methyl-2,6-di-*tert*-butylphenol in 3.0 mL of anhydrous ether (cooled to −10 °C) was added 560 μL of 2 M *n*-butyllithium in hexane. The observed precipitate dissolved upon warming to room temperature. To the homogeneous reaction mixture was added dropwise 95 mg (0.53 mmol) of ketone **11** in 1.0 mL of dry ether followed by addition of 214 mg (2.82 mmol) of carbon disulfide. After 14 h at room temperature, 196 mg (1.40 mmol) of methyl iodide was added and stirring was continued for an additional 5 h. The reaction mixture was quenched by the addition of brine and ether. The aqueous phase was extracted with ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residue (391 mg) was chromatographed on 30 g of silica gel. Elution with ether–hexanes (1:4) gave 45 mg (30%) of pure α-dithiomethylene derivative **12**: IR ($CHCl_3$) 3090, 1690, 1665, 1641 cm^{-1}; NMR δ (CCl_4) 1.04 (s, 3 H), 1.80 (s, 3 H), 2.30 (s, 3 H), 2.38 (s, 3 H). Continued elution gave 14 mg of pure α-dithiomethylene derivative **13**.

To a stirred suspension of copper iodide (29.6 mg, 0.16 mmol) in 1.0 mL of anhydrous ether at 0 °C was added 132 μL (0.31 mmol) of a 2.37 M solution of methyllithium in ether. After cooling to −78 °C, 22 mg (0.078 mmol) of compound **12** in 1.0 mL of dry ether was added dropwise. The reaction mixture was stirred for 20 min at −78 °C followed by quenching with methanol. Isolation of product by ether extraction[17] afforded 17 mg of crude β-elemenone which was chromatographed in 5.0 g of silica gel. Elution with ether–pentane (1:5) gave 15.4 mg (90%) of β-elemenone: IR (CCl_4) 3080, 2960, 2930, 2902, 2855, 1680, 1635, 1618, 1442, 1430, 1408, 1370, 1300, 1280, 1271, 1258, 1239, 1210, 1198, 1125, 1050, 1018, 998, 910, 891 cm^{-1}; NMR (CCl_4) δ 1.03 (s, 3 H), 1.80 (s, 6 H), 2.00 (s, 3 H), 2.22–2.71 (m, 5 H), 4.74–5.16 (m, 4 H, terminal vinyl), 5.61–6.07 (m, 1 H); high-resolution mass spectrum *m/e* 218.1667 (calcd for $C_{15}H_{22}O$, 218.1670).

Preparation of Seven-Membered Ring Ether 10. A solution of 15.0 mg (0.058 mmol) of diol **3** in 1.0 mL of tetrahydrofuran containing 13.2 mg (0.058 mmol) of *o*-nitrophenyl selenocyanate was treated with 11.7 mg (0.058 mmol) of tri-*n*-butylphosphine at room temperature. After 30 min the solvent was removed in vacuo and the residue was chromatographed on 5 g of silica gel. Elution with ether–hexane (1:2) afforded 12.1 mg (87%) of pure ether **10**: IR ($CHCl_3$) 2950, 2890, 1460, 1389, 1365, 1335, 1300, 1265, 1220, 1165, 1145, 1120, 1100, 1085, 1070, 1064, 1022, 1015, 995, 955, 900 cm^{-1}; NMR (CCl_4) δ 0.95 (d, 3 H, J = 7 Hz), 1.01 (s, 3 H), 1.1–2.3 (m, 10 H), 3.3–3.7 (m, 4 H), 3.83 (m, 4 H).

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Registry No.—**2**, 30824-86-3; **3**, 62183-43-1; **4**, 54316-77-7; **5**, 13944-80-4; **6**, 13944-79-1; **6** enol phosphate, 62183-44-2; **7**, 62183-45-3; **8**, 62183-46-4; **9**, 62183-47-5; **10**, 62183-48-6; **11**, 30824-87-4; **12**, 62183-49-7; 1-chloropentan-3-one, 32830-97-0; *o*-nitrophenyl selenocyanate, 51694-22-5; 4-methyl-2,6-di-*tert*-butylphenol, 128-37-0; carbon disulfide, 75-15-0; methyl iodide, 74-88-4; diethyl chlorophosphate, 814-49-3.

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A General Method for the Preparation of α-Labeled Amino Acids[1]

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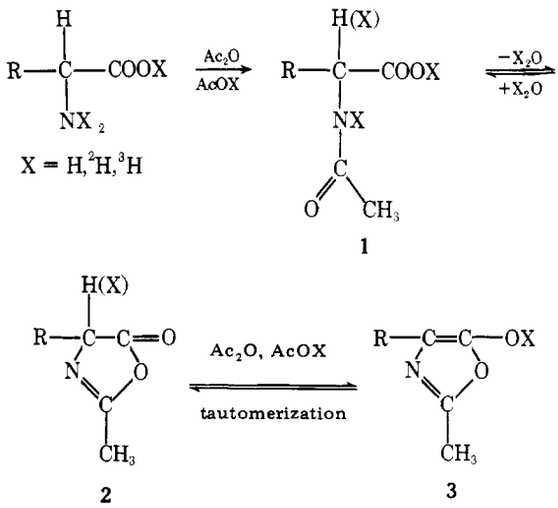
The usefulness of specifically deuterated amino acids for studying peptides and proteins is becoming more widely appreciated.[2-6] For example, with the deuterium labels providing unique nuclei for observation using modern biophysical techniques, information relevant to the conformation and dynamics of peptides and to the binding of peptide hormones to carrier proteins (or receptors) may be gathered.[7] One impediment for such studies has been the limited availability and/or high cost of specifically labeled amino acids.

Previous attempts to exchange the α proton of amino acids have met with limited success.[8-12] The most successful methods require high pressure and long reaction times,[13] or preparation, separation, and reduction of cobalt(III) complexes of amino acids.[14]

We report here a rapid, inexpensive, and generally applicable preparation of α amino acids starting from commercially available amino acids. The reaction is an adaptation of a method for racemization of amino acids which employs refluxing acetic acid and acetic anhydride to give racemic *N*-acetyl amino acids.[15] In our procedure, a mixture of excess acetic anhydride with D_2O is used to give a solution of Ac_2O in AcOD. Treatment of amino acids with this solution at reflux for a few minutes leads to acylation, racemization, *and* exchange at the α position. One possible mechanism for the reaction is given by the following equations [other mechanism(s) may also be used to account for the exchange].



From examination of the suggested mechanism, several points emerge. First, it is not necessary to use the more expensive stereopure L amino acids in this reaction since tautomerization proceeds through a planar intermediate. Second, this process is unlikely to affect the stereointegrity of asymmetric sites other than the α position thus simplifying the

Table I. Deuteration of Amino Acids at the α Position

Amino acid	α-Deuteration, % One exchange	Two exchanges	Registry no.
Isoleucine	77	>95[a]	62076-83-9
Leucine	83	91	62076-84-0
Methionine	79	>95[a]	62076-85-1
Valine	81	>95[a]	62076-86-2
Alanine	82	92	5046-58-2
Tyrosine	80	95	62076-87-3
S-Benzylcysteine	67	89	57866-79-2
Proline	73	86	62076-88-4

[a] No measurable α protons were detected by ^{1}H NMR.

problem of stereoisomer resolution. The resolution scheme for the four stereoisomers of isoleucine, for example, is quite lengthy. Third, this process directly yields *N*-acetyl-α-labeled amino acids which are the starting compounds for enzymatic resolution using hog renal acylase, carboxypeptidase, or other enzymes capable of selective cleavage of an acetyl group from one stereoisomer without a significant cleavage of the enantiomeric compound. Fourth, if the D isomer is not desired, it can be recycled. Fifth, the exchange efficiency is related to the proportional excess of available deuterons to protons. To achieve high levels of exchange, a high ^{2}H/^{1}H ratio is required. This condition can be approached in several ways: (a) a high molar excess of acetic acid-*d* relative to the amino acid can be used; (b) labile hydrogens of the amino acid can be subjected to prior exchange; (c) the exchange reaction can be repeated.

With the methods we have used thus far, one treatment generally leads to 70–80% exchange. A second treatment raises the level of exchange to 90–100% in most cases studied (Table I).

Experimental Section

Synthesis of *N*-Acetyl-DL-[α-^{2}H$_1$]alanine. The following procedure exemplifies the experimental procedure used. All-protio alanine (0.89 g, 0.01 mol) was shaken with 3.7 mL of D_2O to exchange labile protons. The mixture was frozen and lyophilized to dryness. Immediately, 21.7 mL of Ac_2O and 2.5 mL of D_2O were added to the resulting powder and the flask was placed in a 170 °C bath. The solution was refluxed for 2 min, then cooled (drying tube) and 2 mL of D_2O was added to destroy the remaining Ac_2O and convert any azlactone **2** back to the *N*-acetyl amino acid. The solvents were removed by rotary evaporation. Crystals appeared as the evaporation neared completion. The residue was recrystallized from ethyl acetate. The crystals were filtered, washed with ether, and dried in vacuo over KOH: yield 1.17 g (89%); mp 127–128 °C; NMR (Me_2SO-d_6) δ 1.55 (s, 3 H), 2.15 (s, 1.1 H), 2.80 (Me_2SO), 4.4–4.6 (α-CH, 0.18 H). After the reaction was repeated, 0.08 α hydrogens were detectable by proton nuclear magetic resonance spectroscopy, yield 1.06 g (80%). Similar procedures were used for other amino acids and the results are summarized in Table I.

There was exchange of deuterium into the acetyl methyl groups. This fact effectively decreases the ^{2}H/^{1}H ratio and is undoubtedly responsible for some, if not most, of the nondeuteration at the α carbon. Clearly, this method could also be used for the exchange of tritium into the α position.

Registry No.—DL-Isoleucine, 443-79-8; DL-leucine, 328-39-2; DL-methionine, 59-51-8; DL-valine, 516-06-3; DL-alanine, 302-72-7; DL-tyrosine, 556-03-6; DL-*S*-benzylcysteine, 5680-65-9; DL-proline, 609-36-9.

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Conformational Analysis. 127. Force Field Calculations on the Dodecahydrophenanthrenes[1,2]

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In an earlier paper the structures and relative stabilities of the isomeric octahydronaphthalenes were discussed.[3] It was felt that the relative energies of the various isomers could be accurately calculated, and simultaneous but independent experimental work showed that this was indeed so.[4] In the course of continuing studies on the isomers of perhydrophenanthrene,[5] various synthetic sequences were projected which involved a dodecahydrophenanthrene with a trans,syn,trans backbone as an intermediate. Because of the possibility of rearrangement, it was desirable to know something about the relative stabilities of some of these compounds. The previously used calculational methods (molecular mechanics) were expected to yield reliable predictions here, so the calculations were carried out (1973 force field[6]) and the results are reported herein.

There are 25 isomers of dodecahydrophenanthrene which were considered in this work. They are shown in Table I. The calculated heat of formation (H_f, gas, 25 °C) is −29.60 kcal/mol for the most stable compound (**7**). The values of $\Delta H_f°$ are given for each conformation. Also, the values of ΔH for each *compound* (conformational mixture) relative to the most stable isomer are shown, together with the relative entropies if nonzero, calculated by taking into account symmetry numbers and entropies of mixing. The relative free energies (80 °C) are also shown for isomers within 4 kcal/mol of the most stable one.

A few experimental investigations of the relative stabilities of some of the isomers of dodecahydrophenanthrene have appeared in the literature, together with suggestions regarding possible bond migrations in the course of a synthesis of a perhydrophenanthrene[7]. Christol and co-workers, in a series of papers,[8] carried out some equilibration studies, and isolated what they believed to be the isomers indicated, in the yields