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Concerning the Stereochemistry of Cyclohexenone Alkylations

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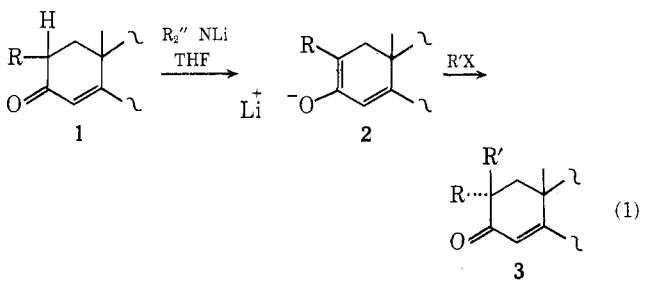
Recently we reported[1] that substituted cyclohexenone systems can be selectively alkylated at the α' position via the kinetically favored cross-conjugated dienolate base (eq 1). In the case of cholest-4-en-3-one (1, R = H) the product



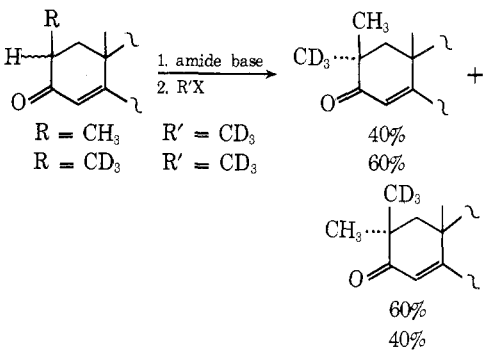
1 2 3 (1)

of methylation (R′X = CH_3I) was regarded as the previously unknown 2β-methyl epimer (3, R′ = CH_3, R = H) because it appeared to be homogeneous (TLC analysis on silical gel and alumina), melted sharply at 110–111°, and was different from the known α epimer[2] (mp 122–124°) into which it was transformed by the action of base.

A subsequent study of the 100-MHz ^1H NMR spectrum of this substance suggested that it might be a mixture of epimers, and this has now been confirmed by high-pressure liquid chromatography on a 15-cm column packed with Zorbex (a small diameter porous silica provided by Du Pont). The roughly 60:40 α:β composition of this epimeric mixture has been further indicated by careful europium shift measurements conducted by Dr. D. N. Kirk and R. D. Burnett of Westfield College, University of London. In the latter work the C-2 methyl doublets, which normally overlapped at ca. δ 1.05 ppm, were caused to shift to a lower field than the C-19 methyl signals for the α and β epimers. Although the methyl doublets still overlapped, they were easily discernible and well separated from the other methyl signals.

At this point, two possible explanations for the inhomogeneous nature of the methylation product were considered. (1) The alkylation reaction itself may have been essentially nonstereoselective. (2) A stereoselective alkylation step may have been followed by a partial epimerization of the kinetically favored β-methyl product. A combination of these factors may also be operating. Since the same mixture of product epimers was obtained from several experiments in which the time and temperature of the alkylation step varied, we were inclined to favor the first rationale. However, it seemed appropriate to settle the question by effecting the alkylation of a similar substrate, chosen so that product epimerization could not take place.

The possibility of effecting a second alkylation reaction at C-2 was demonstrated by methylation of 2α-methylcholest-4-en-3-one (1, R = CH_3) under the conditions noted in eq 1. Formation of 2,2-dimethylcholest-4-en-3-one (3, R = R′ = CH_3)[3] in 97% yield follows the previously stated general rule[1,4] that *α'-proton abstraction is kinetically favored in α,β-unsaturated ketones*. By effecting this sequential dimethylation with CH_3I followed by CD_3I, and in a second case with CD_3I followed by CH_3I, we have been able to ascertain the stereoselectivity of the second alkylation step (eq 2).



(2)

The very poor stereoselectivity observed for these alkylation reactions is similar to that reported for the methylation of 2-cyanocholest-4-en-3-one,[5] and is presumably due in part to a flattening of the six-membered ring caused by the double bond. Since other factors may influence the stereochemistry of β-keto nitrile alkylation reactions,[6] this similarity may not be very significant. While this manuscript was being prepared, Girard and Conia reported[7] that cyclopropanation of the trimethylsiloxy derivative of the 2-enolate base derived from testosterone proceeded with essentially no stereoselectivity.

Experimental Section

All reactions involving strong bases were conducted under dry nitrogen or argon, using solvents purified by distillation from suitable drying agents. Melting points were obtained with a Hoover-Thomas apparatus or on a Reichert hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer. Nuclear magnetic resonance (NMR) spectra were recorded on Varian A-60, T-60, and HA-100 spectrometers with deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6D spectrometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

General Procedure for α'-Methylation. To a cold solution of 1.30 mmol of isopropylcyclohexylamine in 0.5 ml of dry tetrahydrofuran (THF) was added 1.25 mmol of *n*-butyllithium in hexane. After this mixture was stirred at 0° for 15 min, 1.0 mmol of the α,β-unsaturated ketone in 5 ml of THF was slowly added and the resulting solution was maintained at 0° for 90 min. Following rapid addition of 4.00 mmol of methyl iodide, the reaction mixture was allowed to warm to room temperature and held there for 3 hr before being mixed with water and extracted with ether. The combined ether extracts were washed (twice each) with water and brine, dried, and distilled under reduced pressure.

Results of Specific Methylations. A. Cholest-4-en-3-one. The yield of crude 2-methylcholest-4-en-3-one was 98%. Recrystal-

lization from methanol afforded 95% colorless crystals, mp 110–111°, $[\alpha]_D$ 33.76° (2.14 g/100 ml $CHCl_3$).

Anal. Calcd for $C_{28}H_{46}O$: C, 84.36; H, 11.63. Found: C, 84.28; H, 11.69.

This mixture of 2α- and 2β-methylcholest-4-en-3-one (150 mg) was treated with 50 mg of potassium hydroxide in 25 ml of methanol for 3 hr at 25°. The usual work-up gave 2α-methylcholest-4-en-3-one (**3**, R = CH_3; R = H) in 98% yield, mp 122–124° (lit.[2] mp 122–124), $[\alpha]_D$ 89° (lit.[2] 94°).

B. 2-Methylcholest-4-en-3-one. The yield of crude 2,2-dimethylcholest-4-en-3-one (**3**, R = R′ = CH_3) was 97%. Recrystallization from methanol afforded 93% of pure material, mp 94–95° (lit.[3] mp 94–95°), molecular ion (70 eV) *m/e* 412.

C. 2-Methyl-d_3-cholest-4-en-3-one. A mixture of diastereoisomers (**3**, R = CH_3; R′ = CD_3 and R = CD_3; R′ = CH_3) was obtained in 90% yield: mp 86–87°; ir (KBr) 2220 cm^{-1} (C–D stretch); molecular ion (70 eV) *m/e* 415.

Results of Specific Methylation with CD_3I. A. Cholest-4-en-3-one. The yield of crude 2-methyl-d_3-cholest-4-en-3-one was 75%, mp 98–100°, ir (KBr) 2220 cm^{-1}.

B. 2-Methylcholest-4-en-3-one. A mixture of diastereoisomers (**3**, R = CD_3; R′ = CH_3 and R = CH_3; R′ = CD_3) was obtained in 40% yield after preparative TLC on a 2-mm silica gel plate eluent 9:1 cyclohexane–ethyl acetate): mp 80–82°; ir (KBr) 2220 cm^{-1}; molecular ion (70 eV) *m/e* 415.

Analysis of the diastereoisomeric mixtures of deuterium-labeled 2,2-dimethylcholest-4-en-3-ones was effected by observing the relative intensities of the resonance signals at δ 1.06 and 1.12 ppm in the 100-MHz spectra of these mixtures.

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Registry No.—1 (R = H), 601-57-0; **3** (R = H; R′ = CH_3), 54446-37-6; **3** (R = CH_3; R′ = H), 54446-38-7; **3** (R = R′ = CH_3), 17305-84-9; **3** (R = H; R′ = CD_3), 54446-39-8; **3** (R = CD_3; R′ = H), 54446-40-1; **3** (R = CH_3; R′ = CD_3), 54515-22-9; **3** (R = CD_3; R′ = CH_3), 54515-23-0; CH_3I, 74-88-4; CD_3I, 865-50-9.

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Conversion of Amino Acids to β-Lactam Derivatives via Cyclopropanone

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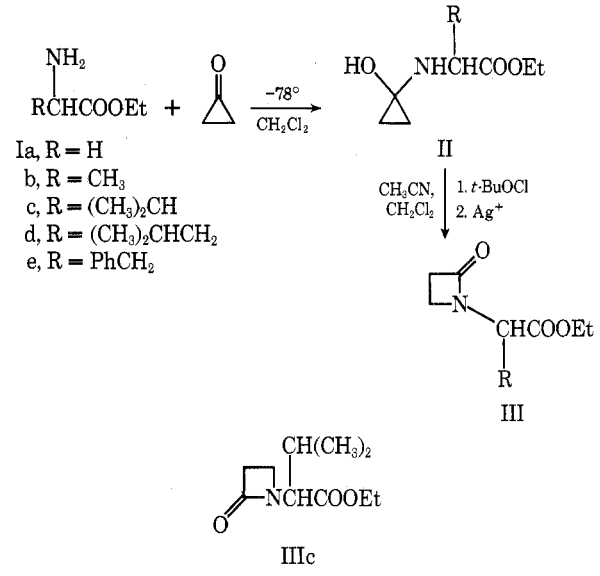
During studies on ring-enlargement reactions of cyclopropanones[2,3] we have recently reported a convenient synthesis of *N*-alkyl β-lactams via the silver ion catalyzed rearrangement of the corresponding *N*-chloro cyclopropylcarbinolamines.[2] We now report the extension of this procedure to the preparation of novel derivatives of amino acids. In particular, the method may be used as a simple route to β-lactams related to the penicillins, such as IIIc.

Scheme I

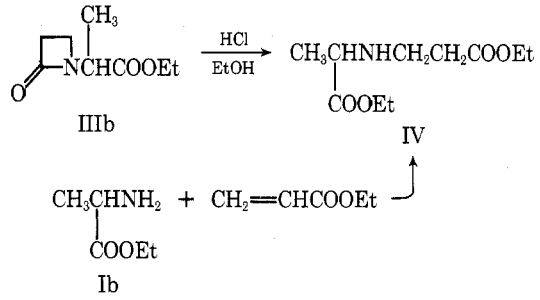


As outlined in Scheme I, the method involves addition of an equimolar amount of the amino acid ester to a purified solution of cyclopropanone[4] (or a suitable cyclopropanone precursor such as 1-acetoxycyclopropanol)[5] in methylene chloride at −78°. The resulting carbinolamine (II) in methylene chloride–acetonitrile (1:1) is then treated with 1 equiv of *tert*-butyl hypochlorite at ca. −10°, followed by addition of a threefold excess of silver nitrate. The reaction mixture is worked up in a manner identical with that reported for the simple alkyl primary amines.[2,6]

The β-lactams were characterized by NMR, ir, and mass spectra, as well as by the hydrolytic procedure described below. The NMR spectra show characteristic multiplets for the β-lactam ring protons[7] near δ 3.2 (2 H) and 2.9 (2 H), while the ir spectra exhibit the expected lactam carbonyl peaks at 1745 cm^{-1}.[8] Table I lists β-lactams derived from the ethyl esters of glycine, alanine, phenylalanine, valine, and leucine.

Chemical confirmation of the presence of the β-lactam ring in these systems was obtained by ethanolysis of IIIb with dry hydrogen chloride gas in absolute ethanol. The structure of the acyclic amino diester IV was established by its synthesis from ethyl acrylate and the ethyl ester of alanine as shown in Scheme II.

Scheme II



Experimental Section

Preparation of Cyclopropanone Solutions. Solutions of cyclopropanone in methylene chloride were prepared by the reaction at −78° of ketene with diazomethane, according to established procedures.[4b] Best results were obtained by using doubly distilled ketene and rigorously dried solvent.

1-Acetoxycyclopropanol. To a solution of cyclopropanone (50 mmol) in methylene chloride at −78° was added glacial acetic acid (2.3 g). Removal of solvent on the rotary evaporator at 0° gave 1-