sponding amines **1a**–**7a** or with the Δs values were not successful. However, a qualitative trend as anticipated does occur for the species **1a**–**3a** and for the secondary amines **3a**, **5a**, and **6a**, while the tertiary amine **4a** is found to be out of place owing to the steric B-strain. As we have suggested earlier,[4] acidity constant of a compound depends on several factors. Hybridization of an acid and its conjugate base, of course, may be one of the most important ones governing the relative energy difference between them. However, steric effect may also play a significant role.

Registry No. **1a**, 7664-41-7; **1a** (carbanion), 15194-58-8; **1b**, 14798-03-9; **2a**, 74-89-5; **2a** (carbanion), 25013-41-6; **2b**, 17000-00-9; **3a**, 124-40-3; **3a** (carbanion), 25012-80-0; **3b**, 17000-01-0; **4a**, 75-50-3; **4a** (carbanion), 65114-21-8; **4b**, 16962-53-1; **5a**, 151-56-4; **5b**, 24151-28-8; **6a**, 503-29-7; **6a** (carbanion), 60211-41-8; **6b**, 66203-35-8; **7a**, 100-76-5; **7a** (carbanion), 89849-42-3; **7b**, 49623-78-1; **8**, 1724-45-4.

Supplementary Material Available: Figure 4 showing the optimized geometries for all amines and protonated amines (4 pages). Ordering information is given on any current masthead page.

Thallium in Organic Synthesis. 65. A Novel Synthesis of Benzoxazoles from Anilides[1,2]

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Although benzoxazoles are conventionally prepared from *o*-aminophenols by cyclization with carboxylic acids, imino ethers, nitriles, etc.[3] a few procedures have been described which commence with an anilide and subsequently introduce the requisite ortho-situated oxygen substituent. Several groups have reported the formation of benzoxazoles by intramolecular trapping of an aryne intermediate generated in situ from 2- or 3-haloanilides.[4] Anodic oxidation of *N*-methyl-4-alkoxyanilides gives the corresponding benzoxazolium salts in good yield.[5] α,*N*-Diaryl nitrones rearrange upon prolonged heating (1–7 days) at 150 °C in the presence of *O*-methyl diphenylphosphinothioate to give 2-arylbenzoxazoles.[6] Benzoxazoles have also been prepared from aryl azides substituted in the para position with electron-withdrawing substituents by heating in PPA and a carboxylic acid.[7] Finally, 1,2-diacetamido-4-bromobenzene has been reported to undergo intramolecular oxidative coupling in low yield to a benzoxazole when treated with thallium(III) tris(trifluoroacetate) (TTFA) in refluxing TFA.[8]

We have established in previous work that a wide variety of anilides undergo smooth ortho thallation when treated with TTFA in a mixture of TFA and ether.[9] We now report that benzoxazoles are readily formed upon photolysis of these ortho-thallated anilides in cyclohexane suspension (see Table I). In most cases, moderate yields were obtained within 2–6 h, although occasionally an increase in photolysis time resulted in a slight increase in yield. Of the substrates examined, only (3-chloro-2-acetamidophenyl)thallium(III) bis(trifluoroacetate), failed to produce a benzoxazole, perhaps because of the photolability of the C–Cl bond.

Since unsymmetrical biaryls can be obtained in almost quantitative yield by photolysis of arylthallium(III) bis(trifluoroacetates) in benzene,[10] an attempt was made to convert the above ortho-thallated anilides into 2-aminobiphenyl derivatives by irradiation in benzene. Photolysis of (2-acetamidophenyl)thallium(III) bis(trifluoroacetate) (**1a**) in benzene suspension at 300 nm for 3 h gave a very small amount (6%) of 2-acetamidobiphenyl; the major product formed was 2-methylbenzoxazole, indicating that intramolecular trapping of the aryl radical (formed by homolysis of the C–Tl bond) readily predominated over intermolecular capture by solvent.

This route to benzoxazoles, which commences with an aromatic amine and introduces the *o*-hydroxyl group by an intramolecular route, appears to be more flexible than conventional procedures which require an *o*-aminophenol as starting material. As a demonstration of the utility of this route to benzoxazoles, we have carried out a new synthesis of 2-(4-chlorophenyl)-α-methyl-5-benzoxazoleacetic acid (**3**) (benoxaprofen)[11] (see Scheme I). *m*-Nitropropiophenone (**4**) was reduced with hydrogen/Pt in ethanol to give *m*-aminopropiophenone, which was aroylated under Schotten–Baumann conditions with *p*-chlorobenzoyl chloride to give amide **5** (77% overall yield). This material was then converted with thallium(III) trinitrate (TTN) in a solution of methanol and trimethyl orthoformate (TMOF)[12] to **6**, which was thallated with TTFA in a mixture of ether and TFA; the arylthallium bis(trifluoroacetate) **7** precipitated directly from the reaction mixture in 38% overall yield. Photolysis of **7** in cyclohexane solution in a Rayonet reactor at 300 nm then gave benoxaprofen methyl ester (**8**) (90%), identical in all respects with an authentic sample.[13] Alkaline hydrolysis of **8** gave benoxaprofen (**3**).

(1) For the previous paper in this series, see: Taylor, E. C.; Katz, A. H.; Alvarado, S. I.; McKillop, A. *J. Organomet. Chem.* **1985**, *285*, C9–C12.

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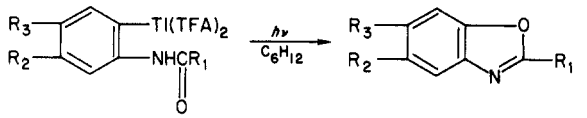
(11) This compound was introduced several years ago for the treatment of arthritis (Roberts, P. J. *Drugs Future* **1980**, *5*, 461. Huskisson, E. C. *Eur. J. Rheumatol. Inflammation* **1979**, *3*, 29), but fatalities resulting from its use led to its withdrawal from both the British and American markets. Several syntheses of this interesting representative of the α-methylarylacetic acid family of antiinflammatory agents have been reported (Dunwell, D. W.; Evans, D.; Hicks, T. A.; Cashin, C. H.; Kitchen, A. *J. Med. Chem.* **1975**, *18*, 53. Drew, R.; Meffin, P. J.; Hugel, H. M. *Synth. Commun.* **1985**, *15*, 1075); all of them employ the classical procedure for benzoxazole formation from an *o*-aminophenol precursor and standard methodology for the preparation of the α-methylacetic acid side chain.

(12) These reaction conditions for effecting the "acetophenone rearrangement" are critical, since propiophenones are known to undergo oxidation at the α-carbon atom in the absence of TMOF: McKillop, A.; Taylor, E. C. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Eds.; Pergamon: Oxford, 1982 Vol. 7, p 465. McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3340).

(13) We are grateful to Eli Lilly & Co. for providing us with an authentic sample of this material.

0022-3263/86/1951-1607$01.50/0

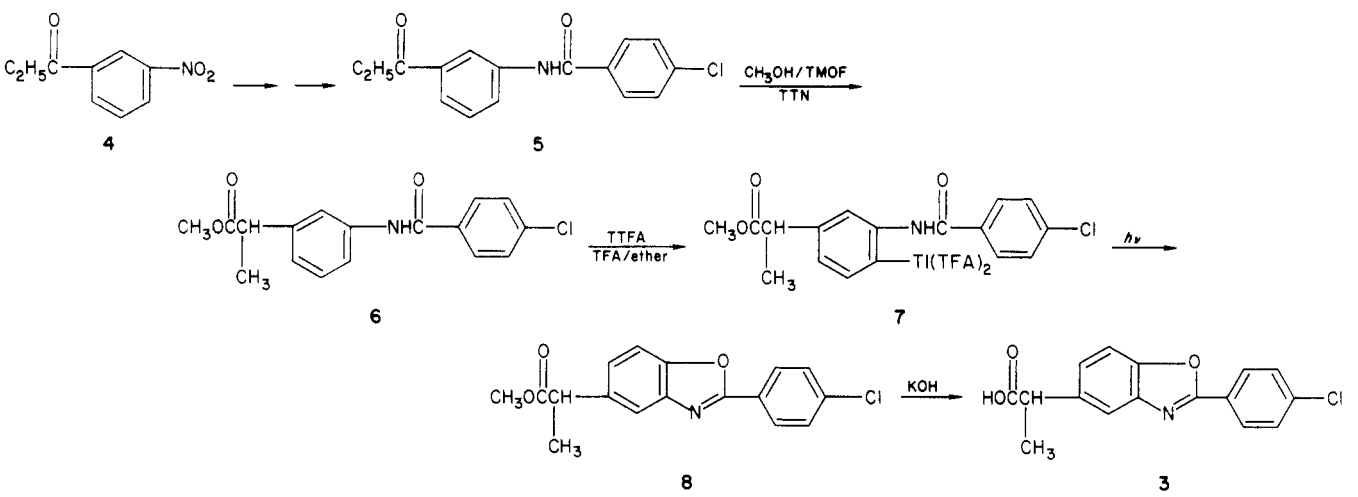
Table I. Synthesis of Benzoxazoles by Photolysis of Ortho-Thallated Anilides



compd	R_1	R_2	R_3	time, h	yield, %	ref
a	CH_3	H	H	2	54	a
b	C_6H_5	H	H	2	53	b
c	CH_3	CH_3	H	3	33	a
				8	47	
				16	60	
d	CH_3	H	CH_3	6	43	c
e	p-ClC_6H_4	H	H	6	44	d
				24	55	

[a] Aldrich Chemical Co. [b] Hubner, H.; Morse, H. *Chem. Ber.* **1981**, *24*, 4170. [c] Matsuo, M; Murogama, Y. Japan Kokai 7 431 662 (Cl. 16E34). [d] Bywater, W. G.; Coleman, W. R.; Kamm, O.; Merrit, H. H. *J. Am. Chem. Soc.* **1945**, *67*, 905.

Scheme I



In summary, benzoxazoles may be prepared from anilides by regiospecific ortho thallation, followed by photolysis of the resulting arylthallium intermediates. Extensions of this methodology to other ortho-thallated arenes are under investigation.

Experimental Section

Boiling points and melting points are uncorrected; the latter were determined in open capillaries with a Thomas-Hoover apparatus. IR spectra were recorded as thin films on KBr salt plates by using Perkin-Elmer 457 and 1320 grating IR spectrometers. NMR spectra were obtained on JEOL FX-90Q 90-MHz, Perkin-Elmer R32 90-MHz and Bruker WM250 255-MHz spectrometers. MS data were obtained on an AEI MS-902 instrument at 70 eV. TLC data were obtained on 2.5 × 7.5 cm silica gel plates (Bakerflex 1B2-F), and products were detected by UV and/or iodine staining. The silica used in column chromatography separations was Merck 60 (230–400 mesh ASTM-catalog no. 9385).

General Procedure for the Preparation of Benzoxazoles from Ortho-Thallated Anilides. A slurry of 10 mmol of the ortho-thallated anilide[9] in 100 mL of cyclohexane was placed in a quartz phototube and the suspension deoxygenated with argon for 30 min. The reaction mixture was then photolyzed at 300 nm for 2 h in a Rayonet RPR-100 chamber reactor. The reactions appeared to be complete when the reaction mixture became clear, and a yellow solid lined the inside of the reaction vessel. The mixture was filtered and concentrated under reduced pressure, the crude product was dissolved in chloroform, and the solution was passed through a dry column of silica gel. Evaporation of the chloroform eluate gave the pure benzoxazole (see Table I).

***m*-(4-Chlorobenzamido)propiophenone (5).** A solution of 8.95 g (0.05 mol) of *m*-nitropropiophenone in 125 mL of ethanol was reduced with hydrogen and a catalytic amount of platinum oxide at 10 psi for 20 min, the catalyst removed by filtration, and the solvent evaporated to give crude *m*-aminopropiophenone. This material was slurried in 100 mL of 5% sodium hydroxide, 8.75 g (0.05 mol) of *p*-chlorobenzoyl chloride added, and the mixture shaken for a few minutes. The solid which precipitated was collected by filtration and recrystallized from ethanol to give 10.47 g (77%) of **3**, mp 128–129 °C: IR (KBr) 1695, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.38 (s, 1 H), 7.70 (m, 8 H), 3.95 (q, 2 H), 1.15 (t, 4 H); MS, *m/e* calcd 287.289, found 287.289.

Methyl 4-(Bis(trifluoroacetyl)thallio)-3-(4-chlorobenzamido)-α-methylphenylacetate (7). *m*-(4-Chlorobenzamido)-propiophenone (2.45 g, 8 mmol) was added to a solution of 3.55 g (8 mmol) of TTN in 50 mL of a 1:1 mixture of methanol and TMOF. The reaction mixture was heated under reflux for 2 h, by which time all of the Tl(III) had been consumed (starch iodide paper). The solvents were removed by evaporation under reduced pressure, the residue was dissolved in chloroform and filtered, and the filtrate was washed with water (2 × 25 mL). Filtration and evaporation of the filtrate then gave methyl (4-chlorobenzamido)-α-methylphenylacetate (**6**, 2.09 g, 82% crude yield) as an orange oil: IR (neat) 1730, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.40 (s, 1 H), 7.60 (m, 8 H), 3.55 (s, 3 H); 3.00 (q, 1 H), 1.60 (d, 3 H).

To a solution of 4.57 g (14.4 mmol) of **6** in a solution of 7.82 g (14.4 mmol) of TTFA and 15 mL of ether was added (slowly) 15 mL of trifluoroacetic acid. The resulting dark brown solution was stirred at room temperature overnight, and the white precipitate which had separated was collected by filtration, washed with dichloroethane, and dried to give 4.88 (38% overall yield from **5**) of **7** as a colorless, crystalline solid, mp 188–190 °C: ^1H NMR (Me_2SO-d_6) δ 10.40 (d, 1 H, J = 45 Hz), 8.06 (d, 2 H, J = 7 Hz), 7.75 (d, 1 H, J = 513 Hz), 7.65 (d, 1 H, J = 1070 Hz), 7.64 (d, 2 H, J = 7 Hz), 7.28 (d, 1 H, J = 266 Hz), 4.2–3.30 (m, 1 H), 3.69 (s, 3 H), 1.50 (d, 3 H, J = 7 Hz).

Anal. Calcd for $C_{21}H_{15}NClO_7F_6Tl$: C, 33.76; H, 2.02; N, 1.88; Cl, 4.74; F, 15.26. Found: C, 33.47; H, 2.07; N, 1.65; Cl, 4.50; F, 15.26.

Benoxaprofen Methyl Ester (8). The above arylthallium(III) bis(trifluoroacetate) **7** (0.5 g, 0.67 mmol) was slurried in 100 mL

of cyclohexane in a quartz tube, and argon was bubbled through the suspension for 30 min. The mixture was then irradiated for 15 h at 300 nm in a Rayonet RPR-100 chamber reactor. Filtration, concentration of the filtrate under reduced pressure and filtration through a short column of Celite gave 0.19 g (90%) of benoxaprofen methyl ester, mp 91–93 °C, identical in all respects with an authentic sample.[13]

Benoxaprofen (3). Benoxaprofen methyl ester (180 mg) was dissolved in 10 mL of 5% methanolic potassium hydroxide and the mixture was heated under reflux for 30 min. The solvent was then removed under reduced pressure, and the remaining solid was dissolved in water. Addition of HCl led to the separation of a heavy white precipitate which was collected by filtration and recrystallized from ethanol to give 152 mg (75%) of benoxaprofen, mp 188.5–190 °C, identical in all respects with an authentic sample.[13]

Registry No. 3, 51234-28-7; 4, 17408-16-1; 5, 101010-08-6; 6, 101010-09-7; 7, 101010-10-0; 8, 101010-11-1; a, 95-21-6; b, 833-50-1; c, 5676-58-4; d, 53012-61-6; e, 1141-35-1; *o*-$AcNHC_6H_4Tl(TFA)_2$, 101010-04-2; *o*-$PhCONHC_6H_4Tl(TFA)_2$, 101010-05-3; 4-Me-2-$AcNHC_6H_3Tl(TFA)_2$, 101010-06-4; 5-Me-2-$AcNHC_6H_3Tl(TFA)_2$, 101010-07-5; *p*-ClC_6H_4-*o*-$CONHC_6H_4Tl(TFA)_2$, 101030-87-9; *m*-$EtOCC_6H_4NH_2$, 1197-05-3; *p*-ClC_6H_4COCl, 122-01-0.

A ^{199}Hg NMR Study of the Complexation of Methylmercury with Thia-Crown Ethers. The Absence of a Macrocyclic Ligand Effect

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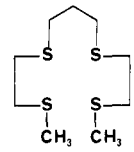
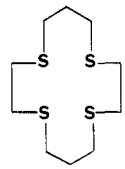
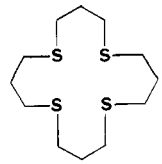
Macrocyclic multidentate ligands typically form more stable complexes with metals than their corresponding acyclic analogues. This *macrocyclic effect* in the homologous series of ligands that comprise the polythia cyclic ethers has been attributed by Rorabacher to the more favorable entropy associated with less flexible cyclic ligands.[1a] This group has also established that a 16-membered cyclic tetrathiaether ([16]aneS$_4$) is required to provide a cavity large enough for the Hg^{II} ion.[1b] An X-ray study on such a "crown-like" complex showed the Hg^{II} ion to be completely circumscribed by the macrocyclic ligand.[1b] Of particular relevance to the present study, it was also reported that open-chain complexes of $Hg(ClO_4)_2$ in $MeOH–H_2O$ solvent were more stable than their macrocyclic thia-crown counterparts.

As part of a related study aimed at designing an effective therapeutic agent for CH_3Hg^{II}, we have measured the formation constants for the complexation of CH_3HgX with a variety of sulfur-containing ligands.[2] This ^{199}Hg NMR method has now been extended to include the quantitative measurement of the K_f for $CH_3HgOCOCF_3$ with a series of cyclic and acyclic thiaethers. The data in Table I clearly demonstrate that simple sulfides and disulfides exhibit a surprisingly low affinity for CH_3Hg^{II} and that the proclivity for complexation with an acyclic dithiaether is at least 2 orders of magnitude greater than a 16-membered macrocyclic tetrathiaether.

The formation constants were measured by evaluating a least-squares fit of ^{199}Hg NMR data as described previously.[2] As anticipated, the K_f for interaction of the relatively ionic $CH_3HgOCOCF_3$ with di-*n*-butyl sulfide is much higher in methanol solvent than in methylene chloride.[2] The extent of complexation of $CH_3HgOCOCF_3$ is apparently much less than that with $Hg(ClO_4)_2$ ($CH_3OH–H_2O$) where a log K_f = 10.48 was noted for the [16]-aneS$_4$ thia-crown and 9.55 for the [14]-aneS$_4$ ligand.[1b] These data tend to contradict liquid–liquid extraction data in 1,2-dichloroethane solution where $HgSO_4$ and CH_3HgSO_4 exhibited a comparable electrophilicity toward [14]-aneS$_4$ thia-crown.[3] Our data, which were measured in CH_2Cl_2 for solubility purposes, also demonstrate that a dithiaether is a slightly more effective ligand than a linear acyclic tetrathiaether. This trend may be ascribed to an entropy effect associated with conformational rigidity required for "encapsulating" the CH_3Hg^{II} with all four sulfur donor atoms. The striking decline in the efficacy of the donicity of the cyclic thiaethers, irrespective of ring size, is much more difficult to explain. Since an absence of the classical macrocyclic effect has also been observed with Hg^{II} in $CH_3OH–H_2O$,[1b] this phenomenon cannot be attributed to the methyl group or to solvent polarity. These observations remain an enigma that awaits a more definitive theory and suggests that macrocyclic thiaethers would not suffice as effective antidotes for methylmercury poisoning. The striking difference between the affinity of a mercaptide ion[4] (RS^-) where $K_f = 10^{14}–10^{16}$ and a sulfide or disulfide toward CH_3Hg^{II} is also worthy of note.

Table I. Formation Constants for

$$CH_3HgOCOCF_3 + L \overset{K_f}{\rightleftharpoons} CH_3HgOCOCF_3{\cdot}L$$

ligand	K_f	solvent
CH_3SSCH_3	0.07	CH_2Cl_2
$(n\text{-}Bu)_2S$	0.07	CH_2Cl_2
$(n\text{-}Bu)_2S$	50	CH_3OH
$CH_3S(CH_2)_3SCH_3$	67	CH_2Cl_2
	45	CH_2Cl_2
 [14]-ane S$_4$	0.25	CH_2Cl_2
 [16]-ane S$_4$	0.36	CH_2Cl_2

Measurement of Equilibrium Constants

The sensitivity of the ^{199}Hg nucleus to both its primary ligands and the immediate solvation shell surrounding the metal is reflected in the range of chemical shifts that extend over 4000 ppm. Thus even relatively small formation constants K_f can be precisely determined by measuring the

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