spectral properties and TLC behavior with those of authentic samples prepared as described below.

Thermal Decarboxylation of the Cinchophens. Preparation of Protio Compounds 2a–e. Typically, a 1.0-g sample (2.9 mmol) of **1a** was melted by placing a test tube containing the sample blanketed with nitrogen into a Wood's metal bath at 275 °C for 4 min. Chromatography of the reaction product (silica gel, benzene eluent) gave 0.25 g (29%) of **2a** as the only mobile spot on TLC with benzene as an eluent. Recrystallized (benzene) constant-melting samples gave: **2a,** mp 189–190 °C; **2b,** mp 152–153 °C; **2c,** mp 95–97 °C; **2d,** mp 129–130 °C;[13] **2e,** mp 67 °C.[14]

Preparation of Alcohols 3a–d. Typically, 2.1 g (5.9 mmol) of the methyl ester of acid **1a** was treated with 0.250 g (6.6 mmol) of lithium aluminum hydride in ether. The usual workup gave 1.56 g (80%) of alcohol **3a,** mp 203–205 °C. Similarly, reduction of the methyl ester of **1b** gave **3b,** mp 188–189 °C, reduction of the methyl ester of **1c** gave **3c,** mp 195–196.5 °C, and **1d** led to **3d,** mp 138.5–139.5 °C.

Preparation of the 4-Methyl Derivatives 4a–c. Procedure A: A solution of 0.500 g (1.85 mmol) of alcohol **3c** in 10 mL of chloroform was treated with 0.500 g (2.40 mmol) of phosphorus pentachloride for 24 h. The crude α-chloro compound was subjected to hydrogenolysis using 50 mg of platinum oxide as a catalyst, ethanol solvent, and hydrogen at 45 psi for 1 h. Chromatography of the isolated product (1:1 hexane–benzene, silica gel) gave 0.180 g (38%) of **4c,** mp 95–97 °C. Procedure B: The direct photolysis of alcohols **3a** and **3b** in 2-propanol under nitrogen using a Hanovia 450 W mercury lamp and a Pyrex filter gave respectively **4a,** mp 148–150 °C, and **4b,** mp 130–131 °C. Characteristically, these 4-methyl compounds showed an NMR absorption at δ 2.6–2.7 as a singlet integrating for three protons.

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Registry No.—**3b,** 66324-20-7; **3c,** 66324-21-8.

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Convenient New Procedures for the Synthesis of Ethoxythiocarbonyl Derivatives of Amino Acids[1a]

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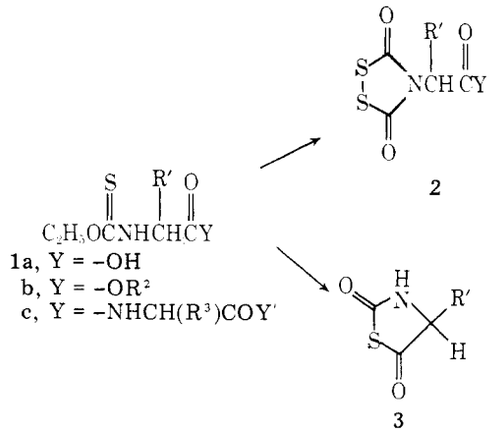
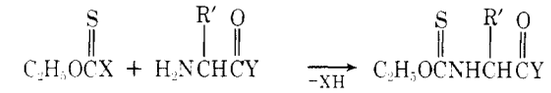
Ethoxythiocarbonyl (Etc) derivatives of amino acids **1a** and their esters **1b** are synthetic precursors to the thiol-labile dithiasuccinoyl (Dts) N^{α}-amino protecting group[2] recently developed for peptide synthesis (**2** in Scheme I). They are also intermediates in the preparation of *N*-thiocarboxy anhydrides **3** of α-amino acids (1,3-thiazolidine-2,5-diones),[3a,b] which were reported to have certain advantages for peptide synthesis[4,5] by comparison to their oxygen analogues, *N*-carboxy anhydrides. Etc derivatives **1a** and **1c** have also been explored for use as reversible amino protecting groups[6] and in a scheme for stepwise degradation of peptides,[7,8] but these applications appear to be of limited scope.

Scheme I. Synthetic Applications of Ethoxythiocarbonyl (Etc) Amino Acids and Derivatives



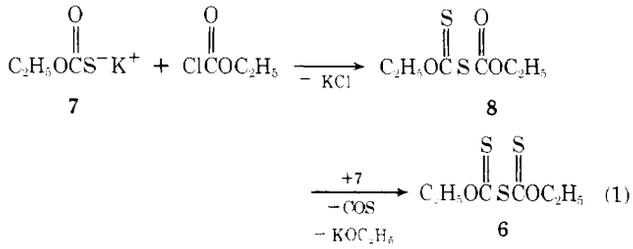
Scheme II. Synthesis of Ethoxythiocarbonyl (Etc) Derivatives of Amino Acids



4, X = -Cl
5, X = $-SCH_3$
6, X = $-SCSOC_2H_5$
10, X = $-SCH_2CO_2H$

Etc derivatives of amino acids can in principle be prepared with one of the following known reagents: ethoxythiocarbonyl chloride (**4**),[9–11] *O*-ethyl *S*-methyl dithiocarbonate (**5**),[12,13] or bis(ethoxythiocarbonyl) sulfide (**6**)[14–17] (Scheme II). Compound **4** is difficult to prepare and handle.[18] Compound **5,** while allowing formation of Etc derivatives in high yields under alkaline conditions,[4,7,8,19] is unattractive due to the stench of the methanethiol evolved in the reaction. Compound **6** does not have the disadvantages of compounds **4** and **5.** We found that it is easy to prepare and that it reacts rapidly with amino acids in aqueous solutions at pH 8–10 to give the desired derivatives in nearly quantitative yields after a straightforward workup. Progress of the reaction can be followed titrimetrically (an equivalent of base is consumed) or spectrophotometrically (Etc derivatives of amino acids have λ_{max} 245 nm with ϵ 1.3–1.5 × 10^4).

Compound **6** was originally isolated as a by-product from the synthesis of diethyl thionothiodiformate (**8**) on reaction of equimolar amounts of potassium ethyl xanthate (**7**) and ethyl chloroformate (eq 1).[14,20] We found that compound **6** can be easily obtained as the main product in place of compound **8** when the molar ratio of ethyl chloroformate to ethyl



(1)

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xanthate is decreased to 0.5. The method of preparation reported here is substantially more straightforward than others given in the literature.

Compound **6**, mp 52–53 °C, is completely stable on storage under ambient conditions over a period of years. It is relatively resistant to hydrolysis at pH 10 (estimated half-life 4.5 h). By contrast, the oxa analogue of compound **6**, diethyl pyrocarbonate, has a half-life of 18 min at pH 10.[21] Compound **6** may prove to have comparable utility to diethyl pyrocarbonate[21-24] as a reagent for chemical modification of proteins, and it has the added advantage that the resulting Etc derivatives may be characterized by ultraviolet spectrophotometry.

We also found a general new procedure to prepare pure Etc–amino acid esters **1b** in essentially quantitative yields. Amino acid ester hydrochlorides **9** were reacted with a slight excess of *O*-ethyl *S*-carboxymethyl dithiocarbonate (**10**)[20] in the presence of 2 equiv of triethylamine (eq 2). The reactions

$$\underset{\mathbf{10}}{C_2H_5OC(=S)SCH_2CO_2H} + \underset{\mathbf{9}}{HCl\cdot H_2NCH(R')CO_2R^2} + 2N(C_2H_5)_3 \xrightarrow[\text{chloroform}]{24\text{ h},\ 25\,^\circ C} \mathbf{1b} + HSCH_2CO_2^-\overset{+}{H}N(C_2H_5)_3 + HCl\cdot N(C_2H_5)_3 \quad (2)$$

were conducted in homogeneous chloroform solution (yields were somewhat lower in heterogeneous ether solution) at room temperature for 1 day. A standard aqueous acid–base workup isolated the desired Etc–amino acid ester **1b** in the organic phase.

Reagent **10** has often been applied previously[20,25-29] to the preparation of Etc derivatives of primary and secondary aliphatic or aryl amines in moderate to good yields. The xanthate ester has generally[25,27] been generated in situ from sodium or potassium ethyl xanthate and sodium chloroacetate, and the reactions with amines have been carried out in aqueous alkaline solutions. The use of crystalline **10**,[20,28] mp 58–59 °C, as well as the anhydrous reaction conditions reported here, offers several advantages. Among the possible side reactions which appear to be avoided are saponification (under aqueous conditions) of the ester moieties of starting **9** and formation of bis(carboxymethyl) trithiocarbonate[26,29] from further reaction of released mercaptoacetate with the Etc group.

Experimental Section

Melting points were determined in glass capillaries with a Thomas-Hoover apparatus and are uncorrected. Infrared absorption spectra were obtained on a Perkin-Elmer 237 B grating spectrophotometer, proton nuclear magnetic resonance spectra on a Varian Model T-60, and ultraviolet absorption spectra on a Cary Model 14 PM recording spectrophotometer. Elemental analyses were performed by Mr. S. T. Bella.

Bis(ethoxythiocarbonyl) Sulfide (Ethylxanthic Anhydride, 6). Potassium hydroxide (85%; 84.2 g, 1.27 mol) was dissolved in 330 mL of absolute ethanol, and 80 mL of carbon disulfide (1.33 mol) was added dropwise. The reaction mixture started boiling spontaneously, and a considerable amount of orange potassium ethyl xanthate crystallized out of solution. All of the crystals were redissolved again upon addition of 220 mL of water. Ethyl chloroformate (57 mL, 0.6 mol) was added, and a yellow oily lower phase immediately separated. Small crystals soon formed, which grew dramatically overnight. These were collected (100 g, crude yield 79%, but gave considerable ash upon combustion) and recrystallized from 800 mL of hot (60 °C) ethanol/water (3:1) to give 72 g (57% overall) of pale yellow needles, mp 52–53 °C (lit.[15] mp 52 °C, lit.[14] mp 55 °C after repeated recrystallizations from absolute ethanol): IR (KBr) 2970 (w), 1390 (w), 1365 (m), 1290 (s), 1240 (w, sh), 1095 (m), 1000 (s), 980 (s), 840 (w) cm^{-1}; NMR ($CDCl_3$) δ 4.70 (q, J = 7 Hz, 2 H, CH_2), 1.48 (t, J = 7 Hz, 3 H, CH_3); UV (ethanol) λ_{max} 302 nm (ϵ 1.8×10^4) and 249 nm (ϵ 6.7×10^3).

Anal. Calcd for $C_6H_{10}O_2S_3$, mol wt 210.34: C, 34.26; H, 4.79. Found: C, 34.38; H, 4.88.

Diethyl Thionothiodiformate (8). Ethyl chloroformate (19 mL, 0.2 mol) was slowly added to a solution of potassium ethyl xanthate (32 g, 0.2 mol) in 50 mL of water, in an exothermic reaction. After cooling to room temperature, the product oil was extracted into ether and dried over sodium sulfate. The title compound was obtained (20 g, 52%) after vacuum distillation under nitrogen, bp 69–75 °C (0.4 mm) [lit.[20] bp 133 °C (18 mm), lit.[30] bp 84–94 °C (1 mm)]: IR (neat) 2980 (w), 1785 (w), 1755 (s), 1720 (sh), 1440 (w), 1365 (w), 1260 (s), 1135 (s), 1100 (s), 1050 (s), 840 (w), 690 (s); UV (ethanol) λ_{max} 273 nm (ϵ 9.4×10^3).

A brown residue from the distillation step spontaneously solidified. After recrystallization from ethanol/water (3:1), this substance was shown to be identical with **6** by mixture melting point and IR.

The stability of reagent **8** in aqueous solutions was evaluated by UV spectroscopy. In pH 8.1, 0.1 M $NaHCO_3$ buffer, hydrolysis proceeded with a half-time of 9 min. The product was sodium ethyl xanthate (101%): λ_{max} 303 nm (ϵ 1.15×10^4) and 227 nm (ϵ 6.13×10^3).

***O*-Ethyl *S*-Carboxymethyl Dithiocarbonate (10).** Solid potassium ethyl xanthate (690 g, nominally 4.3 mol, practical grade pellets) was added to a chilled solution of sodium chloroacetate (500 g, nominally 4.3 mol, practical grade) in 2.2 L of water. After 3 h at room temperature, the reaction mixture was acidified with concentrated sulfuric acid (110 mL, 3.9 mol), and the yellowish-brown lower phase was taken. After standing for 2 weeks in the presence of petroleum ether (bp 30–60 °C), a substantial mass (220 g, 1.2 mol) of large light-brown crystals, mp 53–54 °C, suddenly formed. Further crystalline material (total initial isolated yield 57%) was obtained by extraction of the mother liquor into aqueous sodium bicarbonate and subsequent reacidification.

All material was effectively recrystallized (average yield 60%) by dissolving in chloroform (1 g/2.5 mL) and layering on several volumes of petroleum ether. Crystals initially formed at the interphase as the petroleum ether diffused; after a while, the phases were stirred up. Crystals were collected and washed liberally with petroleum ether; the color was completely removed by washing with a small amount of chloroform/petroleum ether (1:3). Various batches were white needles, long colorless rods, or beautiful large colorless plates, mp 58–59 °C (lit.[20] mp 58 °C, lit.[28] mp 57–58 °C), pure by thin layer chromatography in chloroform/acetic acid (19:1), R_f 0.59: NMR ($CDCl_3$) δ 11.87 (s, 1 H, COOH), 4.68 (q, J = 7 Hz, 2 H, Etc CH_2), 4.00 (s, 2 H, SCH_2), 1.43 (t, J = 7 Hz, 3 H, Etc CH_3); UV (ethanol) λ_{max} 278 nm (ϵ 1.1×10^4) and 221 nm (ϵ 6.5×10^3).

Anal. Calcd for $C_5H_8S_2O_3$, mol wt 180.25: C, 33.32; H, 4.47. Found (corrected for 0.2% ash): C, 33.37; H, 4.45.

General Procedure for Preparation of Ethoxythiocarbonyl (Etc)-L-amino Acids (1a). An amino acid (50 mmol) and bis(ethoxythiocarbonyl) sulfide (**6**) (12 g, 57 mmol) were suspended in 160 mL of water and 210 mL of ethanol. A total of 110 mL of 1 N sodium hydroxide was added at room temperature: half of it at once and the remainder over 10 min. With the last few drops of base, the reaction mixture became homogeneous; the pH was between 8 and 9. After stirring for an additional 1 h, the bright yellow reaction mixture was washed with chloroform (3 × 300 mL) and then acidified with 10 mL of 12 N hydrochloric acid to a final pH of 2. The aqueous phase turned milky white, a clear oil floated to the top, and a carbon disulfide layer settled to the bottom. Ethyl acetate (300 mL) was added to extract the product; this phase was dried over magnesium sulfate and concentrated by rotary evaporation. The products, which were pure by thin layer chromatography, were obtained in yields of 90–95% as colorless oils which often solidified upon standing. When Etc-L-amino acids **1a** were prepared for subsequent conversion to Dts-L-amino acids **2a**,[2] no further purification was necessary. Recrystallizations can often be effectively performed using benzene–petroleum ether mixtures.[8,19] For example, Etc-glycine and Etc-L-valine prepared by this procedure gave respectively mp 95–97 °C (lit.[8] mp 98–99 °C) and mp 66 °C (lit.[19] mp 65 °C) as well as satisfactory elemental analyses.

General Procedure for Preparation of Ethoxythiocarbonyl (Etc)-L-amino Acid Esters (1b). An amino acid ester hydrochloride, **9** (100 mmol), was suspended in 200 mL of chloroform containing *O*-ethyl *S*-carboxymethyl dithiocarbonate, **10** (19.0 g, 106 mmol), and triethylamine (30 mL, 214 mmol) was added. With the last few drops of triethylamine the reaction mixture became completely homogeneous; it generally took on a darkened or pinkish hue. Progress of the reaction was followed by thin-layer chromatography on silica gel GF plates (250 μm). R_f values in chloroform/acetic acid (19:1) were 0 to 0.3 (starting amino acid ester, streak, strongly ninhydrin positive before and after exposure to HCl vapors), 0.59 (starting xanthate ester, UV positive, ninhydrin negative), 0.65 to 0.75 (product Etc-amino acid ester, UV positive, direct ninhydrin negative, weak positive after heating, strong positive after exposure to HCl vapors). After 24 to 40 h at room temperature, the reaction mixtures were worked up by

washing once each with equal volumes of water (to take out the color and triethylamine hydrochloride salt), 5% sodium bicarbonate (to remove mercaptoacetate), and 0.5 N hydrochloric acid (to remove amino acid ester and excess triethylamine). The chloroform phase was dried over magnesium sulfate and concentrated by rotary evaporation. Products were obtained in yields of 97 to 100%, generally as colorless oils (Etc-L-AlaOMe solidified in 1 day to white crystals, mp 60–62 °C). Only trace impurities were occasionally seen by thin-layer chromatography, and the products were carried over for subsequent reactions without further purification.

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Registry No.—**6**, 2905-52-4; **7**, 140-89-6; **8**, 3278-35-1; **9** (R′ = R^2 = CH_3), 2491-20-5; **10**, 25554-84-1; ethyl chloroformate, 541-41-3; sodium chloroacetate, 3926-62-3; glycine, 56-40-6; L-valine, 72-18-4; Etc-glycine, 66270-46-0; Etc-L-valine, 66270-47-1; Etc-L-AlaOMe, 66270-48-2.

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Conjugate Addition of Grignard Reagents to *p*-Nitrotoluene. Competitive Attack of Entering Alkyl Group to Ortho and Para Positions

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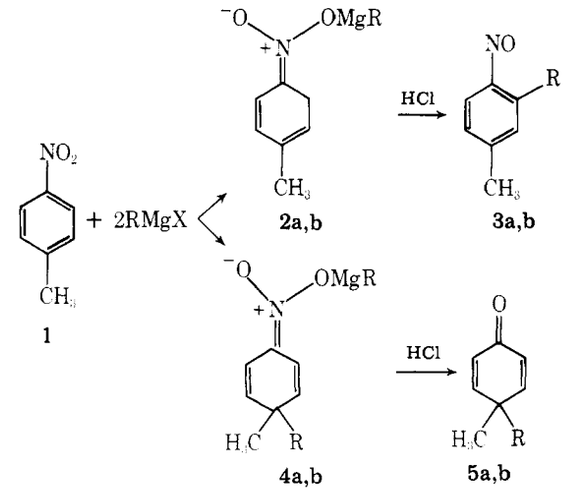
We have recently found[1] that reaction between alkylmagnesium halides and mononitro derivatives of bicyclic aromatic systems proceeds through conjugate addition of RMgX to the nitroarenic system, leading to nitroso compounds alkylated within the aromatic nucleus.

Scheme I



a, R = CH_3; b, R = n-C_4H_9

These results have led us to question the generally held belief[2] that aromatic mononitro compounds undergo 1,2 addition only in reactions with alkyl Grignard reagents.

As preexistent literature data on 1,2 addition were obtained mainly from reactions carried out on monocyclic aromatic systems, while our results were restricted to reactions of bicyclic systems, we were prompted to check the validity of our findings in the case of monocyclic nitroarenes also.

We wish to report now our recent results on reactions of a typical monocyclic substrate such as *p*-nitrotoluene, which show that conjugate addition is predominant with alkyl reagents.

In addition our data indicate that the entering alkyl group has an even likelihood to attack either an alkylated (ipso attack) or a hydrogenated aromatic carbon.

When 2 mol of RMgX were allowed to react for a few seconds with 1 mol of *p*-nitrotoluene (**1**) in tetrahydrofuran or diethyl ether, after addition of aqueous hydrochloric acid two reaction products were isolated in substantial amounts: 2-alkyl-4-methylnitrosobenzene (**3a,b**) and 4-methyl-4-alkyl-2,5-cyclohexadien-1-one (**5a,b**).

The mechanistic pattern of formation of nitroso derivatives such as **3a,b** has been previously described.[1]

Formation of **5a,b** could occur exclusively through a 1,6 addition of RMgX to the nitroarenic system, leading to cyclohexadiene nitronate adducts **4a,b.**

Unlike **2, 4a,b** will not undergo an elimination reaction by addition of hydrochloric acid; therefore they will be hydrolyzed (Nef reaction[3]) to yield **5a,b.**

As shown in the Experimental Section, we were forced to carry out the reaction under conditions considerably milder than those adopted for reactions in bicyclic systems.[1] This was due to the fact that when the reactions were carried out either at room temperature or at 0 °C the yields of **3a,b** and **5a,b** were low, while those in tars were high; in addition small amounts of several unidentified side products appeared.

Yields of nitroso derivatives were larger than those of cyclohexadienone (see Experimental Section). However, if we take into account that the attack in the ortho position is twice as likely as that in the para position, we can conclude that each kind of attack is almost competitive.

The two products can be easily separated by quantitative chromatography on a silica gel column.

Therefore, although the yields of these products are low, our method could represent a reasonable alternative with respect to conventional ways[4] to synthesize cyclohexadienones that require multistage reactions.

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