Cl_2 to give 0.43 g (93%) of 2-tosylamidoethanethiol (**4**) as a colorless oil having ir and mass spectra nearly identical with those of **4** obtained from the reduction of **1**.

C. Reaction with 2-Naphthalenethiol.—A suspension of 100 mg (0.22 mmol) of **6** and 74 mg (0.46 mmol) of 2-naphthalenethiol in 1:1 EtOH–CH_2Cl_2 was treated with 5 drops of Et_3N. The solid dissolved immediately. After *ca.* 16 hr, the solvent was evaporated and the residue was crystallized from EtOH. Analysis of both the solid and the filtrate by tlc (silica gel–benzene) showed the solid to be a mixture of two compounds; one of these, the more mobile, was evidently 2-naphthyl disulfide by tlc comparison; the other probably was 2-tosylamidoethyl 2-naphthyl disulfide (**5**) but was not positively identified. The filtrate contained three compounds; tlc comparison with authentic materials indicated two of them to be **1** and 2-naphthyl disulfide; the third presumably was **5**.

***o*-Tosylamidophenyl Disulfide (8).**—A solution of 10.0 g (40.3 mmol) of *o*-aminophenyl disulfide and 17.4 g (91 mmol) of tosyl chloride in 125 ml of pyridine was allowed to stand for 4 days. Filtration of the solution, dilution with EtOAc, and filtration removed a hygroscopic, water-soluble solid (presumably pyridine·HCl). The filtrate was washed several times with aqueous 10% HCl, dried, and evaporated to give a thick oil that slowly crystallized. Recrystallization from EtOAc and from Me_2CO gave 14.0 g (62%) of **8**: mp 162–167°; ir (Nujol) 3320, 1603, 1580, 1340 (s), 1280, 1165 (s), 1090, 1060, 925, 812, 767, and 660 cm^{-1}; nmr δ 2.16 (s, 3), and 6.7–7.9 (m, 9); mass spectrum *m/e* (rel intensity) 558 (6), 557 (8), 556 (29), 402 (5), 246 (20), 215 (10), 214 (45), 200 (10), 199 (60), 181 (7), 180 (6), 167 (5), 156 (5), 155 (8), 154 (14), 140 (8), 139 (13), 125 (11), 124 (67), 122 (7), 97 (8), 96 (17), 95 (5), 92 (20), 91 (100), 90 (5), 89 (6), 79 (28), 77 (7), 76 (7), and 65 (38).

Anal. Calcd for $C_{26}H_{24}N_2O_4S_4$: C, 56.09; H, 4.34. Found: C, 55.93; H, 4.48.

Attempted Synthesis of the Benzothiazete 10.—A solution of 4.90 g (8.80 mmol) of **8** in 50 ml of CH_2Cl_2 was cooled to −30°, and 8.8 mmol of Cl_2 in CCl_4 was added. The solution was stirred and allowed to warm to 0°. Then 3 ml of Et_3N was added (a considerable amount of solid appeared quickly, although Et_3N·HCl is soluble in the medium). Stirring was continued for 0.5 hr. The suspension was shaken twice with H_2O (solid remained in the organic phase), and then solid was separated to give 1.90 g (39%) of **12** as a white solid: mp >250° (insoluble in $CHCl_3$, CH_2Cl_2, EtOH, C_6H_6, C_5H_5N, H_2O, DMF, and $C_2H_2Cl_4$, soluble in secondary amines and in pyridine solutions of thiols); ir (Nujol) 1603, 1333 (s), 1300, 1170 (s), 1090, 915, 890, 851, 810, 731, and 669 cm^{-1}; mass spectrum *m/e* (rel intensity) 556 (24), 554 (4), 443 (15), 260 (5), 246 (18), 244 (9), 214 (50), 199 (57), 181 (6), 180 (6), 156 (8), 155 (14), 139 (17), 124 (43), 92 (10), 91 (100), and 65 (40). The filtrate contained only **8** (tlc).

Reaction of 12 with Diethylamine.—When 200 mg of **12** was placed in 30 ml of Et_2NH and heated under reflux for 5 min, dissolution occurred. After a reflux period of 3 hr, the excess Et_2NH was removed and the resulting oil was analyzed by tlc (silica gel, EtOAc) and by mass spectrometry, giving the same spectrum as authentic **11**. After 2 days at *ca.* 25°, analysis of the hardened oil by mass spectrometry showed only Et_2NH (trace) and disulfide **8**, consistent with virtually complete decomposition of **11**.

***o*-Tosylamidobenzenesulfenyl Diethylamide (11).**—A stirred solution of **8** (556 mg, 1.00 mmol) in 20 ml of CH_2Cl_2 was cooled to −30°, and Cl_2 (1.05 mmol) was added. After 0.5 hr, the solution was allowed to warm to *ca.* 25°, and 0.5 ml (4.9 mmol) of Et_2NH was added. After 0.5 hr, the solution was diluted with 30 ml of CCl_4, washed with H_2O, dried ($MgSO_4$), filtered, and evaporated to give 0.75 g (107%) of **11** as a light brown oil; tlc showed the same characteristics as solutions of **11** prepared from **12** and Et_2NH, *viz*, one large spot and two small ones. Attempted distillation resulted only in decomposition, and chromatography over Florisil (*ca.* 50% recovery) failed to provide **11** more pure than the crude product: ir (thin film) 3280, 2990, 1600, 1470, 1345, 1173 (s), 1090, 923, 820, 792, 760, and 665 cm^{-1}; nmr δ 1.10 (t, 6, CH_3CH_2), 2.27 (s, 3, CH_3Ar), 2.84 (q, 4, CH_2CH_3), 6.6–7.8 (m, 8, ArH), and 8.06 (s, 1, NH); mass spectrum *m/e* (rel intensity) 350 (36), 214 (19), 199 (19), 155 (6), 125 (7), 124 (42), 96 (7), 91 (42), 80 (16), 73 (23), 72 (92), 65 (14), 63 (5), 57 (100), 56 (9), 45 (5), 44 (23), 43 (6), 42 (20), and 41 (8).

Decomposition of 2-Aminoethyl 2-Aminoethanethiolsulfonate Monohydrochloride (14).—A solution (pH 4) of 10.0 mmol of **13** in water was neutralized with 10.0 mmol of NaOH (the pH increased to 7–8). Tlc (Brinkmann Polygram MN Polyamide, with 10:1:0.15 EtOH–Me_2CO–Et_2NH) showed two ill-defined spots, R_f 0.5 (by fluorescence) and 0.3 (by I_2 vapor). Evaporation and vacuum drying gave 2.73 g of residue (92% of the 2.97 g of **13** and NaOH used). Ethanol separated 0.35 g of taurine, mp > 210° (lit.[9] mp 300–305° dec); the ir spectrum was virtually identical with that of authentic taurine. The crude residue from an identical experiment was dissolved in H_2O, and 0.80 g of NaOH was added. The mixture then was treated with tosyl chloride. After 6 hr, a CH_2Cl_2 solution was washed thrice with water and evaporated to give 1.20 g, identified as **1** by tlc comparison with authentic **1** (silica gel–*n*-butyl acetate).

Registry No.—**1**, 23516-74-7; **4**, 23516-75-8; **6**, 23516-76-9; **8**, 3982-42-1; **11**, 23516-78-1.

(9) F. Cortese, *J. Amer. Chem. Soc.*, **58**, 191 (1936).

Thallium in Organic Synthesis. XI. Preparation of Azoxy Compounds[1,2]

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Thallium is abundant, inexpensive, and readily available in bulk in a high state of purity. Surprisingly, the literature is virtually devoid of descriptions of direct applications of the metal to organic synthesis. We wish to describe in this paper the use of thallium in a simple, high-yield procedure for the preparation of aromatic azoxy compounds.

During studies on the use of thallium salts in the synthesis of biaryls,[3] we were able to confirm an early report by Spencer and Wallace[4] that small amounts of biphenyl and thallium(I) iodide were formed when thallium and iodobenzene were heated together under reflux. Although more detailed investigation of this reaction has established that the overall process is of little synthetic value as a route to biaryls,[5] an interesting side reaction was observed when nitrobenzene was employed as solvent. In refluxing nitrobenzene thallium underwent slow oxidation to give thallium(III) oxide, with concomitant formation of significant amounts of azoxybenzene (eq 1). The conversion outlined in eq 1 also proceeds smoothly in a number of high boiling solvents such as dimethylformamide, *o*-dichlorobenzene, and diglyme, but extended reaction

$$2C_6H_5NO_2 + 2Tl \longrightarrow C_6H_5\overset{+}{N}(O^-)=NC_6H_5 + Tl_2O_3 \qquad (1)$$

(1) We gratefully acknowledge the financial support of this work by the Smith Kline and French Laboratories, Philadelphia, Pa.

(2) Part X: A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2427 (1969).

(3) A. McKillop, L. F. Elsom, and E. C. Taylor, *J. Amer. Chem. Soc.*, **90**, 2423 (1968).

(4) J. F. Spencer and M. L. Wallace, *J. Chem. Soc.*, **93**, 1827 (1908).

(5) A. McKillop, J. S. Fowler, and E. C. Taylor, unpublished results.

TABLE I
CONVERSION OF SUBSTITUTED NITROBENZENES INTO AZOXY COMPOUNDS

Nitrobenzene derivative	Azoxy compound	Registry no.	Time, hr[a]	Yield, %[b]	Mp, °C	Lit. mp, °C
Nitrobenzene	Azoxybenzene	495-48-7	6	76	34.5–35.5	35[c]
2-Nitrotoluene	2,2′-Dimethylazoxybenzene	956-31-0	6	73	57–58	60[c]
3-Nitrotoluene	3,3′-Dimethylazoxybenzene	19618-06-5	6	77	33–35	38–39[d]
4-Nitrotoluene	4,4′-Dimethylazoxybenzene	955-98-6	5	77	66–68	68[c]
4-Ethylnitrobenzene	4,4′-Diethylazoxybenzene	23595-86-0	8.5	80	Bp 180–185 (0.7 mm)	bp 244 (16 mm)[e]
2,5-Dimethylnitrobenzene	2,2′,5,5′-Tetramethylazoxybenzene	14381-98-7	7.5	64	110–112	111.5–112.5[f]
2-Nitrobiphenyl	2,2′-Diphenylazoxybenzene	7334-10-3	4.5	84	158–160	160–163[g]
2-Nitroanisole	2,2′-Dimethoxyazoxybenzene	13620-57-0	5.5	80	79–80	81–82[c]
4-Nitroanisole	4,4′-Dimethoxyazoxybenzene	1562-94-3	5.5	76	116.5–118.5, 134.5–135.5	118.5, 135[h]
4-*n*-Butyloxynitrobenzene	4,4′-Di-*n*-butyloxyazoxybenzene	17051-01-3	12	80	102–104, 136.5–137	107, 134[i]
4-*n*-Hexyloxynitrobenzene	4,4′-Di-*n*-hexyloxyazoxybenzene	2587-42-0	7	71	80–81.5, 128.5	81, 127[i]
4-Fluoronitrobenzene	4,4′-Difluoroazoxybenzene	326-04-5	12	89	84–86	86–87[c]
2-Chloronitrobenzene	2,2′-Dichloroazoxybenzene	13556-84-8	1.5	86	53.5–55	55–56[c]
3-Chloronitrobenzene	3,3′-Dichloroazoxybenzene	139-24-2	4.5	84	95.5–97	96[c]
4-Chloronitrobenzene	4,4′-Dichloroazoxybenzene	614-26-6	5	93	154–156	155–156[c]

[a] In most cases about 5–10% of the thallium was *not* consumed during the reaction. Increasing the time of reaction had no significant effect on the yield, and resulted in minor amounts of decomposition. [b] No attempt was made to optimize yields. [c] P. H. Gore and O. H. Wheeler, *J. Amer. Chem. Soc.*, **78**, 2160 (1956). [d] L. Zechmeister and P. Rom, *Ann.*, **468**, 117 (1929). [e] B. T. Newbold and D. Tong, *Can. J. Chem.*, **42**, 836 (1964). [f] E. Bamberger, *Chem. Ber.*, **59**, 418 (1926). [g] E. Wenkert and B. F. Barnett, *J. Amer. Chem. Soc.*, **82**, 4671 (1960). [h] R. S. Porter and J. F. Johnson, *J. Phys. Chem.*, **66**, 1826 (1962). [i] C. Weygand and R. Gabler, *Chem. Ber.*, **71B**, 2399 (1938). [j] C. Weygand and R. Gabler, *J. Prakt. Chem.*, **155**, 332 (1940).

times are necessary (24–60 hr) and yields of azoxy compounds are only moderate in most cases (20–60%).

A particularly important feature of the above transformation is the conversion of thallium into thallium(III) oxide, presumably *via* the intermediacy of the much less stable thallium(I) oxide. It was apparent that use of a solvent which could intercept the initially formed thallium(I) oxide, preferably by formation of a soluble thallium(I) derivative, might simplify considerably the experimental procedure. In justification of this simple rationalization, we have found that oxidation of thallium by aromatic nitro compounds proceeds smoothly in refluxing ethanol.[6] The metal dissolves rapidly to give a homogeneous solution containing thallium(I) ethoxide and the corresponding azoxy compound (eq 2). Addition of potassium

$$2ArNO_2 + 6Tl + 6EtOH \longrightarrow ArN(O^-)=NAr + 6TlOEt + 3H_2O \quad (2)$$

iodide to the reaction mixture results in precipitation of thallium(I) iodide. Removal of the inorganic salt by filtration followed by evaporation of the filtrate under reduced pressure gives the azoxy derivative directly. Yield and experimental data for typical conversions are listed in Table I.

The formation of azoxy compounds by treatment of nitroarenes with various specially prepared modifications of thallium has been noted previously by McHatton and Soulal.[7] Unlike these authors, however, we observed no tar formation in any of the examples quoted. Further, the speed and experimental simplicity of the present procedure, in which commercial thallium is used, contrast favorably with the prolonged reaction times (usually 14–28 days) reported by McHatton and Soulal; the necessity of employing a specially prepared form of the metal is also avoided.

(6) The role of ethanol in this reaction is apparently specific. No azoxy compound was isolated when methanol, 2-methyl-2-propanol, or cyclohexanol was employed as solvent. It should be noted that no appreciable conversion of thallium metal into thallium(I) ethoxide takes place in refluxing ethanol in the *absence* of the nitro compound (see Experimental Section).

(7) L. P. McHatton and M. J. Soulal, *J. Chem. Soc.*, 4095 (1953).

In addition to the examples listed in Table I, investigation of a wide range of substituted nitro compounds has defined the scope and limitations of the present synthesis. Electron-withdrawing substituents (–CHO, –COR, –COOH, –COOR, and –CN) totally inhibit the reaction, as do phenolic hydroxyl groups and both substituted and unsubstituted amino groups. High yields of azoxy compounds are obtained from nitro aromatics with ether or alkyl substituents (see Table I), the positional relationship of the substituents in no way influencing the overall reaction. Both fluoro- and chloro-substituted nitro aromatics react smoothly with retention of the halogen, but bromo- and iodo-substituted compounds give complex mixtures from which only low yields of haloazoxy derivatives could be isolated.

Within these limitations, the present method constitutes a useful alternative to the more commonly accepted procedures for the synthesis of azoxy compounds.[8] In particular, it should be noted that a single pure product was obtained in each of the examples listed in Table I and that, under the reaction conditions indicated, standard control experiments established that azoxy compounds were stable to further reduction either by thallium or thallium(I) ethoxide.[9] It is interesting to note also that, unlike the alkali metal alkoxides, thallium(I) ethoxide does not reduce nitroarenes; 4-nitroanisole, for example, was recovered in quantitative yield after being heated under reflux for 12 hr with an excess of thallium(I) ethoxide in ethanol.

(8) See, for example, P. A. S. Smith, "Open-Chain Nitrogen Compounds," Vol. 2, W. A. Benjamin, Inc., New York, N. Y., 1966, pp 321–323; S. Swann, Jr., in "Technique of Organic Chemistry," Vol. II, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, pp 478–481; R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," John Wiley & Sons, Inc., New York, N. Y., 1965, pp 765–768; K. H. Schündehütte in Houben-Weyl's "Methoden der Organischen Chemie," Vol. 10, Part 3, E. Müller, Ed., G. Thieme Verlag, Stuttgart, 1965, pp 752–770.

(9) Formation of small amounts of 2,2′-dichloroazobenzene could be detected when a solution of 2-chloronitrobenzene in ethanol was heated under reflux with thallium for longer than 12 hr. Polyhalonitro compounds, on the other hand, are apparently reduced directly to the corresponding azo compounds. 2,4-Dichloronitrobenzene, for example, gave 2,2′,4,4′-tetrachloroazobenzene in 80% yield on treatment with thallium in refluxing ethanol for 12 hr.

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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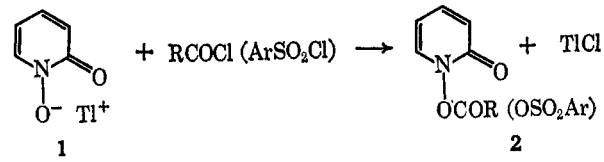
1-Acyloxy-2(1H)-pyridones (2) have been found by Paquette[4] to be useful, extremely reactive active esters, which he has successfully applied to the synthesis of a number of peptides. The procedure used by Paquette for the preparation of 2 involved heating 2-ethoxypyridine 1-oxide, usually at steam-bath 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).

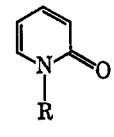
Thus, addition of 1 equiv of an acyl or a sulfonyl chloride to a suspension of the thallium(I) salt of 1-hydroxy-2(1H)-pyridone (1) in anhydrous ether at room



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).

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(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).