Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 257 spectrophotometer; the normal Nujol mull technique was used for solids, and liquids were recorded as liquid films.

Reagents.—All of the aromatic nitro compounds were commercial samples and were purified prior to use either by distillation or crystallization. Commercial grade absolute ethanol was employed.

Reaction of Thallium with Ethanol.—Thallium (12 g) was added to 75 ml of ethanol and the mixture was stirred and heated under reflux for 7 days. The clear colorless solution was decanted free of unchanged thallium (10.8 g, 90% recovery) and the volume was made up to 100 ml with ethanol. Titration of 20-ml portions of this solution (diluted with 80-ml portions of water) against 0.1 *N* hydrochloric acid using screened methyl orange as indicator showed that a total of 1.2 g of thallium had been converted into thallium(I) ethoxide.[10]

Reaction of Thallium with Aromatic Nitro Compounds. Preparation of Azoxy Compounds.—A mixture of the aromatic nitro compound (0.014 mol) and thallium (8.5 g, 0.042 mol) in 75 ml of ethanol was stirred and heated under reflux for the appropriate period of time (see Table I). The cooled solution was decanted to remove any unchanged thallium, potassium iodide (8 g) was added, and the mixture was stirred at room temperature for 1 hr. The precipitated thallium(I) iodide was removed by filtration and the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and the solution was filtered through a short column of alumina (4 × 1 in.) to remove traces of inorganic salts, chloroform being used as eluent. The pure azoxy compound was obtained by evaporation of the chloroform eluate under reduced pressure and crystallization of the residue.

Thallium(I) ethoxide was identified as the inorganic by-product of the reaction in the following manner. A mixture of 4-nitrotoluene (3 g, 0.022 mol) and thallium (13.5 g, 0.066 mol) was heated under reflux for 5.5 hr in 75 ml of ethanol. Unchanged thallium was removed by decantation. A solution of phenol (6.2 g, 0.066 mol) in ethanol was added to the resulting solution, and the precipitated thallium salt was filtered and dried. This gave 16 g (92%) of thallium(I) phenoxide, mp 230–232°, identical in all respects with a genuine sample (lit.[11] mp 231–235°).

Registry No.—Thallium, 7440-28-0.

(10) R. C. Menzies and E. M. Wilkins, *J. Chem. Soc.*, **125**, 1148 (1924).
(11) G. H. Christie and R. C. Menzies, *ibid.*, **127**, 2369 (1925).

Thallium in Organic Synthesis. XII. Improved Syntheses of the 1-Acyloxy-2(1H)-pyridone Class of Active Esters[1,2]

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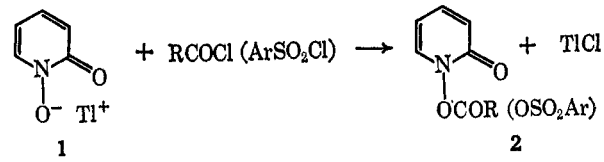
1-Acyloxy-2(1H)-pyridones (2) have been found by Paquette[4] to be useful, extremely reactive active esters, which he has successfully applied to the synthesis of a number of peptides. The procedure used by Paquette for the preparation of 2 involved heating 2-ethoxypyridine 1-oxide, usually at steam-bath temperature, with the appropriate acid chloride; the resulting 1-acyloxy-2(1H)-pyridones were purified by subsequent recrystallization. Previous studies on the use of thallium in organic synthesis have shown that acylation of thallium(I) salts of carboxylic acids,[5] phenols,[5] cyclic lactams,[6] and β-dicarbonyl compounds[7] by treatment with acid halides proceeds extremely rapidly at room temperature in a heterogeneous ether suspension. We now report a simple synthesis of 1-acyloxy-2(1H)-pyridones (2) by the reaction of acid chlorides with the thallium(I) salt of 1-hydroxy-2(1H)-pyridone (1).

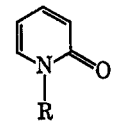
Thus, addition of 1 equiv of an acyl or a sulfonyl chloride to a suspension of the thallium(I) salt of 1-hydroxy-2(1H)-pyridone (1) in anhydrous ether at room



1 2

temperature resulted in the immediate separation of thallium(I) chloride, which was removed by filtration. Evaporation of the ether filtrate gave pure 1-acyl- (or -sulfonyl-) oxy-2(1H)-pyridones (2) in essentially quantitative yield. Representative conversions are given in Table I.

TABLE I
SYNTHESIS OF 1-ACYL- (OR -SULFONYL-) OXY-2-(1H)-PYRIDONES



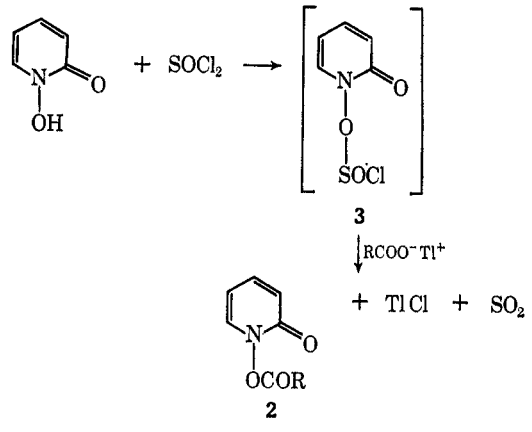
	% yield	
R	Method A[a]	Method B[b]
CH_3COO	95	69
C_6H_5COO	95	60
p-$NO_2C_6H_4COO$	98.5	57
$C_6H_5SO_2$	96	
p-$CH_3C_6H_4SO_2$	95	29

[a] Method A: reaction of the thallium(I) salt of 1-hydroxy-2(1H)-pyridone with the acid halide. [b] Method B: reaction of the thallium(I) carboxylate with 1-hydroxy-2(1H)-pyridone/$SOCl_2$.

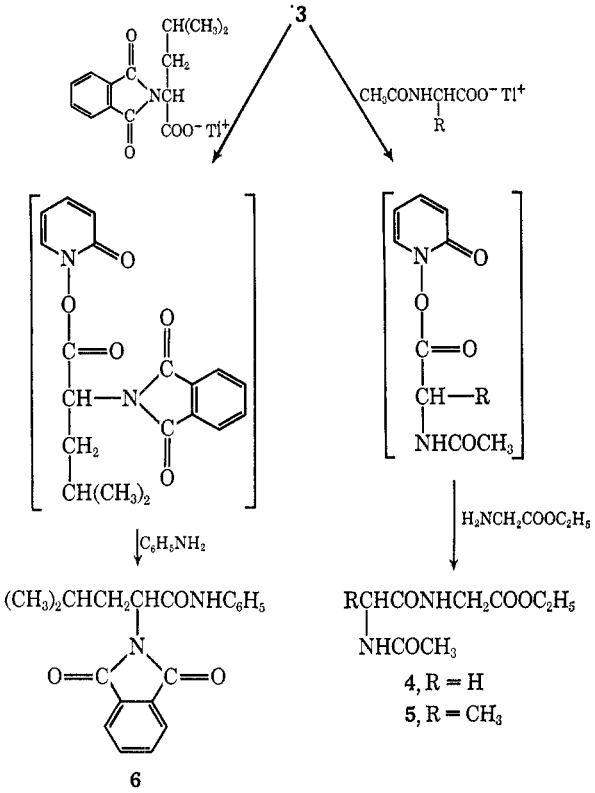
The principle disadvantage of the above synthesis of these active esters (a disadvantage also shared by Paquette's method of synthesis) for the preparation of peptides is the necessity of initial conversion of the amino acid into its corresponding (protected) acid chloride. A synthetic method avoiding the intermediacy of the acid chloride, and allowing the *direct* conversion of the amino acid into the active ester, would have obvious manipulative advantages. We report a method for the direct conversion of the thallium(I) salts of carboxylic acids and N-protected α-amino acids into 1-acyloxy-2(1H)-pyridone active esters (2).

(1) Part XI: A. McKillop, R. A. Raphael, and E. C. Taylor, *J. Org. Chem.*, **35**, 1670 (1970).
(2) We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.
(3) NRCC Postdoctoral Fellow, 1968–1970.
(4) L. A. Paquette, *J. Amer. Chem. Soc.*, **87**, 5186 (1965).
(5) E. C. Taylor, G. W. McLay, and A. McKillop, *ibid.*, **90**, 2422 (1968).
(6) A. McKillop, M. J. Zelesko, and E. C. Taylor, *Tetrahedron Lett.*, 4945 (1968).
(7) E. C. Taylor, G. H. Hawks, III, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2421 (1968).

This procedure has been successfully applied to the preparation of acetylglycylglycine ethyl ester (**4**) and N-acetyl-DL-alanylglycine ethyl ester (**5**) directly from the corresponding thallium(I) carboxylates, without isolation of the intermediate active esters. Thus, treatment of 1-hydroxy-2(1H)-pyridone with excess thionyl chloride[8] at room temperature, followed by evaporation, gave an unstable oil which we presume to be the N-chlorosulfite **3** (see Experimental Section).

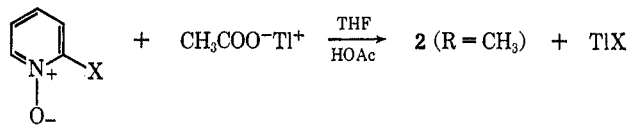


Addition of a thallium(I) carboxylate to a tetrahydrofuran solution of this oil resulted in evolution of sulfur dioxide, immediate deposition of thallium(I) chloride, and the formation of the desired active ester [which could be isolated in crystalline form by filtration of thallium(I) chloride and evaporation of the ether filtrate—see Table I]. For the preparation of amides or dipeptides (*i.e.*, **4** and **5**), however, the active ester was simply treated *in situ* with the desired amine or amino acid ester.



In order to investigate whether optically active amino acids could be converted to their active esters by this procedure with retention of optical purity, the thallium(I) salt of N-phthaloyl-L-leucine was condensed with the chlorosulfite **3** and the resulting active ester, formed *in situ*, was treated with aniline. The optically pure anilide **6** was obtained in 51% yield.

We have briefly investigated an alternate procedure for the direct conversion of thallium(I) carboxylates into the active esters **2**, based on the known propensity for rearrangement of 2-acyloxypyridine 1-oxides to 1-acyloxy-2(1H)-pyridones.[9] Treatment of 2-chloropyridine 1-oxide (**7**) or 2-bromopyridine 1-oxide (**8**) with thallium(I) acetate in tetrahydrofuran containing 20% acetic acid resulted in the formation of 1-acetoxy-2(1H)-pyridone (**2**, R = CH_3) in 58% yield. However, this reaction failed in the absence of excess acetic acid, and also failed in a wide variety of solvent systems (heptane, chloroform, ethyl acetate, pyridine, ether, dimethyl sulfoxide, and dimethylformamide), even in the presence of acid catalysts such as *p*-toluenesulfonic acid. It would thus appear that the effective nucleophile in the conversion of **7** or **8** into **2** (R = CH_3) was acetic acid, and this alternative approach was therefore not further investigated.



7, X = Cl
8, X = Br

Experimental Section[10]

Thallium(I) Salt of 1-Hydroxy-2(1H)-pyridone (1).—Thallium(I) ethoxide (7.47 g, 0.03 mol) was added to a stirred solution of 1-hydroxy-2(1H)-pyridone (3.33 g, 0.03 mol) in 75 ml of tetrahydrofuran. The thallium salt **1** precipitated immediately. Stirring was continued for 10 min, and the solid then was collected and washed well with tetrahydrofuran. The thallium salt, 9.05 g (96.5%), was analytically pure, mp 191–192°.

Anal. Calcd for $C_5H_4NO_2Tl$: C, 19.06; H, 1.28. Found: C, 19.18; H, 1.47.

Thallium(I) Salts of N-Substituted α-Amino Acids. General Procedure.—Thallium(I) ethoxide (0.01 mol) was added to a stirred solution of the amino acid (0.01 mol) in 150–250 ml of acetone. The thallium salt which precipitated immediately was filtered off after 10 min of vigorous stirring, washed well with acetone, and dried *in vacuo*.

Thallium(I) salt of acetylglycine was obtained in 92% yield, mp 76–78° (before drying) and 113° (after drying at 50° *in vacuo* for 5 hr).

Anal. Calcd for $C_4H_6NO_3Tl$: C, 14.99; H, 1.89; N, 4.37. Found: C, 15.04; H, 2.09; N, 4.29.

Thallium(I) salt of N-acetyl-DL-alanine was obtained in 98% yield, mp 165–167°.

Anal. Calcd for $C_5H_8NO_3Tl$: C, 17.95; H, 2.41; N, 4.19. Found: C, 18.29; H, 2.52; N, 4.20.

(8) Open-chain hydroxamic acids are known to rearrange to isocyanates on treatment with thionyl chloride: R. Marquis, *Compt. Rend.*, **143**, 1163 (1906); G. B. Bachman and J. E. Goldmacher, *J. Org. Chem.*, **29**, 2576 (1964). Under milder conditions, however, we have found that N-chlorosulfites analogous to **3** are apparently formed. The synthesis and properties of these interesting intermediates will form the subject of a later report.

(9) A. Ohta, *Chem. Pharm. Bull.* (Tokyo), **11**, 1586 (1963); F. J. Dinah and H. Tieckelman, *J. Org. Chem.*, **29**, 1650 (1964).

(10) Unless otherwise indicated, evaporations were done *in vacuo* at 35–40° (bath temperature). Melting points were determined with a Thomas–Hoover apparatus and are uncorrected. Infrared data refer to Nujol mull spectra taken on a Perkin-Elmer Model 237B grating infrared spectrometer. Nmr spectra were obtained on a Varian A-60A instrument. The term petroleum ether refers to the fraction of bp 30–60°. Colorless thionyl chloride of bp 75.5–76.5° (Matheson Coleman and Bell) was distilled before use.

Thallium(I) salt of N-phthaloyl-L-leucine was obtained in 78.5% yield, mp 197–198°.

Anal. Calcd for $C_{14}H_{14}NO_4Tl$: C, 36.19; H, 2.97; N, 3.02. Found: C, 36.14; H, 3.38; N, 3.22.

1-Acyl- (or -Sulfonyl-) oxy-2(1H)-pyridones (2). Method A. From 1 and Acyl or Sulfonyl Halides.—The thallium salt 1 (5 mmol) was suspended in 100 ml of anhydrous ether and an equimolar quantity of the acyl or sulfonyl halide was added. The mixture was stirred for 30 min at room temperature and filtered and the filtrate was evaporated. The residue was suspended in petroleum ether to which a small amount of ethyl acetate (10%) had been added; filtration then gave the pure products[11] in practically quantitative yield.

Method B. From Thallium(I) Carboxylates.—A suspension of 1-hydroxy-2(1H)-pyridone (2 g) in 20 ml of thionyl chloride was stirred at room temperature for 20 min with exclusion of moisture. Some 1-hydroxy-2(1H)-pyridone hydrochloride, mp 113–134° dec, was filtered off and the filtrate was evaporated. Excess thionyl chloride was removed by keeping the sample for 10 min *in vacuo* (16 mm) and the residual brown syrup was dissolved in 25 ml of anhydrous tetrahydrofuran. The thallium(I) carboxylate (0.9 equiv, based on the assumption[12] that the syrup constituted pure chlorosulfite **3**, mol wt 193) was added and the mixture was stirred vigorously for 30 min at ambient temperature. Thallium(I) chloride was then filtered off and washed well with anhydrous tetrahydrofuran, the combined filtrates were evaporated, the residue was taken up in 15 ml of anhydrous ethyl acetate, and the solution was left at 5° for several hours. After some insoluble material had been removed by filtration, the 1-acyloxy-2(1H)-pyridone crystallized from the evaporated filtrate on scratching. Stirring in ethyl acetate–petroleum ether followed by filtration gave the crude product, which was purified by crystallization from ethyl acetate. Yields of the various active esters prepared in this way are listed in Table I.

Acetylglycylglycine Ethyl Ester (4).—The chlorosulfite **3** (2.50 g, 13 mmol) was obtained from 2.70 g of 1-hydroxy-2(1H)-pyridone as described above (method B) and dissolved in 25 ml of anhydrous tetrahydrofuran. To the stirred solution was added 3.85 g (12 mmol) of thallium(I) acetylglycinate and stirring was continued for 30 min. After the precipitated thallium(I) chloride had been filtered off, glycine ethyl ester (1.24 g, 12 mmol) and 5 drops of triethylamine were added and the mixture was stirred at room temperature for 2.5 hr. A small amount of solid material was removed by filtration and the filtrate was evaporated to yield a syrup which was dissolved in 20 ml of water. The aqueous solution was passed through a column containing (lower half) of 10 g of Dowex 50W-X4 (H^+) and (upper half, separated by a plug of glass wool) 10 g of Dowex 21K (OH^-). The column was thoroughly washed with water and the combined eluates were evaporated. Two coevaporations with absolute ethanol followed by treatment with activated charcoal gave 1.02 g (42%) of a colorless solid, mp 139–141°. Recrystallization from absolute ethanol raised the melting point to 147–148° (lit. mp 152[13] and 150°[14]). The nmr spectrum (in D_2O) confirmed structure **4**.

N-Acetyl-DL-alanylglycine Ethyl Ester (5).—The dipeptide **5** was obtained from **3**, the thallium(I) salt of N-acetyl-DL-alanine, and glycine ethyl ester, in a similar manner to that described for the synthesis of **4**. Crystallization of the crude product, mp 109–111°, from chloroform–petroleum ether gave pure material, mp 113–115°, yield 29%.

Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.98; H, 7.46; N, 13.25. Found: C, 49.64; H, 7.29; N, 13.08.

The nmr spectrum of **5** ($CDCl_3$) showed a triplet at τ 8.73 (3 H), a doublet at 8.60 (3 H), a singlet at 8.00 (3 H), a singlet at 6.02 (2 H), a quartet at 5.80 (2 H), and a quartet at 5.38 (1 H).

N-Phthaloyl-L-leucine Anilide (6).—The chlorosulfite **3** (1.0 g, 5.2 mmol) was dissolved in 20 ml of anhydrous tetrahydrofuran and 1.57 g (4.65 mmol) of the thallium(I) salt of N-phthaloyl-L-leucine added. The mixture was stirred at room temperature for 1 hr, then, without filtration, aniline (510 mg, 5.5 mmol) was added, and stirring was continued for 2 hr. The syrup which was obtained after filtration and evaporation was dissolved in methylene chloride (60 ml), the solution was extracted twice with 20-ml portions of a 5% aqueous sodium bicarbonate solution, the organic layer was dried over anhydrous sodium sulfate, treated with activated charcoal, and filtered, and the filtrate was evaporated. The residue was dried *in vacuo* to give 970 mg of crude product, mp 130–135°. Crystallization from benzene–petroleum ether gave 795 mg (51%) of beautiful needles, mp 154–155°, $[\alpha]D$ −21° (*c* 0.9, glacial acetic acid).[15]

1-Acetoxy-2(1H)-pyridone (2, R = CH_3).—2-Bromopyridine 1-oxide (**8**) hydrochloride (1.2 g, 6.1 mmol) was suspended in 10 ml of anhydrous tetrahydrofuran and 10 g of sodium bicarbonate was added. The slurry was mixed well and filtered after 10 min; the residue was thoroughly washed with tetrahydrofuran. The volume of the filtrate was then approximately 50 ml. Thallium(I) acetate (1.6 g, 6.1 mmol) was added together with 10 ml of glacial acetic acid [to dissolve the thallium(I) salt] and 5 ml of acetic anhydride (to remove traces of water). The clear solution was then heated under reflux; after 30 min a fine precipitate of thallium(I) bromide started to separate. Heating was continued for 18 hr, thallium(I) bromide (1.19 g, 66.9%) was removed by filtration, and the filtrate was evaporated. The syrupy residue was dissolved in anhydrous ethyl acetate and unreacted insoluble thallium(I) acetate was removed by filtration. Addition of petroleum ether resulted in slow crystallization of 510 mg (59%) of **2** (R = CH_3), mp 92–93°. Recrystallization from ethyl acetate–petroleum ether gave beautiful prisms, mp 94–95° (lit.[4] mp 93–94°).[16]

2-Chloropyridine 1-oxide (**7**) under the same conditions gave (R = CH_3) in 58% yield.

Registry No.—Thallium (I) salt of acetylglycine, 23715-40-4; thallium (I) salt of N-acetyl-DL-alanine, 23715-41-5; thallium (I) salt of N-phthaloyl-L-leucine, 23715-42-6; **1**, 23715-39-1; **4**, 3757-98-0; **5**, 23595-74-6.

(11) Identity and purity were determined by comparison of physical data (melting point and ir and uv spectra) with reported values.[4]

(12) Attempted purification of this syrup led to extensive decomposition. We assume that it is the N-chlorosulfite **3** rather than N-chloro-2(1H)-pyridone because reaction with the thallium(I) carboxylate results in vigorous evolution of sulfur dioxide. Gas evolution is almost explosive in the absence of solvent, but is readily controlled if the N-chlorosulfite is dissolved in tetrahydrofuran before the thallium(I) carboxylate is added.

(13) E. Fischer, *Chem. Ber.*, **35**, 1095 (1902).

(14) R. G. Petrova, L. N. Akinova, and N. I. Gavrilov, *Zh. Obshch. Khim.*, **24**, 2239 (1954).

(15) J. C. Sheehan, D. W. Chapman, and R. W. Roth [*J. Amer. Chem. Soc.*, **74**, 3822 (1952)] reported mp 154.5–156°, $[\alpha]D$ −21° (acetic acid).

(16) Uv and ir spectra were also identical with the reported values.[4]

The Addition of N-Bromosuccinimide to 3-Sulfolene

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The use of N-bromosuccinimide (NBS) as an allylic brominating agent has been known for some time and has enjoyed wide applicability.[1] A lesser known, but not entirely unknown, reaction of NBS is the addition of this reagent to the double bond.[1b,2-4] This latter process is usually observed when electron-withdrawing groups[3] or steric factors[2] make stabilization of the allylic radical difficult. Succinimido radicals have been suggested.[2,3]

In connection with the above, we have reexamined the reaction of NBS with 2,5-dihydrothiophene-1,1-dioxide (3-sulfolene, **1**). Backer, *et al.*,[5] reported that

(1) (a) C. Djerassi, *Chem. Rev.*, **43**, 271 (1948); (b) L. Horner and E. H. Winkelmann, *Angew. Chem.*, **71**, 349 (1959).

(2) L. H. Zalkow and C. D. Kennedy, *J. Org. Chem.*, **29**, 1290 (1964), and references cited therein.

(3) W. J. Bailey and J. Bello, *ibid.*, **20**, 525 (1955).

(4) J. R. Shelton and C. Ciadella, *ibid.*, **23**, 1128 (1958).

(5) H. J. Backer, W. Stevens, and N. Dost, *Rec. Trav. Chim. Pays-Bas*, **67**, 451 (1948); *Chem. Abstr.*, **43**, 558 (1948).