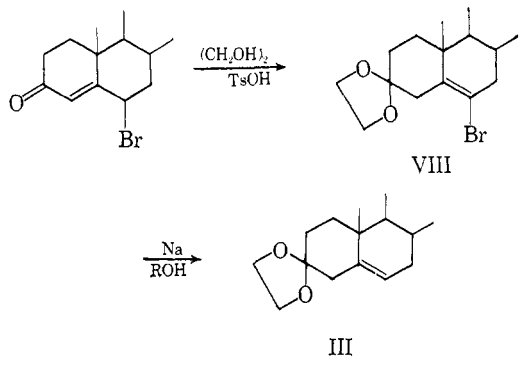


### Experimental[10]

**5(4?)-Cholesten-7-one Ethylene Ketal (IV).**—A solution of 1.0 g. of 5-cholesten-7-one in 100 ml. of benzene was mixed with 2.0 ml. of ethylene glycol and refluxed with a Dean–Stark water take-off in place. After 5 min., a "few crystals" of *p*-toluenesulfonic acid monohydrate were added, and the mixture refluxed for 24 hr. The benzene layer was decanted from the excess ethylene glycol and, after the addition of a drop of pyridine, evaporated under an air stream to provide a solid residue. Crystallization from methanol (pyridine) gave a fibrous, gel-like solid, m.p. 90°. Chromatography on alumina provided 0.97 g. of crystalline fractions melting variously from 100.5–102.5° to 93–101°. This substance was extremely unstable, decomposing to a significant extent if exposed to the atmosphere for 1 hr. The analytical sample showed m.p. 95–102°, $[\alpha]_D$ −2.4°.

*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.3; H, 11.3. Found: C, 81.18; H, 11.52

The infrared spectrum showed no carbonyl adsorption and several peaks in the 900–1200-cm.$^{-1}$ region.

An acetone solution of IV when treated with a drop of concentrated hydrochloric acid and permitted to stand overnight gave, upon evaporation, pure 5-cholesten-7-one.

**4-Cholesten-3-one Ethylene Ketal (V).**—A solution of 1.02 g. of 4-cholesten-3-one in 100 ml. of benzene was mixed with 2.0 ml. of ethylene glycol and refluxed for 40 min. with a Dean–Stark water take-off in place. At the end of this time 0.0052 g. of *p*-toluenesulfonic monohydrate acid was added; the reflux was continued for 7 hr. The resulting mixture was washed three times with 2 *N* potassium bicarbonate and once with water. The benzene solution was filtered through anhydrous sodium sulfate and, after addition of a drop of pyridine, evaporated to a yellow oil which crystallized. The sample was recrystallized from 30 ml. of ethanol (pyridine) to provide 0.89 g. of powdery white solid, m.p. 103–104°, with some individual crystals melting between 92 and 96°. When the same was recrystallized from methanol (pyridine), it gave chunky needles, m.p. 95–97°, $[\alpha]_D$ +75°.

*Anal.* Calcd. for $C_{29}H_{48}O_2$: C, 81.3; H, 11.3. Found: C, 81.05; H, 11.55.

Eight separate preparations of this compound were carried out, in each case the catalyst–steroid ratio ranging between that described above and three times that ratio. In every case the same product was obtained and none of the $\Delta^5$-isomer was observed either by chromatographic separation or spectroscopic examination.

The ketal V apparently held some solvent under normal conditions. Fresh chromatographic fractions occasionally had a m.p. of 102° which declined to 95–97° on short standing in air, in a pyridine–air atmosphere, or upon crystallization from methanol (pyridine). The compound showed adsorption in the infrared as described in the discussion portion of this contribution.

When an acetone solution of V was treated with a few drops of 3 *N* hydrochloric acid and permitted to stand overnight it reverted completely to 4-cholesten-3-one.

(10) Melting points were determined on the hot stage of a polarizing microscope and are corrected to ±1°. Rotations were taken in pyridine at room temperature. Infrared spectra were determined in carbon tetrachloride with a Perkin-Elmer 21 instrument. Ultraviolet spectra were determined in methanol with a Beckman DU instrument. Recrystallizations from solvents containing a drop of pyridine are indicated as "methanol (pyridine)." Microanalyses were by Midwest Microlab Inc., Indianapolis, Ind.

Oxidation of the ketal according to the procedure of Poos, *et al.*,[7] provided, after work-up of the product, only unchanged ketal starting material and its hydrolysis product II.

The ketal also proved to be refractory to catalytic hydrogenation. In two attempts, 1.0 g. of the ketal was shaken with 0.093 g. of 12% palladium on charcoal in a 1% solution of potassium hydroxide in absolute ethanol under positive hydrogen pressure to give no reaction after 12 hr. The starting material was recovered quantitatively from the reaction mixture.

**3,5-Cholestadien-7-one Ethylene Ketal (VI).**—Using the same general techniques described for the previous experiments, 2.0 g. of 3,5-cholestadien-7-one provided 2.0 g. of an oily product which, upon chromatography on alumina, gave several crystalline fractions which could be recrystallized from methanol (pyridine) as long colorless needles, m.p. 102.5–103.5°, $[\alpha]_D$ −100°, $\lambda_{max}$ 236 mμ.

*Anal.* Calcd. for $C_{29}H_{46}O_2$: C, 81.8; H, 10.8. Found: C, 81.34; H, 10.95.

This compound was also obtained each time the preparation of the ethylene ketal of 5-cholesten-7-on-3-ol acetate was attempted using the procedures described above.

**6ξ-Bromo-4-cholesten-3-one Ethylene Ketal (VII).**—A dry mixture of 0.27 g. of V and 0.13 g. of N-bromsuccinimide was added to 20 ml. of dry carbon tetrachloride, and the mixture refluxed under a spotlight for 2 min. The mixture was filtered and evaporated under an air stream to a semisolid which was crystallized from acetone to give rosettes, m.p. 120–122°. The mixture melting point with 4,6-cholestadien-3-one ethylene ketal[11] was depressed to 100°; the analysis of VII was not satisfactory.

*Anal.* Calcd. for $C_{29}H_{47}BrO_2$: C, 68.6; H, 9.3. Found: C, 67.47; H, 8.98.

**6-Bromo-5-cholesten-3-one Ethylene Ketal (VIII).**—Following the same procedure described for the preparation of V above, 2.0 g. of freshly recrystallized 6β-bromo-4-cholesten-3-one provided 1.5 g. of white needles, m.p. 136°. Samples of this material turned pasty on standing in a pyridine atmosphere, but either the paste or the crude crystals readily recrystallized from acetone to long needles, m.p. 145–146°, $[\alpha]_D$ −35.5°.

*Anal.* Calcd. for $C_{29}H_{47}BrO_2$: C, 68.6; H, 9.3. Found: C, 69.44; H, 9.21.

A sample of 0.15 g. of VIII was treated with 30 ml. of hot isopropyl alcohol and 2.0 g. of sodium metal was added. After the reaction was complete (15 min.), the mixture was worked up to produce 0.11 g. of III, m.p. 129–132°, shown to be authentic by mixture melting point and infrared spectrum.

When ketalization of 1.0 g. of the bromo ketone was attempted using 0.005 g. of catalyst, a portion of opaque rosettes, m.p. 105 dec., was obtained. This material showed an infrared spectrum different from either VII or VIII, but all purification attempts led to decomposition of the product.

**Acknowledgment.**—The authors express their appreciation for a grant from the Wolcott Gibbs Fund of the National Academy of Sciences and for a generous gift of 4-cholesten-3-one from the Schering Corporation.

(11) We find this compound (see ref. 4) to show m.p. 122°, $[\alpha]_D$ +63°.

## The Synthesis of O-Acetylhydroxy-α-amino Acids

MEIR WILCHEK AND ABRAHAM PATCHORNIK

*The Department of Biophysics, The Weizmann Institute of Science, Rehovoth, Israel*

*Received November 1, 1963*

O-Acetylhydroxy-α-amino acids are conveniently used as starting materials for the synthesis of peptides and polyhydroxy-α-amino acids.[1] A number of

(1) J. Kurtz, G. D. Fasman, A. Berger, and E. Katchalski, *J. Am. Chem. Soc.*, **80**, 393 (1958).

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.

**Acknowledgment.**—This investigation was supported by Research Grant No. AM-5098 from the National Institutes of Health, U. S. Public Health Service.

(2) G. D. Fasman, E. R. Blout, *J. Am. Chem. Soc.*, **82**, 2262 (1960).
(3) W. Sakami and G. Toennies, *Biochem. J.*, **144**, 203 (1944).
(4) J. C. Sheehan, M. Goodman, and G. Hess, *J. Am. Chem. Soc.*, **78**, 1367 (1956).
(5) S. Fujiwara, S. Morinaga, and K. Norita, *Bull. Chem. Soc. Japan*, **35**, 438 (1962).

## A Convenient Synthesis of Branched Unsymmetrical Sulfides

ERNEST L. ELIEL AND RONALD A. DAIGNAULT

*Department of Chemistry, University of Notre Dame, Notre Dame, Indiana*

*Received November 8, 1963*

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).
(2) B. Weibull, *Arkiv Kemi Mineral Geol.*, **23A**, 1 (1946).