organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to yield 4.1 g (93%) of crude product. Recrystallization from benzene gave pure dialcohol **1d**: mp 98.5–99.5°; ir (KBr), 3.10 (OH), 6.78, 6.91, 8.15, 9.70, 13.2 μ; nmr ($CDCl_3$), δ 3.3 (s, broad, 2, OH), 4.65 (s, 4, CH_2), 6.80–7.50 (m, 8, aromatic).

Anal. Calcd for $C_{14}H_{14}O_3$: C, 73.04; H, 6.09. Found: C, 73.18, H, 6.15.

(Diphenyl ether)-2,2′-dicarbonyl Chloride (4b).—A mixture of 250 ml of $SOCl_2$ (redistilled) and 24.2 g of the diacid **4a** was heated at reflux for 2 hr, and 150 ml of solvent was then removed by distillation. Hexane (300 ml) was added and the mixture was cooled at 5° for 4 hr. The precipitate was filtered and washed with hexane to yield 22.0 g (80%) of **4b**: mp 91–93° (lit.[18] 161°); ir (KBr), 5.63, 5.67 (C=O), 8.06, 13.1 μ; methyl ester **4c**: mp 64–65.5° (lit.[18] 65.5°); amide **4d**: mp 264–266° (lit.[18] 265°).

Arndt-Eistert Synthesis of Dimethyl (Diphenyl ether)-2,2′-Diacetate (3b).—To a solution of 6.0 g (0.020 mol) of **4b** in 40 ml of dry dioxane was added diazomethane solution (0.14 mol) in ether, prepared from N,N′-dinitroso-N,N′-dimethylterephthalamide,[24] and the reaction mixture was allowed to stand overnight. The solvents were removed by distillation, leaving 6.0 g of didiazo ketone **4c** as a gummy yellow solid: ir (KBr), 4.74 (N≡N), 6.24 (C=O), 8.20, 13.3 μ. This was dissolved in 110 ml of methanol, heated at 60°, and over 2.5 hr a slurry prepared from 0.7 g of silver oxide in 20 ml of methanol was added to it. The mixture was refluxed for 16 hr and filtered through a bed of Celite. On evaporation of the methanol, 6.0 g of a brown oil, which showed ir absorption at 5.78 (ester) and 5.91 (ketone) μ was obtained.

The ketone impurity was removed in the following manner. A mixture of 3.5 g of the crude reaction product, 2.3 g of trimethylaminoacetoxyhydrazide chloride (Girard's T Reagent), 40 ml of methanol, and 40 ml of acetic acid was refluxed for 45 min, and then ether and water were added. The ether layer was separated, washed with water, 10% $NaHCO_3$, and water, dried ($MgSO_4$), and evaporated. This afforded 1.4 g (38%) of pale yellow oil with ir absorption at 5.78 but not at 5.91 μ. Distillation of the oil gave the colorless liquid diester **3b**, with properties identical with the material prepared by esterification of the diacid **3a** (above).

4-Carbomethoxy-5-hydroxydibenzo[*b*,*g*]-6H-oxocin (5). A. Preparation by the Dieckmann Reaction.—A cyclic high-dilution apparatus,[26] fitted with a constant-addition dropping funnel and high-speed stirrer, and flushed with nitrogen, was employed. To a refluxing mixture of 300 ml of dry xylene and 2.05 g (0.0183 mol) of potassium *t*-butoxide, was added 2.86 g (0.0091 mol) of diester **3b** in 115 ml of xylene, over 30 hr. After cooling, 5 ml of glacial acetic acid in 5 ml of xylene was added drop by drop, followed by 50 ml of water. The two-phase mixture was filtered, and the organic layer was separated, washed with water, dried ($MgSO_4$), and evaporated to give 1.64 g of a thick red oil. A portion of this oil (1.53 g) was introduced onto a column, prepared from 39 g of Mallinckrodt Silicar, 200–325 mesh, and eluted with benzene–hexane mixtures, gradually increasing the benzene content. With benzene–hexane (90:10) 372 mg (21%) of a white crystalline solid, **5**, was eluted. An analytical sample was prepared by several recrystallizations from hexane: mp 94–100°; ir (KBr), 6.06, 6.18, 6.98, 8.20 μ; nmr ($CDCl_3$), δ 3.32 (m, 2, CH_2), 3.75 (S, 3, OCH_3), 7.00–7.50 (m, 8, aromatic), 12.88 (s, 1, OH). Inspection of molecular models of **5** revealed that the methylene protons were not equivalent; a singlet for them in the nmr was not expected. In subsequent preparations, the product **5** had the following properties: mp 94–99°; ir (KBr), 5.75, 5.82 μ, in addition to the bands listed above; nmr ($CDCl_3$), δ 3.65 (m, CH_2CO), 4.71 (s, $CHCO_2CH_3$), in addition to the bands listed above; molecular weight (mass spectrum), 282; the ratio of aromatic to nonaromatic protons in the nmr was 8:6 and the ratio of $CHCO_2CH_3$ to OH protons was 1:4.

Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.34; H, 4.96. Found: C, 72.56; H, 5.07.

Upon continued elution of the above chromatography column with benzene, 667 mg of starting diester **3b** was recovered.

B. Preparation under Acyloin Conditions.—The apparatus and procedure was the same as in the Dieckmann reaction, using 600 ml of xylene and 7.70 g of a 40% 5-μ dispersion of sodium in toluene and adding 8.35 g (0.0266 mol) of the diester **3b** in 150 ml of xylene over 26 hr. The work-up was similar to that used in the Dieckmann reaction. Twenty milliliters of glacial acetic acid in an equal volume of xylene was added, and the final oil (6.37 g) was applied to 470 g of Silicar column. With benzene–hexane (90:10) 200 mg of di-*o*-tolyl ether was eluted. Elution with benzene–hexane (95:5) yielded a crystalline product **5** (2.42 g, 32%). Its properties agreed with those of the partly ketonic product of the Dieckmann reaction, described above.

5-Oxodibenzo[*g*,*g*]-4H,6H-oxocin (6b).—In a flask were combined 160 mg of **5**, 6 ml of 95% ethanol, and 6 ml of 3 *N* hydrochloric acid. The mixture was refluxed overnight and then allowed to cool to room temperature and poured into a beaker containing 7 g of ice. The precipitate that formed (110 mg, 87%) was collected by filtration and purified by recrystallization from hexane to give **6b** as white crystals: mp 84.5°; ir (KBr), 5.85 (C=O), 8.18, 13.30 μ; nmr ($CDCl_3$), δ 3.76 (s, 4, CH_2), 7.10–7.60 (m, 8, aromatic); molecular weight (mass spectrum), 224.

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.36; H, 5.37. Found: C, 80.58; H, 5.31.

Upon injection of a solution of **5** into a gas chromatograph (Carbowax or silicone grease column, 190–230°), only one major peak was detected. The compound was collected and its ir and nmr spectra were found to correspond to those of **6b**.

Registry No.—**1b**, 10038-43-2; **1d**, 10038-40-1; **3a**, 18993-57-2; **3b**, 18993-58-3; **5**, 19019-48-8; **6b**, 18993-59-4.

Acknowledgment.—We wish to thank Mr. Robert Servis for the nmr spectra and Mr. Stephen Brumm for the mass spectra.

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Quinoline Synthesis by *o*-Amino Ketone–Propiolate Addition[1]

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The significant synthetic utility of dimethyl acetylenedicarboxylate adducts of amines,[2,3] anthranilates,[4] anthranilamides,[5] *o*-aminobenzophenones,[6] and thiosalicyclic acid derivatives[7] in heterocyclic synthesis has been documented in previous contributions from this laboratory. The lack of reactivity displayed by propiolate and phenylpropiolate esters in addition reactions with these *ortho*-substituted aromatic amines has also been noted.[3,6]

In light of published reports on the preparation of

(1) This work was supported in part by Contract No. DA-49-193-MD-3011 from the U. S. Army Medical Research and Development Command and represents Contribution No. 474 from the Army Research Program on Malaria.

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(4) E. C. Taylor and N. D. Heindel, *ibid.*, **32**, 3339 (1967).

(5) N. D. Heindel, V. B. Fish, and T. F. Lemke, *ibid.*, **33**, 3997 (1968).

(6) E. C. Taylor and N. D. Heindel, *ibid.*, **32**, 1666 (1967).

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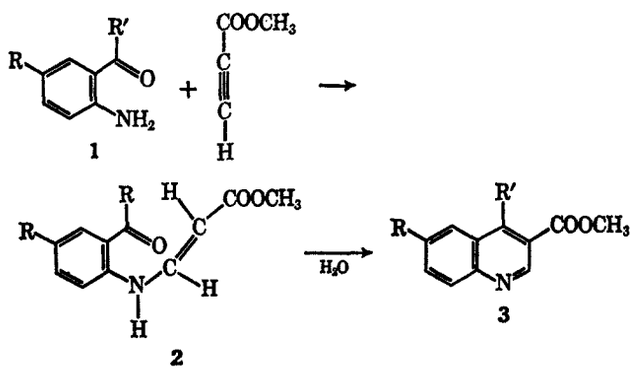
propriolate adducts of aromatic amines[8-10] and, in one case, of their cyclization to a quinolinone,[8] we have reinvestigated our original claim. We have found that under extended reaction conditions (8 days of refluxing of the components in methanol) it is possible to generate adducts of *o*-amino ketones which in most cases cyclize *in situ* to 4-substituted 3-carbomethoxyquinolines. We have not been able to demonstrate any detectable reactivity of *o*-aminobenzophenones toward esters of phenylpropiolic acid. Previous attempts[11] to carry out the Michael addition of aniline to ethyl tetrolate resulted in formation of tetrolic anilide, a possible consequence of steric hindrance and reduced electrophilicity of the β carbon. Similar factors apparently operate diminishing the reactivity of phenylpropiolate esters.



a, R = H; R′ = Ph
b, R = Cl; R′ = Ph
c, R = Br; R′ = Ph
d, R = H; R′ = CH_3

From the *o*-aminobenzophenones and methyl propiolate, 20–31% yields of quinoline esters **3a, b,** and **c** have been isolated. The majority of the reaction mixture consisted of unreacted components. No evidence for uncyclized adducts **2a, b,** and **c** was obtained. As noted before, this result presumes that the initial adduct undergoes a spontaneous enamine closure to the adjacent electrophilic carbonyl.[6]

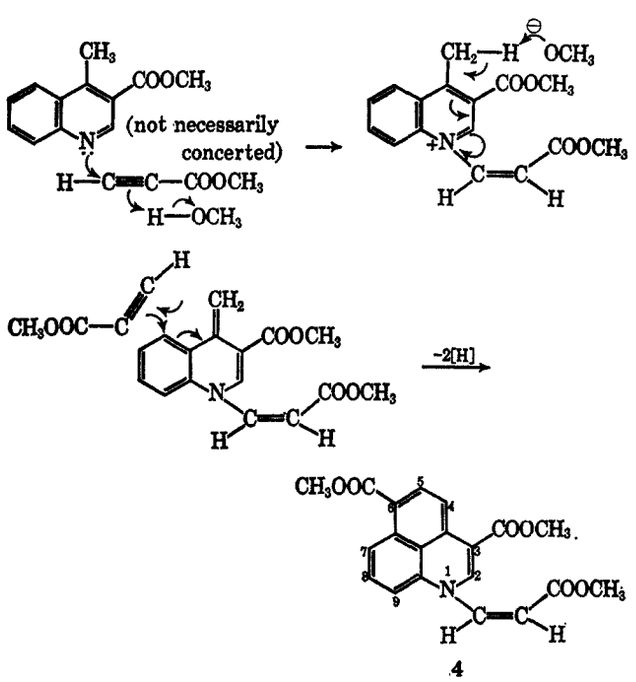
When *o*-aminoacetophenone and methyl propiolate were allowed to react for 8 days in refluxing methanol, a 28% conversion to a mixture of the expected quinoline and the *trans* adduct in a 2:1 ratio was obtained. Because the two compounds were not separable by fractional crystallization, nmr analysis was employed to assay the product balance. The *trans*-vinyl protons of **2d** (J = 13.5 Hz) and the C-4 methyl resonance of **3d** provided convenient and distinct integrals for determination of the relative percentages.

The experiment was repeated employing 14 days reflux and column chromatography on silica gel as an isolation technique. Besides a 40% return of *o*-aminoacetophenone, a 19% yield of **3d** and a 3% yield of orange solid was obtained. No adduct was isolated nor was there any evidence for its presence (*i.e.*, coupled vinyl protons in nmr) in the red resinous materials which comprised the product balance.

This same orange solid could also be obtained from the reaction of authentic **3d** with excess methyl propiolate in methanol. The molecular formula of the orange solid was established as $C_{20}H_{17}NO_6$ by analysis and high-resolution mass spectrometry.[12] The compound thus contains two hydrogen atoms less than an adduct of two molecules of methyl propiolate with one of 3-carbomethoxy-4-methylquinoline.[13]

One possible structure for the orange solid is **4**, 1-(2-carbomethoxyethenyl)-3,6-dicarbomethoxybenzo[*d*,*e*]quinoline. This structure is consistent with the analysis and with the mass spectral cracking pattern. Intense fragment peaks were observed for the successive loss of three carbomethoxy moieties (amu 59) at *m/e* 308, 249, and 190 and for the denuded benzo[*d*,*e*]-quinoline system lacking all pendant functions at *m/e* 164. A plausible mechanism for the formation of **4** is also available (Scheme I).

SCHEME I



From the limited data available it is not possible to eliminate an isomer of **4** in which a carbomethoxy is attached to carbon 5 rather than to carbon 6. This alternative seems less likely since it would require the C_4 and C_6 protons to be fortuitously isochronous—an event more likely to occur for the C_4 and C_5 protons of the proposed structure **4** each of which is flanked by one deshielding ester carbonyl. One sharp singlet in the aromatic region of the nmr of the unknown (δ 8.22 ppm) integrates cleanly for two proton units.

The yields of the 4-substituted 3-carbomethoxyquinolines prepared by this method are modest. Attempts to increase the synthetic merit of the reaction by utilization of higher boiling nonhydroxylic solvents such as diglyme and dimethyl sulfoxide were unsuccess-

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(11) F. Feist, *Ann.*, **345**, 100 (1906).
(12) K. Biemann, "Mass Spectrometry-Organic Chemical Applications," McGraw-Hill Book Co., Inc., New York, N. Y., 1962, pp 196–199.
(13) Acheson and earlier workers have reported a large number of facile "bridging reactions" involving active methyl groups on a quinoline ring and acetylenedicarboxylate. See R. M. Acheson, J. M. F. Gagan, and D. R. Harrison, *J. Chem. Soc.*, *C*, 362 (1968), and references cited therein.

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.

(21) We express our thanks to Mr. Dale Crouse of the Department of Chemistry, University of Delaware, for the spin decoupling experiments.

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(20) Nmr spectra were obtained on a Varian A-60 and are reported in ppm (δ) units. Combustion analyses were provided by Dr. Velmer B. Fish and mass spectral analyses were performed on a Perkin-Elmer Hitachi RMU-6E mass spectrometer by E. William Sarver, both of these laboratories. We acknowledge the financial support of the National Science Foundation which made possible the purchase of nmr and mass spectral facilities.

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