TABLE I

Compd	Mp, °C	Yield, %	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
3a	127–129[a]	31	$C_{17}H_{13}NO_2$	77.55	4.98	5.32	77.67	5.08	5.37
3b	168–170	31	$C_{17}H_{12}ClNO_2$	68.58	4.06	4.70	68.64	4.05	4.61
3c	172–174	20	$C_{17}H_{12}BrNO_2$	59.67	3.53	4.09	59.75	3.31	4.09
3d	122–124	19	$C_{12}H_{11}NO_2$	71.63	5.51	6.96	71.52	5.74	6.67

[a] Previously reported by Borsche,[19] who states mp 116–117°.

ful in our hands; only intractable tars resulted. It has been observed[14] that amine-to-acetylene ester additions proceed with greatest facility in alcoholic solvents. Unfortunately, higher boiling hydroxylic media (glycol, phenol, etc.) cannot be employed, for Moureu[15] and others[16,17] have shown that OH addition to the triple bond occurs at temperatures above 125°. Nevertheless, as outlined herein, this method does constitute a considerably more direct synthesis of this family than that previously reported.[18,19] Borsche and coworkers prepared **3a** in unspecified yield in a four-step synthesis from malonic ester and *o*-aminobenzophenone.

Experimental Section[20]

Condensation of 2-Amino-5-Substituted Benzophenones with Methyl Propiolate. Preparation of 3a, b, and c.—A solution of 10.0 mmol of the appropriate aminobenzophenone and 10.0 mmol of methyl propiolate in 25 ml of methanol was refluxed for 8 days. The solvent was removed *in vacuo* and the residue sublimed at 120–150° (0.05 mm) to yield a mixture of the starting amino ketone and the desired quinoline (**3a, b,** and **c**). Recrystallization from methanol separated the less soluble quinolines (white to pale yellow solids) from the more soluble aminobenzophenones. An analytical sample was prepared by one additional recrystallization from methanol followed by vacuum sublimation at a temperature 20° below the melting point of the quinoline. Yields, analyses, and physical properties are reported in Table I. In the case of the 6-bromo-4-phenyl-3-carbomethoxyquinoline detailed examination of all residues demonstrated the absence of vinyl protons (*i.e.*, no enamine adduct was present). All the quinoline products displayed an ester methyl at δ 3.71 ± 0.01 and a C-2 proton singlet at 9.36 ± 0.02 in the nmr region ($CDCl_3$ solvent, TMS reference).

Condensation of 2-Aminoacetophenone with Methyl Propiolate. Preparation of 3d. Method A.—The reactants were condensed under the conditions described above and, after vacuum removal of solvent, the unreacted materials were distilled off in the sublimation apparatus [100° (0.05 mm)]. The temperature was then raised to 120°, and the sublimation was continued. Recrystallization of the yellow sublimate from methanol yielded 1.14 g (28% calculated on the basis of quinoline product) of crystalline material, mp 93–114°, whose melting point could not be sharpened by repeated recrystallization from methanol or by column chromatography on silica gel.

The nmr spectrum revealed that the yellow solid was a mixture of 67% quinoline product (**3d**) and 33% *trans* adduct (**2d**). The spectrum of the adduct, after subtraction of the quinoline's resonances, was nmr ($CDCl_3$) δ 2.63 (s, 3, CH_3CO–), 3.77 (s, 3, CH_3OOC–), 5.44 (d, 1, J = 13.5 Hz, –NHCH=$CHCOOCH_3$), 7.05 (q, 1, J = 9 and J = 13.5 Hz, –NHCH=$CHCOOCH_3$), and 6.83–8.30 (m, 4, aromatics).

Method B.—Equimolar quantities (20 mmol) of the two components were dissolved in 50 ml of methanol and heated at reflux for 14 days. The solution was evaporated *in vacuo* and the residue chromatographed on a silica gel column (300 g, 10% methanol in benzene elutant). By concentration of the eluted fractions, there was obtained successively a 40% return of *o*-aminoacetophenone, 0.13 g (3%) of **4**, and 0.59 g (15%) of **3d**. The mother liquors from the recrystallization of the two solid components described above were evaporated and the residue vacuum sublimed to yield an additional 0.17 g (4%) of **3d**. An analytical sample was prepared by sublimation (see Table I for analytical results): nmr ($CDCl_3$) δ 2.97 (s, 3, 4-CH_3), 4.00 (s, 3, CO_2CH_3), 7.33–8.25 (m, 4, Ar**H**), and 9.26 (s, 1, 2**CH**).

The orange solid, **4**, was obtained in analytical purity by vacuum sublimation [180° (0.1 mm)] followed by recrystallization from methanol: mp 195–196°; ir (Nujol) 1724 sh, 1712, 1696 sh cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.80 (s, 3, CO_2CH_3), 3.88 (s, 3, CO_2CH_3), 3.97 (s, 3, CO_2CH_3), 5.93 (d, 1, J = 9 Hz, NCH=$CHCO_2CH_3$), 6.70 (d, 1, J = 9 Hz, NCH=$CHCO_2CH_3$), 6.52 (d, 1, J = 7 Hz, H_9), 8.68 (d, 1, J = 7 Hz, H_7), 7.43 (t, 1, J = 7 Hz, H_8), 7.97 (s, 1, H_2) and 8.22 (s, 2, H_4, and H_5). These couplings were confirmed by spin decoupling which collapsed the coupled protons to their expected multiplicities.[21]

Anal. Calcd for $C_{20}H_{17}NO_6$: C, 65.39; H, 4.66; N, 3.81. Found: C, 65.39; H, 4.75; N, 3.77.

Reaction of 3-Carbomethoxy-4-methylquinoline with Methyl Propiolate.—A solution of 0.59 g (2.9 mmol) of 3-carbomethoxy-4-methylquinoline, 1.0 g (12 mmol) of methyl propiolate and 20 ml of methanol was refluxed for 36 hr. Upon cooling the solution, 0.13 g (12%) of orange solid **4** precipitated. This material was identical (ir, nmr, mp) with that obtained directly by the reaction of *o*-aminoacetophenone and methyl propiolate. The mother liquors of the reaction mixture produced 0.71 g of a red resinous material which was shown to be a complex mixture of at least five components by tlc (10% ethyl acetate in benzene). Retreating the red resin with more methyl propiolate gave no additional **4**. The residue was not investigated further.

Registry No.—**2d,** 18936-30-6; **3a,** 18936-31-7; **3b,** 18936-32-8; **3c,** 18936-33-9; **3d,** 18936-34-0; **4,** 18936-35-1.

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Thallium in Organic Synthesis. V. 9-Alkylation of Purines[1]

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Previous papers in this series have demonstrated the remarkable efficacy of thallium(I) salts of β-dicarbonyl

compounds, carboxylic acids and phenols as reaction substrates for alkylations, acylations, aroylations, and tosylations.[3,4] We wish to report on the formation of thallium(I) salts of purines and their utility in alkylations. The manipulative disadvantages and synthetic limitations of the conventional alkylation techniques on purines have received adequate recent review.[5,6]

Thallium(I) salts of purine and 6-chloropurine were readily prepared by addition of thallium(I) ethoxide[7] to stirred ethanolic solutions of purine and 6-chloropurine, respectively. Addition of thallium(I) ethoxide to a solution of adenine in dimethylacetamide resulted in the separation of the thallium(I) salt of adenine. These salts are stable, crystalline solids obtained analytically pure as isolated in 90, 87 and 94% yield, respectively.

The thallium(I) salts of purine, 6-chloropurine and adenine were benzylated with benzyl bromide in dimethylformamide at room temperature to give 9-benzylpurine,[8] 9-benzyl-6-chloropurine[8] and 9-benzyladenine[9] in 56, 69 and 48% yield, respectively. In each case, the product was isolated simply by filtration of the reaction mixture to remove thallium(I) bromide, concentration, and recrystallization from ether–petroleum ether (bp 30–60°) or ethanol.[10]

Treatment of the thallium(I) salt of purine with 1 equiv of methyl iodide in dimethylformamide gave a mixture of 9-methylpurine[11–13] (30%) and 9-methylpurine methiodide (15%). This latter compound, which could be prepared directly in 65% yield by treatment of the thallium(I) salt of purine in dimethylformamide with excess methyl iodide, was identical with the methiodide prepared by reaction of 7-methylpurine with methyl iodide[13] and must thus be 7,9-dimethylpurinium iodide. Sublimation of this methiodide gave pure 9-methylpurine in 25% yield.

Preliminary experiments have shown that the thallium(I) salts of purine and purine derivatives may be employed in nucleoside synthesis. Crystalline nebularine [9-β-(D-ribofuranosyl)purine] was prepared by the reaction of the thallium(I) salt of purine with 2′,3′,5′-tri-O-acetyl-D-ribofuranosyl chloride, followed by deacetylation with ammonia and chromatography on silica gel. Adenosine was prepared analogously by ribosidation of the thallium(I) salt of adenine, followed by deacetylation and chromatography. Yields in both cases were low, however, and further experiments are in progress.

The ease of formation, stability, high purity, solubility and reactivity of these purine thallium(I) salts, coupled with the fact that alkylation occurs primarily at position 9[14] independent of the substituent at position 6, may presage a general utility for purine thallium(I) salts in nucleoside synthesis, and have stimulated us to extend these studies to other heterocyclic systems.

Experimental Section[15]

Purine Thallium(I) Salt.—Purine (0.5 g) was dissolved in 15 ml of absolute ethanol and a solution of thallium(I) ethoxide[16] in ethanol added dropwise to turbidity. After several hours standing, the precipitated thallium(I) salt was collected by filtration. Evaporation of the filtrate to *ca.* 10 ml followed by further addition of thallium(I) ethoxide in ethanol gave an additional crop of purine thallium(I) salt: total yield, 1.2 g (90%); mp 255° dec.

Anal. Calcd for $C_5H_3N_4Tl$: C, 18.58; H, 0.93; N, 17.03. Found: C, 18.46; H, 0.93; N, 16.98.

6-Chloropurine Thallium(I) Salt.—To a solution of 1.0 g of 6-chloropurine in 20 ml of absolute ethanol was added dropwise a solution of thallium(I) ethoxide in ethanol. The reaction mixture was allowed to stand at room temperature for 5 hr and was then filtered. Concentration of the filtrate followed by further addition of thallium(I) ethoxide in ethanol resulted in the separation of additional 6-chloropurine thallium(I) salt: total yield, 2.0 g (87%); mp >330°.

Anal. Calcd for $C_5H_2N_4ClTl$: C, 16.76; H, 0.56; N, 15.66. Found: C, 16.79; H, 0.62; N, 15.64.

Adenine Thallium(I) Salt.—Adenine (1.0 g) was dissolved in 25 ml of hot dimethylacetamide and the solution cooled to room temperature. A slight excess of thallium(I) ethoxide in ethanol was added, and the mixture was allowed to stand at room temperature for 5 hr and then filtered. Concentration of the filtrate followed by further addition of thallium(I) ethoxide in ethanol resulted in the precipitation of additional adenine thallium(I) salt: total yield, 2.3 g (94%); mp >330°.

Anal. Calcd for $C_5H_4N_5Tl$: C, 17.75; H, 1.18; N, 20.71. Found: C, 18.01; H, 1.35; N, 20.42.

9-Benzylpurine.—To a suspension of 1.2 g of purine thallium(I) salt suspended in 25 ml of dimethylformamide was added 0.64 g of benzyl bromide, and the reaction was stirred for 5 hr at room temperature. The bright yellow thallium(I) bromide was removed by filtration and the filtrate evaporated to dryness under reduced pressure. The residue was dissolved in chloroform and passed through a short silica gel column; evaporation of the chloroform eluant gave a crystalline solid which was extracted with 200 ml of hot ether–petroleum ether (1:1). Concentration of the extract followed by cooling resulted in the separation of 0.42 g (56%) of 9-benzylpurine, mp 95°. One recrystallization from ether–petroleum ether (1:1) raised the melting point to 99–100° (lit.[8] mp 100–101°).

6-Chloro-9-benzylpurine.—To a suspension of 2.0 g of 6-chloropurine thallium(I) salt in 25 ml of dimethylformamide was added 0.8 g of benzyl bromide and the mixture was stirred at room temperature for 5 hr. Thallium(I) bromide was removed by filtration and the filtrate was concentrated to dryness under reduced pressure. The residue was extracted with water and then dried over P_2O_5 at 20° *in vacuo* for several hours. The resulting viscous mass was extracted several times with warm ether–petroleum ether (3:7), the extracts were concentrated to dryness and the residue was recrystallized from ether–petroleum ether (3:9) to give 0.91 g (69%) of 6-chloro-9-benzylpurine, mp 86–87°. This material was identical with authentic 6-chloro-9-benzylpurine prepared by the method of Montgomery and Temple.[8] Attempts to isolate another crystalline product from

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(14) Careful thin layer chromatography of the crude alkylation reaction mixtures usually revealed traces of other alkylated products.

(15) Microanalyses were performed by George Robertson, Florham Park, N. J. Melting points were determined with a Thomas–Hoover apparatus and are uncorrected.

(16) Ethanolic thallium(I) ethoxide prepared by the method described in ref 7 deposits thallium(I) ethoxide as a heavy oil on standing. In the present experiments, the saturated upper layer was employed.

the residue of the ether–petroleum ether extraction were unsuccessful.

9-Benzyladenine.—To a suspension of 2.3 g of adenine thallium(I) salt in 25 ml of dimethylformamide was added 1.1 g of benzyl bromide, and the mixture was stirred at room temperature for 10 hr. The suspended thallium(I) bromide was removed by filtration, the filtrate concentrated to dryness and the residue recrystallized from ethanol to give 0.70 g (48%) of 9-benzyladenine, mp 230°, identical with an authentic sample prepared by the method of Montgomery and Thomas.[9]

Methylation of Purine Thallium(I) Salt.—To a suspension of 1.0 g of purine thallium(I) salt in 25 ml of dimethylformamide was added 0.54 g of methyl iodide, and the mixture was stirred at room temperature for 8 hr. The orange thallium(I) iodide was removed by filtration and the filtrate was evaporated to dryness. The residual yellow-brown solid was extracted first with 50 ml of hot petroleum ether and then with 30 ml of hot methanol–acetone (1:1). The petroleum ether extract was decolorized with charcoal, filtered, and the filtrate evaporated to dryness. Recrystallization of the crystalline residue from *n*-hexane gave 0.12 g (30%) of 9-methylpurine, mp 159–160° (lit. mp 158–159,[11] 161–162,[12] 162–163°[13]). Evaporation of the methanol–acetone extract to dryness followed by recrystallization of the residue from methanol–acetone gave 0.13 g (15%) of 7,9-dimethylpurinium iodide as light yellow needles, mp 225–226° dec.

Anal. Calcd for $C_7H_9N_4I$: C, 30.43; H, 3.26; N, 20.29. Found: C, 30.58; H, 3.45; N, 20.02.

Treatment of 1.0 g of purine thallium(I) salt with an excess of methyl iodide in 25 ml of dimethylformamide under the above conditions, followed by filtration, evaporation to dryness, extraction of the residue with hot petroleum ether, and recrystallization of the residual solid from methanol–acetone gave 0.55 g (65%) of 7,9-dimethylpurinium iodide, mp 225–226° dec. Pyrolysis of 0.5 g of this material at 220–230° gave a white crystalline sublimate which was extracted with hot petroleum ether. Tlc on the extract (ethanol–chloroform 2:8) showed the presence of 9-methylpurine and a trace of 7-methylpurine. The petroleum ether extract was treated with charcoal, filtered and the filtrate evaporated to dryness. Recrystallization of the residue from *n*-hexane gave 0.063 g (25%) of pure 9-methylpurine as colorless crystals, mp 158–159°.

Nebularine was prepared crystalline in 2% yield by utilizing the procedure of Brown and Weliky[17] with the modification that the chloromercuri salt was replaced by the purine thallium(I) salt and the ribosidation was conducted in anhydrous dimethylformamide at room temperature. Utilization of the thallium(I) salt of adenine in the procedure of Davoll and Lowy,[18] modified as above, gave **adenosine**, as determined by chromatographic comparison with authentic material. No attempts were made to find optimum conditions for these ribosidation reactions.

Registry No.—Purine thallium(I) salt, 19165-45-8; 6-chloropurine thallium(I) salt, 19365-46-9; adenine thallium(I) salt, 19165-47-0; 7,9-dimethylpurinium iodide, 19165-48-1.

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Thallium in Organic Synthesis. VI. Synthesis of Primary Aliphatic Bromides[1]

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The reaction of halogens with dry metal salts of carboxylic acids to give halides, with concomitant decarboxylation, is known as the Hunsdiecker reaction.[2,3] When a 1:1 ratio of halogen to a silver carboxylate is employed (the normal experimental conditions), the reaction can be summarized as shown in eq 1. This reaction is most useful for the preparation

$$RCO_2Ag + X_2 \longrightarrow RX + AgX + CO_2 \quad (1)$$

of bromides, and yields (particularly with aliphatic carboxylic acids) are generally good. The extreme sensitivity of the reaction to trace amounts of water and the difficulty encountered in preparing dry silver carboxylates have led to a number of modifications of the Hunsdiecker reaction. The most useful appears to be the method of Cristol and Firth,[4-6] which involves the addition of bromine to a slurry of excess red mercuric oxide in a refluxing solution of the carboxylic acid in carbon tetrachloride, bromotrichloromethane,[7] or 1,2-dibromoethane.[7]

Thallium(I) carboxylates, in contrast to silver carboxylates, are easily prepared and purified by recrystallization, and are stable indefinitely.[8] We have found that treatment of aliphatic thallium(I) carboxylates with bromine in carbon tetrachloride leads to a smooth Hunsdiecker reaction, with formation of primary alkyl bromides. Inspection of the inorganic product of this reaction, however, showed that it was neither thallium(I) bromide nor thallium(III) bromide, indicating that the stoichiometry of the conversion was not analogous to that observed in the normal silver salt procedure. Its properties were in closest agreement with those reported for the so-called "thallium dibromide" (Tl_2Br_4) $[Tl^{+1}(Tl^{+3}Br_4)^-]$.[9] The actual stoichiometry for the bromine–thallium(I) carboxylate reaction would thus appear to be as shown in eq 2 in which

$$2RCO_2Tl + 3Br_2 \longrightarrow 2RBr + 2CO_2 + Tl_2Br_4 \quad (2)$$

the intervention of thallium(III) is seen to play a key role. Facile interchanges between the Tl^{+1} and Tl^{+3} oxidation states appear to be a common feature of thallium chemistry.[10] As a consequence of these considerations, the following sequence (eq 3–5) for the Hunsdiecker reaction with thallium(I) carboxylates and bromine can be postulated, which demands a ratio

$$RCO_2Tl + Br_2 \longrightarrow RCO_2TlBr_2 \quad (3)$$

$$2RCO_2TlBr_2 + Br_2 \longrightarrow 2RCO_2Br + Tl_2Br_4 \quad (4)$$

$$RCO_2Br \longrightarrow RBr + CO_2 \quad (5)$$

of RCO_2Tl/Br_2 of 1:1.5. Indeed, use of this ratio of reactants rather than the 1:1 ratio initially employed by analogy with the common silver salt method raised

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