fluorides, these stretching frequencies are shifted to 1420–1395 and 1235–1200 cm^{-1}. In addition a very strong peak, due to the vibrational stretching of the sulfur–fluorine bond, appears at 800–750 cm^{-1}.[6]

Several encouraging aspects of this work include the high yields obtainable with small quantities of starting material (Table I), and the applicability of this technique to the synthesis of aliphatic sulfonyl fluorides. This type of compound is more difficult to synthesize than analogous aromatic sulfonyl fluorides. It is reported by Davies and Dick to require longer reaction times at higher temperatures, and produces lower yields of product.[7] When methanesulfonyl chloride was passed through the fluoride resin in this work, under the identical conditions used for aromatic analogs, methanesulfonyl fluoride (**8**) was produced in 71% yield.

The choice of solvents for the described technique was fairly critical. Since at least some of the reacting species were ionic, the dielectric constant of the solvent was a determining factor. An added consideration was that the solvent should not undergo reaction with the starting material or product. Acetonitrile was the obvious choice, and proved to give excellent results. Methanol was also tried, but infrared analysis of the products obtained using methanol as solvent and eluent indicated that only a portion of the starting material had been converted to the sulfonyl fluoride, while the major portion of the product was undoubtedly the methyl sulfonate.

Strongly basic quaternary amine type anion exchange resins have a low affinity for fluoride ion.[8] In fact, fluoride has the lowest affinity for Bio-Rad AG1 resins of some 16 monovalent anions reported in the commercial literature of this compound.[9] Sulfonyl fluorides are also much less reactive than the corresponding sulfonyl chlorides.[2,10] Thus, when fluoride exchanges with the chloride in the sulfonyl chlorides, the chloride generated binds tightly to the resin and the resulting more stable sulfonyl fluoride is easily isolated in the eluent from the resin. Another advantage of using the resin technique is that any sulfonic acids resulting from hydrolysis of the sulfonyl halides would have a very strong affinity for the resin,[8] and would thus be separated from the sulfonyl fluoride.

The large amount of fluoride necessary to convert a small amount of the resin from the chloride to the fluoride form bear out the observations of Gregor, *et al.*[8] This large amount of fluoride is rather prohibitive if one were to attempt to use this technique to synthesize sulfonyl fluorides in large quantities. Still, we feel that it is a very valuable method where small quantities or difficult-to-obtain starting materials are involved.

We are pursuing the use of the fluoride ion exchange resin described here in the synthesis of other fluorine-containing compounds.

Registry No.—2,4-Dinitrobenzenesulfonyl fluoride, 35426-71-2; 1,4-benzenedisulfonyl fluoride, 35426-72-3.

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The Stepwise Removal of the *S*-*p*-Nitrobenzyl Protecting Group

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In the course of our work on 4-thio-substituted β-lactams[1] the need for a sulfhydryl protecting group which can be removed without destroying the β-lactam ring arose. It was initially considered that the *p*-nitrobenzyl group, proposed by Berse and coworkers[2] as a sulfur protecting group, can fulfill this requisite. According to these authors the *p*-nitrobenzyl group is removable from *S*-*p*-nitrobenzyl-L-cysteine by catalytic hydrogenation in the presence of palladium/charcoal. A similar reductive cleavage was postulated by Baker and Kozma[3] who reported that catalytic hydrogenation of 2- and 8-*p*-nitrobenzylthiohypoxanthine afforded the respective 2- and 8-mercaptohypoxanthine and *p*-toluidine; unfortunately no quantitative figures were given. Although it could have been expected that a protective group having this quality would be widely used in peptide syntheses, the removal of the *S*-*p*-nitrobenzyl group from peptide derivatives has not yet been described.[4] This protecting group was applied by Katsoyannis[5] for the protection of cysteine in the synthesis of some peptides related to insulin, but no experiments describing its removal were reported. Ondetti and Bodanszky[6] reported that *N*-benzyloxycarbonyl-*S*-*p*-nitrobenzyl-L-cysteinylglycine was catalytically hydrogenated to *N*-benzyloxycarbonyl-*S*-*p*-aminobenzyl-L-cysteinylglycine, and *S*-*p*-nitrobenzyl-L-cysteine was reduced to *S*-*p*-aminobenzyl-L-cysteine (only R_f values are given for the last compound). Similarly Hiskey and Tucker[7] observed the absorption of the required amount of hydrogen for the catalytic hydrogenation of ethyl *N*-benzyloxycarbonyl-*S*-*p*-nitrobenzylcysteinate but could not isolate any thiol. The stepwise removal of the sulfur protecting group from *S*-*p*-nitrobenzyl-L-cysteine which is described in the present paper might offer an explanation for the discrepancy between the reported[2,6,7] results.

Hydrogenation of *S*-*p*-nitrobenzyl-L-cysteine in the presence of 10% palladium/charcoal, under the condi-

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tions reported by Berse and coworkers,[2] afforded in our hands *S*-*p*-aminobenzyl-L-cysteine. The reduction involved the absorption of 3 equiv of hydrogen and the hydrogenated mixture gave a negative nitroprusside test for sulfhydryl. Berse and coworkers[2] who claimed that hydrogenation of *p*-nitrobenzyl-L-cysteine afforded cysteine have used the Hopkins reagent (10% $HgSO_4$ in 5% aqueous H_2SO_4)[8] for its isolation as a mercury mercaptide. The mercaptide was finally converted to L-cystine by treatment with hydrogen sulfide followed by aerial oxidation. Pursuing exactly the same procedure we have obtained L-cystine from *S*-*p*-aminobenzyl-L-cysteine.

It is therefore concluded that the benzylic C–S bond in *S*-*p*-nitrobenzyl-L-cysteine did not undergo hydrogenolysis during the catalytic hydrogenation, while the benzylic C–S bond in the resulting *S*-*p*-aminobenzyl-L-cysteine was readily cleaved by mercury salts. Comparative experiments showed that *S*-benzyl- and *S*-*p*-nitrobenzyl-L-cysteine are unaffected by the Hopkins reagent under similar conditions.

Experimental Section

Melting points were determined with a Büchi apparatus under controlled conditions: heating the oil rapidly to a temperature ~20° lower than the melting point and then raising the temperature 5°/min until decomposition occurred. Nmr spectra were recorded with a Varian A-60 spectrometer.

***S*-*p*-Nitrobenzyl-L-cysteine.**—L-Cysteine hydrochloride monohydrate (17.5 g, 0.10 mol) was added, under a nitrogen atmosphere, at 0–3°, to 1 *N* NaOH (300 ml). To this was added with vigorous stirring, during 30 min, a solution of *p*-nitrobenzyl chloride (17.2 g, 0.10 mol) in freshly distilled peroxide-free dioxane (150 ml). After being stirred for additional 30 min at 0–3°, and 30 min at room temperature, the mixture was washed with ether and then acidified (pH 4–5) with concentrated hydrochloric acid (~10 ml). Concentration to 300 ml *in vacuo* (10 mm), followed by cooling (to 5°), afforded a precipitate which was filtered and washed successively with water (100 ml), ethanol (100 ml), and ether (100 ml). The crude product (23.3 g), mp 192–195°, was recrystallized from water to give 17.5 g (68%) of light yellow crystals, mp 202° dec (lit. mp 172.5–174°,[7] mp 233–234° for hydrate[2]). Two more recrystallizations from water followed by drying during 20 hr at 50° (1 mm) over P_2O_5 afforded an analytical sample: mp 197° dec; $[\alpha]^{20}D$ −4.0° (*c* 1.0, 1 *N* HCl); nmr (D_2O + CF_3CO_2D)[9] δ 2.84 (d, 2, *J* = 6 Hz, $CHCH_2S$), 3.63 (s, 2, SCH_2Ar), 4.11 (t, 1, *J* = 6 Hz, CH), 7.23 (d, 2, *J* = 9 Hz, Ar), 7.77 (d, 2, *J* = 9 Hz, Ar).

Anal. Calcd for $C_{10}H_{12}N_2O_4S$: C, 46.9; H, 4.7; N, 10.9; S, 12.5. Found: C, 47.0; H, 4.8; N, 10.7; S, 12.6.

The ethyl ester hydrochloride had mp 172–173° (lit. mp 172–173°,[2] mp 161–163°[7]).

***S*-*p*-Aminobenzyl-L-cysteine Monohydrochloride.**—A solution of *S*-*p*-nitrobenzyl-L-cysteine (1.37 g, 5.3 mmol) in ethanol (100 ml) and 1 *N* hydrochloric acid (50 ml) was hydrogenated at room temperature and at atmospheric pressure over 10% palladium/charcoal (345 mg). After the absorption of 3 equiv of hydrogen (7–8 hr) the catalyst was removed by filtration. The filtrate, which gave a negative nitroprusside test for sulfhydryl, was evaporated *in vacuo*. The oily residue was dissolved in ethanol–water (19:1 v/v 25 ml) and the solution was brought to pH 4–5 by addition of pyridine (~0.8 ml). Crystallization of the product started immediately. After this was kept for 24 hr at 5°, the yellow crystalline precipitate was filtered and washed with ethanol (10 ml) and then with ether (10 ml). The crude product (1.17 g), mp 207–208° dec, was recrystallized from ethanol–water (50 ml, 9:1 v/v) to give 0.95 g (68%) of the title compound: mp 215–216° dec; $[\alpha]^{20}D$ −5.5° (*c* 1.0, 1 *N* HCl); nmr (D_2O) δ 2.94 (d, 2, *J* = 6 Hz, $CHCH_2S$), 3.80 (s, 2, SCH_2Ar), 3.90 (t, 1, *J* = 6 Hz, CH), 7.25–7.65 (m, 4, Ar).

Anal. Calcd for $C_{10}H_{15}ClN_2O_2S$: C, 45.7; H, 5.7; N, 10.7; S, 12.2. Found: C, 45.6; H, 5.9; N, 10.4; S, 12.1.

Action of Mercury Salts on *S*-*p*-Aminobenzyl-L-cysteine.—To a stirred solution of *S*-*p*-aminobenzyl-L-cysteine (1.13 g, 4.3 mmol) in ethanol (100 ml) and 1 N hydrochloric acid (50 ml) Hopkins reagent (10% $HgSO_4$ in 5% aqueous H_2SO_4,[8] 75 ml) was added. Precipitation of a mercury mercaptide started within a few minutes. The mixture was stirred for additional 20 hr, filtered, and washed successively with water (20 ml), ethanol (20 ml), and ether (20 ml). The solid (1.86 g), mp >250°, was suspended in water (50 ml) and then saturated with H_2S. After 15 min the precipitated mercury sulfide was filtered off and excess of H_2S was removed *in vacuo*. The mixture was made alkaline by addition of 3 *N* NaOH (~4 ml), and air was bubbled through during 2.5 hr. Crystallization began on adjusting the pH to ~4 by addition of 3 *N* hydrochloric acid. The mixture was kept overnight at 5° and then filtered and washed successively with water (10 ml) and acetone (10 ml) to give crude cystine (0.41 g) mp 245–248° dec. This was dissolved in 1 *N* NaOH (3.4 ml) and then precipitated by addition of 1 *N* hydrochloric acid (3.4 ml). The solid was filtered and washed successively with water (10 ml), ethanol (10 ml), and ether (10 ml) to give 0.39 g (76%) of cystine, mp 248–250° dec (lit.[2] mp 255–260°), $[\alpha]^{25}D$ −212° (*c* 1.04, 1 *N* HCl) {lit.[2] $[\alpha]^{25}D$ −225° (*c* 1.04, 1 *N* HCl)}.

Registry No.—*S*-*p*-Nitrobenzyl-L-cysteine, 6341-94-2; *S*-*p*-aminobenzyl-L-cysteine monohydrochloride, 35340-27-3.

Acknowledgment.—The authors thank Professor W. Taub for discussions and encouragement.

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Enol Esters. XV.[1] Synthesis of Highly Hindered Esters *via* Isopropenyl Ester Intermediates

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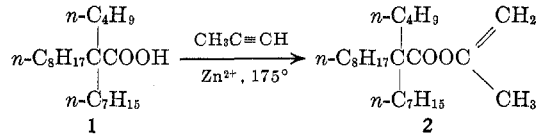
In recent years we have demonstrated the powerful acylation properties of isopropenyl esters, compounds capable of acylating even weakly nucleophilic secondary amides and imides.[3] We presently report the application of isopropenyl esters to the facile acylation of highly hindered alcohols. Our test compound, 2-butyl-2-heptyldecanoic acid[4] (**1**), was totally inert to esterification with ethanolic hydrogen chloride under reflux for periods up to 70 hr[5] but the isopropenyl ester of compound **1** rapidly acylated hindered as well as normal alcohols in a few minutes under our usual operating conditions.[3] Conversion of compound **1** to its isopropenyl ester **2** was obtained by our standard method[6] in accordance with the reaction shown by eq 1. Isopropenyl ester **2** efficiently acylated the fol-



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