixture, after uptake of 1 equiv of hydrogen, whose NMR spectrum indicated the same components present as in the aqueous equilibration mixture of **1a**. Here also the content of the minor component, here proposed to be **1d**, was close to 10%. Hydrogenation of **1c** in dioxan over solid disodium hydrogen phosphate heptahydrate yielded the same mixture again but with 30% of the minor component. Elemental analysis of the *p*-bromophenacyl ester of the latter mixture (which still contained ca. 30% of the minor component by NMR) was identical, within the accepted limits to that of the ester of **1a**.

We believe that the above data show that we have prepared (but not yet separated from its 6-epimer **1a**) **1d** and that the latter does arise from epimerization of **1a** in aqueous solution to an equilibrium level of some 12%. Our attempts to separate the two epimers by several methods, including high pressure liquid chromatography, were not successful. In view of the available data[1] 12% does not seem to be an impossibly high equilibrium concentration of **1d**. It is of interest to note, for example, that Bose et al.[14] have shown that although *cis*-1,4-diphenyl-3-phthalimidoazetidin-2-one epimerizes completely to the trans β-lactam in the presence of base (as does the methyl ester of 6-phthalimidopenicillin[2]), the analogous bromo compound, *cis*-3-bromo-1,4-diphenylazetidin-2-one, equilibrates with 30% of the cis isomer remaining. We do not understand, at present, the failure of Clayton et al.[6] to observe **1d** in their spectra. We have carried out the epimerization under their reported conditions (NaOH or NaO^{2}H at pH 10–11) and have observed **1d** in quantities comparable to those under our conditions described above.

We are currently investigating the properties of **1d** and its analogues. In particular the epimeric mixtures of **1a** and **1d** are potent irreversible inhibitors of β-lactamases. Since pure **1a** has no effect on these enzymes, the inhibitor must be **1d**. Experiments with purified β-lactamases of *Bacillus cereus* and *Escherichia coli* suggest that **1d** is at least as effective as the naturally occurring inhibitor clavulanic acid.[15] Details of these inhibition studies are reported elsewhere.[16]

Experimental Section

Proton nuclear magnetic resonance spectra were run on the 270 MHz Brüker instrument at the Southern New England High Field NMR Facility at Yale University, New Haven, Conn. Internal standards were 2,2-dimethyl-2-silapentane 5-sulfonate in ^2H_2O and tetramethylsilane in $CDCl_3$.

6α-Bromopenicillanic Acid (1a). The *N,N'*-dibenzylethylenediamine salt of 6α-bromopenicillanic acid was prepared from 6β-aminopenicillanic acid (Aldrich Chemical Co.) by diazotization in the presence of sodium bromide[4] and recrystallized from methanol to a constant melting point, 159.5–160.5 °C (lit.[4] mp 159–160 °C). A solution of the sodium salt of this compound was obtained by stirring a suspension of the above amine salt in water with an excess of Dowex 50W-X8 resin in the sodium form. The solid sodium salt was obtained by freeze–drying this solution.

Hydrogenation of 6,6-dibromopenicillanic acid (1c) prepared from 6β-aminopenicillanic acid by diazotization in the presence of bromine[7].

(a) In Aqueous Solution. Routinely 0.5-g samples of 6,6-dibromopenicillanic acid dissolved in water (ca. 50 mL) containing 0.9 g (2.5 equiv) of disodium hydrogen phosphate heptahydrate and 0.1

g of 10% Pd/C were hydrogenated at room temperature and pressure until 1 equiv of hydrogen had been taken up (ca. 1 h) after which the rate of uptake slowed essentially to zero. The filtered solution was then freeze–dried to obtain the sodium salts of the products. To obtain the products free of phosphate, the reaction mixture was stirred at 0 °C under a layer of diethyl ether and the pH of the aqueous layer reduced to 1 by the addition of 1 M hydrochloric acid. The ether layer was separated, dried over magnesium sulfate, and evaporated to dryness. The resulting acid, an oil, could be used as such or converted into the sodium salt (add 1 equiv of aqueous sodium bicarbonate and freeze–dry) or the *N,N'*-dibenzylethylenediamine salt (oil dissolved in ether and 1 equiv of the amine added).

(b) In Dioxan. Samples of 6,6-dibromopenicillanic acid (0.5 g) dissolved in 50 mL of dioxane (freshly distilled from sodium) to which had been added 1.8 g of disodium hydrogen phosphate heptahydrate and 0.1 g of 10% Pd/C were hydrogenated at room temperature and pressure for 2 h. The filtered solution was evaporated to dryness under reduced pressure. The residue was extracted with ether and the solution dried and evaporated. The residual acidic oil could be converted to its sodium or *N,N'*-dibenzylethylenediamine salts as above.

Total isolated monobromopenicillanic acid yields were about 50% in each case.

The infrared spectra of the amine salt of **1a** and the amine salts from the hydrogenation mixtures were very similar. Their NMR spectra, which are discussed in detail above, indicate that the hydrogenation products were mixtures of **1a** and **1d** with the latter making up approximately 10% (aqueous hydrogenation) or 30% (dioxane hydrogenation) of the total. It is clear also from the NMR spectra that the amine salts from the hydrogenations contained small but variable quantities of excess amine and thus these salts were not suitable for chemical analysis. Consequently, sodium salts of pure **1a** and of the dioxan hydrogenation mixture were converted essentially quantitatively into *p*-bromophenacyl esters by the method of Bamberg and co-workers.[17] The **1a** ester (mp 93.5–94 °C) was purified by recrystallization from methanol and yielded the following spectral data: IR (KBr) 1775 (β-lactam C=O), 1740, 1700 cm^{-1}; NMR ($CDCl_3$) τ 8.32 (6 H, broad s, $(CH_3)_2$), 5.34 (1 H, s, 3-H), 5.19 (1 H, d, J = 1.5 Hz, 6-H), 4.63 (2 H, s, CH_2), 4.58 (1H, d, J = 1.5 Hz, 5-H), and 3.20, 2.09 (4 H, AB quartet, J = 8.5 Hz, Ar-H). Anal. Calcd for $C_{16}H_{15}Br_2NO_4S$: C, 40.28; H, 3.17; N, 2.94; Br, 33.49. Found: C, 40.35; H, 3.09; N, 3.28; Br, 33.20. The hydrogenation product esters, an oil, were purified as a mixture by elution from a silica column with benzene and yielded the following spectral data: IR (neat) 1775 (β-lactam C=O), 1750, 1700 cm^{-1}; NMR ($CDCl_3$), the peaks of the α-epimer as above and the following peaks integrating to ca. 30% of the total: τ 8.28 (6 H, s, $(CH_3)_2$), 5.37 (1 H, s, 3-H), and 4.71, 4.34 (2 H, AB quartet, J = 4.6 Hz, 5-H, 6-H). The remaining peaks of the β-epimer are superimposed on those of the α-epimer. Anal. Calcd for $C_{16}H_{15}Br_2NO_4S$: as above. Found: C, 40.25; H, 3.27; N, 3.11; Br, 33.60.

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Registry No.—**1a,** 24138-28-1; **1a** *p*-bromophenacyl ester, 66842-39-5; **1c,** 24158-88-1; **1d,** 26631-90-3; **1d** *p*-bromophenacyl ester, 66842-40-8.

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Reaction of α-Aryl-*N*-alkyl- and α,*N*-Diarylnitrones with Aroyl Chlorides. A New Synthesis of *N*-Alkyl-*O*-aroylhydroxylamines

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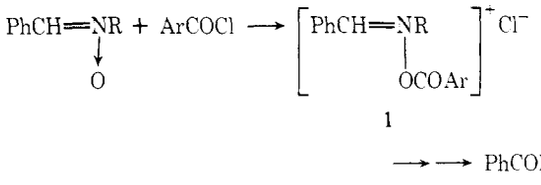
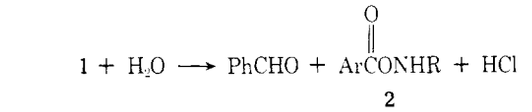
In 1890 Beckmann observed that acetyl chloride, benzoyl chloride, and acetic anhydride catalyzed the isomerization of α-phenyl-*N*-benzylnitrone to *N*-benzylbenzamide.[1] Since then many examples of the isomerization of nitrones into amides by acylating reagents have been reported.[2] Discussion continues on the mechanism of the rearrangement,[2-5] but all investigators agree that the first step of the reaction is a nucleophilic displacement by the nitrone oxygen on the electrophilic carbon of the acylating reagent. Thus, in the case of the isomerization of an α-phenyl-*N*-alkylnitrone by an aroyl chloride it is presumed that the aroyloxy(benzylidene)ammonium chloride **1** is formed initially (eq 1). With the exception of a few compounds obtained from the interaction of heterocyclic *N*-oxides with very electrophilic acyl halides,[6-8] compounds such as **1** have not been isolated.



We have augmented the evidence for the existence of **1** by treating α-phenyl-*N*-alkylnitrones and aroyl chlorides at ambient temperature in moist solvents (acetone, ether, and acetonitrile). The products, which apparently arise by the hydrolysis of **1**, are *N*-alkyl-*O*-aroylhydroxylamines (**2**) and aldehydes (eq 2).



The crude hydrochlorides **2**·HCl separated from the reaction mixture and were hydrolyzed to give the bases **2** (Table I). In those cases where **2** were oils ($PhCO_2NHMe$, $PhCO_2NH$-*t*-Bu, and 3,4-$Cl_2C_6H_3CO_2NH$-*t*-Bu) the corresponding hydrochlorides (**2**·HCl) were isolated and purified (Table I). *N*-Methyl-*O*-(*p*-nitrobenzoyl)hydroxylamine hydrochloride was also prepared in 58% yield when α-(*p*-nitrophenyl)-*N*-methylnitrone was substituted for α-phenyl-*N*-methylnitrone in the reaction with *p*-nitrobenzoyl chloride.

The proof of structure for **2** consists of NMR, IR, and mass spectroscopy. Unequivocal characterization was provided by utilizing a synthesis developed by Zinner[9] to prepare *N*-methyl- and *N*-*tert*-butyl-*O*-(*p*-nitrobenzoyl)hydroxylamine hydrochlorides and *N*-methyl- and *N*-*tert*-butyl-*O*-benzoylhydroxylamine hydrochlorides. The spectral and physical properties of the *N*-alkyl-*O*-aroylhydroxylamine hydrochlorides made by our method and that of Zinner's were identical. The yields were comparable by the two methods in those in-

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