TABLE I

O-ACETYLHYDROXY-α-AMINO ACID HYDROCHLORIDES

O-Acetyl hydrochloride of	Yield, %	M.p.,[e] °C.	Formula	% calcd. C	H	N	Cl	Neut. equiv.	% found C	H	N	Cl	Neut.[a] equiv.
Hydroxy-L-proline	91	179	$C_7H_{12}ClNO_4$	40.20	5.74	6.70	16.71	104.5	40.20	5.75	6.73	16.54	104
L-Serine	95	167[b]	$C_5H_{10}ClNO_4$	32.78	5.46	7.65	19.10	91.5	32.84	5.55	7.74	19.00	92
DL-Serine	93	158[c]	$C_5H_{10}ClNO_4$	32.78	5.46	7.65	19.10	91.5	32.75	5.40	7.60	19.00	91
L-Threonine	93	153[d]	$C_6H_{12}ClNO_4$	36.46	6.07	7.08	17.90	98.5	36.63	6.16	6.90	17.80	99

[a] The neutralization equivalent was determined by titration in ethanol with 0.1 *M* sodium methoxide using thymol blue as indicator [A. Patchornik and S. Ehrlich-Rogozinski, *Anal. Chem.*, **31**, 985 (1959)]. [b] $[\alpha]^{25}D$ +11.5° (*c* 2.2, ethyl alcohol; *c* 2, water); lit.[4] m.p. 160°, $[\alpha]^{27}D$ −7.4° (*c* 2.2, ethyl alcohol). [c] Lit.[3] m.p. 158–162°. [d] $[\alpha]^{25}D$ +15.3° (*c*, 2 water). [e] All melting points are uncorrected.

methods are known for the synthesis of O-acetylhydroxy-α-amino acids,[2-5] but these methods are relatively time consuming and laborious. We wish to report a simple, rapid, and general procedure for the synthesis of O-acetyl derivatives of hydroxyamino acids.

The amino acid is dissolved in a mixture of hydrochloric acid and glacial acetic acid and acetylated by the slow addition of acetyl chloride at 0°. The pure O-acetylhydroxyamino acid hydrochloride precipitates from the reaction mixture in a crystalline form. By this method we were able to prepare the O-acetyl derivatives of several hydroxyamino acids in 90% yield.

Experimental

The general experimental procedure is as follows. The amino acid (0.1 mole) is dissolved in 6 *N* hydrochloric acid (20 ml.). Glacial acetic acid (20 ml.) is added, and the solution is cooled to 0° in an ice bath. Acetyl chloride (200 ml.) is then added slowly to the beaker (caution, this reaction should be carried out in the hood as rapid evolution of hydrogen chloride takes place). The o-acetylhydroxyamino acid hydrochloride precipitates within a few minutes and quantitative precipitation may be brought about by adding two to three volumes of ether. The compound is filtered off, washed with ether, and dried *in vacuo*. The compounds obtained have been found to be chromatographically pure and the yields are all above 90% (Table I). The free O-acetylhydroxyamino acids can be obtained as usual[4] by dissolving the hydrochloride in solute ethanol and adding an equivalent amount of triethylamine.

O-Acetyl-N-carboxy-L-threonine Anhydride.—O-Acetyl-L-threonine hydrochloride (10.0 g.) was suspended in 100 ml. of absolute dioxane. Phosgene was passed through the suspension for 40 min. at room temperature, and a clear solution was obtained. The excess phosgene was removed by passing a stream of dry nitrogen through the solution. The dioxane was evaporated *in vacuo* at 50°. The oily residue that was obtained was shaken with petroleum ether three to four times, the petroleum ether being removed each time by decantation. The oil was then dissolved in a minumum amount of ethyl acetate, and a semicrystalline precipitate was obtained on addition of petroleum ether. The material was recrystallized twice from ethyl acetate–petroleum ether. The yield was 8.0 g. (85%), m.p. 94–95°.

Anal. Calcd. for $C_7H_9NO_5$: C, 44.92; H, 4.81; N, 7.48. Found: C, 44.85; H, 5.00; N, 7.72.

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A Convenient Synthesis of Branched Unsymmetrical Sulfides

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It was discovered by Pettit and Kasturi[1] that the combination of lithium aluminum hydride ($LiAlH_4$) and a large excess of boron trifluoride etherate is a reagent for the reduction of esters and lactones to ethers and cyclic ethers. It has now been found that sulfides can also be conveniently prepared from the corresponding thiol esters by means of the same reagent.

Thus cyclohexyl thiolacetate gave cyclohexyl ethyl sulfide in 80% yield; cyclohexyl thiolisobutyrate gave cyclohexyl isobutyl sulfide in 73% yield, and cyclohexyl thiolpivalate gave cyclohexyl neopentyl sulfide in 37% yield. The low yield in the latter reduction may have been due to steric hindrance by the *t*-butyl group neighboring the carbonyl carbon, which apparently causes arrest of the reaction at an intermediate stage.

The reduction products were characterized by their elemental analyses and nuclear magnetic resonance spectra. Cyclohexyl ethyl sulfide is a known compound; cyclohexyl isobutyl sulfide was prepared independently and compared to the material obtained by reduction.

The starting thiol esters are readily available through well-known procedures.

Experimental

All boiling points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Infracord instrument. Nuclear magnetic resonance spectra were recorded with a Varian Associates high resolution instrument at 60 Mc. Elementary analyses were performed by Midwest Microlab, Indianapolis, Ind.

Cyclohexyl Thiolacetate.—This was prepared by the method of Weibull[2] involving the reaction of cyclohexene and thiolacetic acid in the presence of a few drops of di-*t*-butyl peroxide. Distillation gave cyclohexyl thiolacetate in 74% yield, b.p. 96–97° (15 mm.), lit.[2] b.p. 94–96° (15 mm.).

Cyclohexyl Thiolisobutyrate.—The thiol ester was prepared by adding 11.6 g. (0.1 mole) of cyclohexyl mercaptan to a solution containing 15.8 g. (0.1 mole) of isobutyric anhydride in 100 ml. of dry pyridine in an ice bath. The solution was shaken oc-

(1) G. R. Pettit and T. R. Kasturi, *J. Org. Chem.*, **25**, 875 (1960); **26**, 986, 4553, 4557 (1961); G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *ibid.*, **26**, 1685 (1961); G. R. Pettit, T. R. Kasturi, B. Green, and J. C. Knight, *ibid.*, **26**, 4773 (1961).
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casionally and allowed to stand at room temperature for 24 hr. After the usual work-up, the ethereal solution was concentrated and the residue was distilled to give cyclohexyl thiolisobutyrate, 7.9 g. (43%), b.p. 70–72° at 1.5 mm. Its infrared spectrum showed carbonyl absorption at 5.9 μ.

Anal. Calcd. for $C_{10}H_{18}OS$: C, 64.47; H, 9.74; S, 17.21. Found: C, 64.62; H, 9.87; S, 17.29.

Cyclohexyl Thiolpivalate.—This thiol ester was prepared by adding 11.6 g. (0.1 mole) of cyclohexyl mercaptan to a solution containing 12.1 g. (0.1 mole) of pivaloyl chloride in 100 ml. of dry pyridine at ice-bath temperature. The solution was then allowed to stand with occasional shaking at room temperature for 24 hr. After the usual work-up, distillation gave cyclohexyl thiolpivalate in 84% yield, b.p. 68° (0.6 mm.). Its infrared spectrum showed carbonyl absorption at 5.93 μ and the characteristic *t*-butyl bands at 7.19 and 7.34 μ.

Anal. Calcd. for $C_{11}H_{20}OS$: C, 65.95; H, 10.06; S, 16.00. Found: C, 66.23; H, 10.24; S, 16.29.

General Procedure For Lithium Aluminum Hydride–Boron Trifluoride Reductions.—The procedure used in the reductions of the thiol esters was identical with that of Pettit[1] using a 2:1 mole ratio of $LiAlH_4$ to thiol ester and a 15:1 mole ratio of $BF_3{\cdot}Et_2O$ to thiol ester. A solution containing both the thiol ester and $BF_3{\cdot}Et_2O$ (no diluent) was placed in a three-necked, round-bottomed flask fitted with condenser, drying tube, stirrer, and dropping funnel at ice-bath temperatures. A standard solution (*ca.* 1 *M*) of $LiAlH_4$ was then added dropwise. The mixture was allowed to stir for 45 min. The ice bath was removed and the reaction mixture was refluxed for 2 hr. Upon cooling, the mixture was hydrolyzed with 10% hydrochloric acid till two layers formed. The ether layer was separated and the aqueous layer was extracted with ether. The combined ether extracts were washed with water, saturated sodium bicarbonate solution, and saturated salt solution and then were dried over anhydrous potassium carbonate. Concentration of the ether and distillation of the residue gave the sulfide.

Cyclohexyl Ethyl Sulfide.—Cyclohexyl thiolacetate, 8 g. (0.05 mole), was reduced with $LiAlH_4$–boron trifluoride to give 5.8 g. (80%) of cyclohexyl ethyl sulfide, b.p. 74–76° (10 mm.), lit.[3] b.p. 68–70° (10 mm.), lit.[4] b.p. 72–74° (12 mm.); $n^{20}D$ 1.4885, lit.[3] 1.4908, lit.[4] 1.4890. Its infrared spectrum was identical with that of an authentic sample.[4]

Cyclohexyl Isobutyl Sulfide. A. From Cyclohexyl Thiolisobutyrate.—Cyclohexyl thiolisobutyrate, 4.65 g. (0.025 mole) was reduced with $LiAlH_4$–boron trifluoride to give 3.15 g. (73%) of cyclohexyl isobutyl sulfide, b.p. 74–76° (2.5 mm.). Its infrared spectrum was identical with an authentic sample (*vide infra*). Its nuclear magnetic resonance spectrum gave a doublet at τ 9.01 corresponding to $(CH_3)_2C$– and doublet at τ 7.67 corresponding to the methylene hydrogens neighboring the sulfur atom, *i.e.*, $-S-CH_2-C\equiv$.

Anal. Calcd. for $C_{10}H_{20}S$: C, 69.70; H, 11.70. Found: C, 69.69; H, 11.85.

B. From Cyclohexene and Isobutyl Mercaptan.—To a 100-ml., three-necked, round-bottomed flask equipped with condenser, dropping funnel, immersion thermometer, and magnetic stirrer was added 9.8 g. (0.12 mole) of cyclohexene and a few crystals of benzoyl peroxide. Isobutyl mercaptan, 9.0 g. (0.10 mole), was then added dropwise at room temperature. The reaction mixture was heated to 90° for 12 hr. Distillation of the solution gave 12 g. (70%) of cyclohexyl isobutyl sulfide, b.p. 74–76° (2.5 mm.). Its infrared spectrum was identical with that of the product obtained in the $LiAlH_4$–boron trifluoride reduction of cyclohexyl thiolisobutyrate.

Cyclohexyl Neopentyl Sulfide.—Cyclohexyl thiolpivalate, 5 g. (0.025 mole), was reduced with $LiAlH_4$–boron trifluoride. The crude material obtained before distillation showed B–H bands at 4.07 and 4.10 μ and a broad OH band at 3.13 μ indicating a boron complex. Hydrolysis of the crude material, 4.25 g., was completed by boiling at reflux for 17 hr. in 50 ml. of 10% alcoholic potassium hydroxide. The mixture was neutralized and extracted with five 50-ml. portions of ether. The combined ethereal extracts were washed with water, saturated sodium bicarbonate solution, and saturated salt solution and then were dried over anhydrous potassium carbonate. Concentration of the ether and distillation of the residue gave, in addition to a considerable still-pot residue, 1.7 g. (37%) of cyclohexyl neopentyl sulfide, b.p. 76° (0.8 mm.). Its infrared spectrum showed the usual *t*-butyl bands at 7.1 and 7.3 μ. Its nuclear magnetic resonance spectrum showed a singlet at τ 9.01 corresponding to $(CH_3)_3C$ and a singlet at τ 7.6 corresponding to the methylene hydrogens neighboring the sulfur atom, *i.e.*, $S-CH_2-C\equiv$.

Anal. Calcd. for $C_{11}H_{22}S$: C, 70.89; H, 11.90. Found: C, 71.20; H, 12.09.

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Novel Solvolytic Reactions in Dimethyl Sulfoxide

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The versatility of dimethyl sulfoxide (DMSO) as a solvent medium in organic reactions has received very widespread attention in recent years. In some cases, the ability of dimethyl sulfoxide to act as an oxidant in the course of reaction has been recognized. Kornblum and co-workers[1,2] first reported the base-catalyzed oxidation of primary tosylates and halides to aldehydes[3]; this method was extended to secondary tosylates.[4] The oxidation of ethyl bromoacetate to ethyl glyoxalate by dimethyl sulfoxide has been reported.[5] More recently, the boron fluoride-catalyzed oxidation of epoxides to α-hydroxy ketones by dimethyl sulfoxide has been described.[6]

We wish herein to report the novel oxidative solvolysis of a keteneimine and a ketene in dimethyl sulfoxide under acidic conditions.

If a few drops of aqueous acid were added to a solution of diphenylketene-N-*p*-tolylimine in dimethyl sulfoxide, a high yield of N-(*p*-tolyl)-α-hydroxydiphenylacetamide (I) was obtained. Likewise, addition of diphenylketene to a dilute dimethyl sulfoxide solution of aqueous acid produced an equally high yield of benzilic acid.

If the solution of keteneimine were diluted with an excess of methanol prior to the addition of acid, N-(*p*-tolyl)-α-methoxydiphenylacetamide (II) was produced in 70% yield. This product was verified by synthesis from N-(*p*-tolyl)-α-chlorodiphenylacetamide, methanol, and triethylamine. That this product did not arise *via* etherification of the α-hydroxyamide was evident from the failure of the latter to react with methanolic hydrogen chloride. With either ketene or keteneimine, dimethyl sulfoxide, and a poor nucleophile, *i.e.*, benzoic acid, in the presence of aqueous acid, only α-hydroxy acid or α-hydroxyamide was obtained. The formation of dimethyl sulfide in this reaction was proved by converting the gas to its trimethylsulfonium salt.

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