uppermost occupied orbital in calculating the energy changes. As our discussion of the various polymethine species has indicated, this uppermost orbital may dominate in small rings, but becomes a minor factor for larger sizes. By putting sole emphasis on the small ring determinant, Dewar misses the crossover from antiaromatic to aromatic character and the limiting degree of aromaticity for all large rings.

On the other hand, our conclusions parallel resonance energies, calculated by the Pople method (including bond alternation),[12] for the first ten annulenes that show negative resonance energies (antiaromaticity) for cyclobutadiene and cyclooctatetraene, but positive values for all the others (including, incidentally, the smallest value for cyclododecahexaene) which seem to quickly converge to a constant value (2.8 kcal/mol) as the ring dimension increases.

In addition to the qualifications on the FEMO model mentioned at the beginning of this section, it should be pointed out that our simple model also neglects any effects arising from the noncircular shape of the cyclic molecules, and perhaps more importantly bond alternation, although it is hoped in the latter case that the effects on the linear and the corresponding ring compounds are approximately the same and cancel in the calculation of the π stabilization energy.

(12) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, p 179.

Acknowledgment.—The idea of this paper was stimulated by several conversations with Professor Stephen J. Weininger of Worcester Polytechnic Institute.

A New Synthesis of Substituted 2(1*H*)-Pyridones. Synthesis of a Potential Camptothecin Intermediate

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The acylation of 3-carbalkoxycitraconic esters 1 with amide acetals provides a good method for the synthesis of dimethylaminoalkylidene malonates **3**; these compounds upon treatment with a primary amine cyclize to 2,3-dicarbalkoxy 6-substituted 2(1*H*)-pyridones **4**. Application of this reaction to the acetal or imminium salt from *o*-cyanoarylamides **9a,b** similarly affords the corresponding enamines **3d,e**; hydrogenation of **3** leads directly to the fused pyridones **11** and **13**, a potential camptothecin intermediate.

The acylation of active methylene compounds with acetals of dimethylformamide to give the corresponding dimethylaminomethylene compounds has been reported.[2,3] The analogous condensation between an acetal derived from an alkyl- or arylamide and an alkylidine malonic ester would afford a vinylogous amide which, upon treatment with a primary amine, might undergo enamine exchange and cyclization to a 6-substituted 2(1*H*)-pyridone. Because of the nucleophilic reactivity reported[4] for amide acetals possessing an α hydrogen [arising *via* elimination of alcohol to give the enamine C=C(OEt)NR_2], we chose to restrict our investigation to the hydrogen- and aryl-substituted systems (2, R = H or aryl). We describe below the successful completion of this sequence and its application *via* an intramolecular cyclization to the facile synthesis of **13**, a potential intermediate in the synthesis of the antitumor alkaloid camptothecin (**14**).[5]

Initial studies were carried out using ester **1a**, readily prepared from diethyl malonate and ethyl pyruvate.[6] When equimolar quantities of **1a** and the diethyl acetal of dimethylformamide (**2a**) were heated in DMF at 80° for 5 hr, the yellow enamine **3a** was obtained in 87% yield. The enamine double bond in **3a** was assigned as trans on the basis of the vinyl hydrogen coupling constant of 13 Hz in the nmr spectrum. Subsequent reaction of **3a** with benzylamine afforded the *N*-benzylpyridone **4a** in 90% yield.

The feasibility of this approach as a route to camptothecin required the selective transformation of the 3-carbethoxy group into a hydroxymethyl group; the carboxyl group remaining at C_4 would provide the basis for assembly of the α-hydroxy acid moiety. Differentiation of the carbethoxy groups was readily accomplished *via* hydrolysis with 1 equiv of potassium hydroxide to give the acid ester **5a** in 78% yield. Assignment of **5a** as the saponification product was based on the fact that reaction of **5a** with trichloroethanol and *N,N*-dicyclohexylcarbodiimide afforded an ethyl trichloroethyl ester whose nmr spectrum was clearly different from that of the pyridone ester prepared from di(trichloroethyl) malonate and ethyl pyruvate. Extensive efforts to carry out selective reduction of the carbethoxy group proved fruitless. Thus our approach was modified to permit the specific synthesis of the "alternate" acid ester **5b** (Scheme I).

The triester **1b**, prepared from dimethyl malonate,[6] condensed smoothly with **2a** to give the corresponding enamine **3b** in 83% yield; reaction with benzylamine as above led to the crystalline pyridone diester **4b**. When pyridone **4b** was refluxed with anhydrous lithium iodide in pyridine[7] for 1 hr, a single acid ester **5b** was isolated in 86% yield. The nmr spectrum demonstrated unequivocally that the methyl ester had been

(1) Alfred P. Sloan Foundation Fellow.

(2) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).

(3) An acylation of this general type has been utilized in the synthesis of the pyrone ring in fulvoplumierin; see G. Büchi and J. A. Carlson, *J. Amer. Chem. Soc.*, **90**, 5336 (1968).

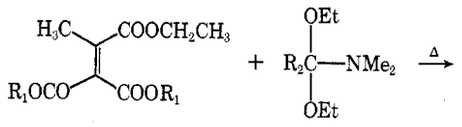
(4) (a) T. Oishi, M. Ochiai, T. Nakayana, and Y. Ban, *Chem. Pharm. Bull.*, **17**, 2314 (1969); (b) for a recent review of amide acetals, see J. Gloede, L. Haase, and H. Gross, *Z. Chem.*, **9**, 201 (1969).

(5) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966); A. T. McPhail and G. A. Sim, *J. Chem. Soc. B*, 923 (1968).

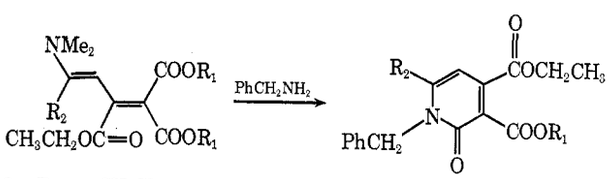
(6) R. Malachowski and W. Czornodola, *Chem. Ber.*, **68B**, 363 (1935).

(7) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1961).

SCHEME I

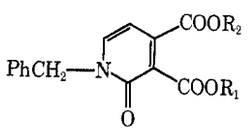


1a, $R_1 = -CH_2CH_3$ 2a, $R_2 = H$
b, $R_1 = -CH_3$ b, R_2 = 3-pyridyl
c, R_2 = 2-cyanophenyl
d, R_2 = 3-cyano-2-quinolyl

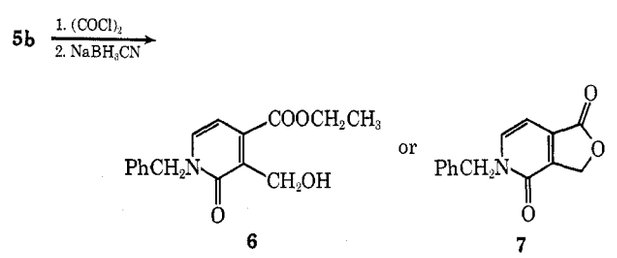


3a, $R_1 = -CH_2CH_3$; $R_2 = H$
b, $R_1 = -CH_3$; $R_2 = H$
c, $R_1 = -CH_3$; R_2 = 3-pyridyl
d, $R_1 = -CH_3$; R_2 = 2-cyanophenyl
e, $R_1 = -CH_3$; R_2 = 3-cyano-2-quinolyl

4a–c



5a, $R_1 = -CH_2CH_3$; $R_2 = -H$
b, $R_1 = -H$; $R_2 = -CH_2CH_3$



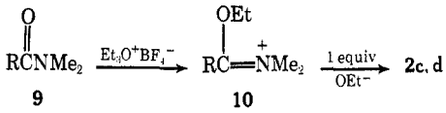
6 7

cleaved selectively; regeneration of **4b** by reaction of **5a** with diazomethane ruled out possible ester interchange.

The model sequence was completed by conversion of **5b** to the 3-hydroxymethylpyridone **6**. The acid ester **5a** was converted to the acid chloride by reaction with oxalyl chloride in methylene chloride; reduction with sodium cyanohydridoborate ($NaBH_3CN$)[8] in tetrahydrofuran led to the hydroxy ester **6** or the lactone **7** depending on the work-up conditions.

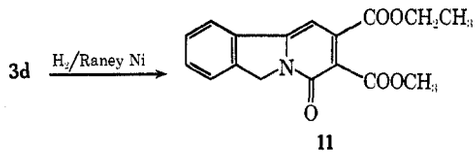
Having thus demonstrated the feasibility of this sequence for preparing a 2-hydroxymethylpyridone derivative, we turned our attention to the synthesis of the 5-aryl pyridones. We were initially concerned about the preparation of the amide acetals **2b** and **2d** derived from heterocyclic amides, inasmuch as the standard conditions[2] for their preparation require initial treatment with the powerful alkylating agent triethyloxonium fluoroborate. When *N,N*-dimethylnicotinamide was treated with 1 equiv of triethyloxonium fluoroborate, alkylation occurred primarily on the pyridine nitrogen to give the quaternary pyridinium salt as the major product. Another reported method[9] for the synthesis of amide acetals ultimately proved successful in this case. Exposure of *N,N*-dimethylnicotinamide (**8**) to refluxing thionyl chloride, followed by reaction of the chloroimminium intermediate with 2 equiv of sodium ethoxide, afforded a product which contained *ca.* 50% **2b** by nmr analysis. Condensation of this crude product with **1b** gave the oily enamine **3c** in low yield (14% based on amide). The stereochemistry of the trisubstituted double bond in enamine **3c** (and in the other arylenamines **3d** and **3e** reported below) is assigned as shown on the basis of the large shielding effect of the aromatic ring on the $-OCH_2-$ protons of the ethyl ester in the nmr spectrum (see Experimental Section). Conversion of **3c** to **4c** by refluxing with benzylamine in ethanol completed the pyridone synthesis.

SCHEME II

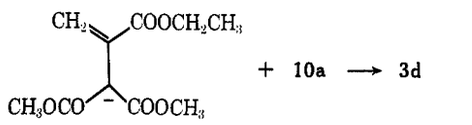


9 10

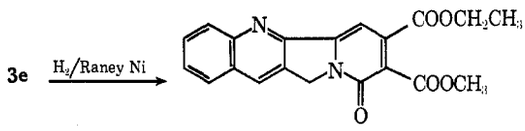
a, R = 2-cyanophenyl
b, R = 3-cyano-2-quinolyl



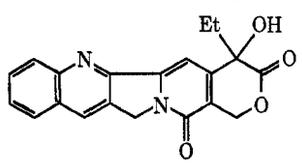
11



12



13



14

The application of this method to the synthesis of **13** required the presence of a potential aminomethyl group ortho to the amide on the aromatic ring, thus permitting utilization of an *intramolecular* enamine exchange–cyclization reaction to form the tetracyclic system in one step. *N,N*-dimethyl-*o*-cyanobenzamide (**9a**) was chosen as a model for this conversion. When amide acetal **2c** was heated with triester **1b**, the crystalline enamine **3d** was obtained in 23% yield. Hydrogenation of this enamine with W-2 Raney nickel in ethanol caused reduction of the nitrile with concomitant enamine exchange and cyclization to give a 42% yield of the tricyclic pyridone **11** (Scheme II).

We finally turned our attention to the synthesis of the potential camptothecin intermediate **13**. *N,N*-Dimethyl-3-cyanoquinaldamide (**9b**) was prepared by Friedlander condensation between *o*-aminobenzaldehyde and ethyl 3-cyanopyruvate;[10] the resulting ester

(8) (a) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971); (b) R. F. Borch and H. D. Durst, *ibid.*, **91**, 3996 (1969).

(9) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

(10) A. Rossey and H. Schinz, *Helv. Chim. Acta*, **31**, 473 (1948).

was converted to **9b** by reaction with dimethylamine in ethanol. Using the method successfully applied to the synthesis of **2b**, cyanoamide **9b** was refluxed wth thionyl chloride and the intermediate was subsequently treated with sodium ethoxide. No trace of the desired acetal was observed; instead, a new product was isolated which was isomeric with the starting amide. The infrared spectrum showed no nitrile absorption at 2220 cm^{-1} but showed an intense carbonyl absorption at 1700 cm^{-1}. It was subsequently demonstrated that this product was formed in the thionyl chloride reaction and was unaffected by treatment with sodium ethoxide. Thus it was apparent that the ortho cyano group was participating in the reaction.

The only alternative remaining was to ignore the difficulties inherent in the reaction of amide **9b** with triethyloxonium fluoroborate and attempt the preparation of acetal **2d** by this route. Remarkably, sequential treatment of **9b** with $Et_3O^+BF_4^-$ and sodium ethoxide gave acetal **2d** in 60% yield. Presumably the ring nitrogen is sufficiently hindered in this case to be inert toward alkylation. Having finally prepared the quinoline acetal, we were disappointed to discover that under all conditions investigated **2d** could not be condensed with triester **1b**. We attribute this recalcitrance to the destabilizing effect of the 3-cyano-2-quinolyl group on the presumed reactive intermediate **10b**. This hypothesis was supported by the fact that the alkoxy groups of **2d** could not be exchanged in alcohol; this type of exchange is known to occur readily for amide acetals *via* an imminium intermediate.[2,4b]

Inasmuch as the condensation of amide acetals with **1b** presumably occurs *via* intermediates **10** and **12**, we attempted to prepare and react intermediates of this type directly in the hope of overcoming the lack of reactivity of the acetal itself. Using **9a** as a model, the corresponding imminium salt **10a** was treated with the triester anion **12** to give the corresponding crystalline solid in 32% yield. When this sequence was repeated using imminium salt **10b**, the unstable oily enamine **3e** was obtained in 52% yield. Catalytic hydrogenation of **3e** converted the enamine to the desired tetracyclic pyridone diester **13** in one step.

The conversion of **13** into camptothecin is currently under investigation.

Experimental Section

General.—Melting points were determined on a Kofler hot stage and are uncorrected. Ultraviolet (uv) spectra were determined on a Beckman DK-2A or Cary 11 spectrophotometer. Infrared (ir) spectra were measured on a Perkin-Elmer Model 257 grating spectrometer. Nuclear magnetic resonance (nmr) spectra were measured on Varian Associates T-60 and A-60D instruments and are given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were determined at 70 eV on a Hitachi RMU-6 instrument; the abbreviation M^+ refers to the molecular ion. Elemental analyses were determined by M–H–W Laboratories, Garden City, Mich. Anhydrous magnesium sulfate was employed as a drying agent.

Ethyl 2,3-Dicarbethoxy-*trans*-5-dimethylaminopenta-2,4-dienoate (3a).—To a solution of 3.0 g (11.6 mmol) of **1a** in 3 ml of dry dimethylformamide was added 4.2 g (12.0 mmol) of a 66 mol % solution of dimethylformamide diethyl acetal in dimethylformamide;[11] the resulting solution was heated at 80° for 5 hr. The solution was cooled to room temperature, 60 ml of benzene was added, and the solution was washed with 1 *N* hydrochloric acid and water. The benzene solution was dried and the solvent was removed *in vacuo* to give 3.49 g of orange oil. Trituration with hot petroleum ether (bp 30–60°) gave a solid which was recrystallized from CCl_4–petroleum ether to give 3.17 g (87%) of **3a**: mp 88–89°; ir (Nujol) 1725, 1695, and 1625 cm^{-1}; uv max (95% EtOH) 382 nm (ϵ 38,000); nmr (CCl_4) δ 1.25 (m, 9), 2.94 (s, 6), 4.12 (m, 6), 5.58 (d, 1, J = 13 Hz), and 6.65 (d, 1, J = 13 Hz).

Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.15; H, 7.51; N, 4.32.

1-Benzyl-3,4-dicarbethoxy-2(1*H*)-pyridone (4a).—To a solution of 1.0 g (3.2 mmol) of enamine **3a** in 5 ml of absolute ethanol was added 367 mg (3.35 mmol) of benzylamine; the resulting solution was refluxed for 5 hr. The cooled solution was evaporated *in vacuo* and the residue was dissolved in 15 ml of ether. The ether solution was washed with 1 *N* hydrochloric acid and water, dried, and evaporated to give 962 mg (90%) of oil which was homogeneous on tlc: ir (liquid) 1740, 1655, and 1610 cm^{-1}; uv max (95% EtOH) 345 nm (ϵ 6200); nmr (CCl_4) δ 1.33 (m, 6), 4.25 (m, 4), 5.01 (s, 2), 6.34 (d, 1), 7.23 (s, 5), and 7.35 (d, 1); mass spectrum m/e 329 (M^+).

1-Benzyl-3-carbethoxy-4-carboxy-2(1*H*)-pyridone (5a).—A solution of 489 mg (1.48 mmol) of the diester **4a** in 16.4 ml (1.48 mmol) of 0.9 *N* ethanolic potassium hydroxide was stirred at room temperature for 4.5 hr. The ethanol was removed *in vacuo*, 4 ml of water was added, and the solution was acidified with 6 *N* hydrochloric acid. The aqueous solution was extracted with chloroform and dried, and the solvent was removed *in vacuo* to give 346 mg (78%) of a thick oil which indicated the presence of a single ethyl group by nmr analysis. The product was crystallized from benzene: mp 126–128°; ir (Nujol) 2900 (broad), 1750, 1730, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.33 (t, 3), 4.37 (q, 2), 5.18 (s, 2), 6.61 (d, 1), 7.31 (s, 5), 7.37 (d, 1) and 12.5 (s, 1); mass spectrum m/e (rel intensity) 301 (2, M^+), 255 (80), 91 (100).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.85; H, 5.07; N, 4.57.

Methyl 2-Carbomethoxy-3-carbethoxy-*trans*-5-dimethylaminopenta-2,5-dienoate (3b).—A solution of 10 g (43.5 mmol) of triester **1b**,[6] 7.3 g (45.0 mmol) of a 85 mol % solution of dimethylformamide diethyl acetal in dimethylformamide, and 7 ml of dimethylformamide was heated at 80° for 3 hr. The cooled solution was poured into 100 ml of benzene, washed four times with water, dried, and evaporated *in vacuo* to give 11.25 g of crude product. Crystallization from carbon tetrachloride gave 9.40 g (83%) of **3b**: mp 116.5–118°; ir (Nujol) 1725, 1695, 1620 cm^{-1}; uv max (95% EtOH) 385 nm (ϵ 42,000); nmr ($CDCl_3$) δ 1.34 (t, 3), 2.97 (s, 6), 3.70 (s, 3), 3.80 (s, 3), 4.37 (q, 2), 5.71 (d, 1, J = 13 Hz), and 6.83 (d, 1, J = 13 Hz).

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.90. Found: C, 54.72; H, 6.61; N, 4.72.

1-Benzyl-3-carbomethoxy-4-carbethoxy-2(1*H*)-pyridone (4b) was prepared according to the procedure described for **3b**. The crude product was recrystallized from carbon tetrachloride to give **4b** in 89% yield: mp 78.5–80.5°; ir (Nujol) 1750, 1730, 1650, 1610 cm^{-1}; uv max (95% EtOH) 343 nm (ϵ 6400); nmr ($CDCl_3$) δ 1.32 (t, 3), 3.91 (s, 3), 4.32 (q, 2), 5.13 (s, 2), 6.55 (d, 1), 7.35 (s, 5), and 7.49 (d, 1); mass spectrum m/e (rel intensity) 3.15 (26, M^+), 283 (58), 91 (100).

Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 65.01; H, 5.51; N, 4.37.

1-Benzyl-3-carboxy-4-carbethoxy-2(1*H*)pyridone (5b).—To a refluxing solution of 6.15 g (46 mmol) of anhydrous lithium iodide in 50 ml of dry pyridine under nitrogen was added a solution of 3.67 g (11.65 mmol) of **4b**. Refluxing was continued for 1 hr. The solution was cooled and the pyridine was removed *in vacuo* (bath temperature 40°). The residue was dissolved in 50 ml of water, acidified with 6 *N* hydrochloric acid, and extracted with chloroform. The extracts were dried and evaporated *in vacuo* to give a residue which was crystallized from absolute ethanol to give 3.02 g (86%) of **5b**: mp 96–100°; ir (Nujol) 1740, 1630, 1450 cm^{-1}; nmr ($CDCl_3$) δ 1.27 (t, 3), 4.34 (q, 2), 5.19 (s, 2), 6.33 (d, 1), 7.30 (s, 5), 7.65 (d, 1) and 12.5 (s, 1); mass spectrum m/e (rel intensity) 301 (4, M^+), 255 (39), 91 (100).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.82; H, 5.12; N, 4.51.

1-Benzyl-3-hydroxymethyl-4-carboxy-2(1*H*)-pyridone Lactone (7).—To a solution of 320 mg (1.06 mmol) of **5b** in 5 ml of methylene chloride was added 1 ml of oxalyl chloride. The resulting solution was stirred for 16 hr at room temperature. The excess oxalyl chloride was removed *in vacuo*, and a solution of 130 mg

(11) Available from Aldrich Chemical Co., Milwaukee, Wis.

(2.1 mmol) of sodium cyanohydridoborate[7,12] in 5 ml of dry tetrahydrofuran was added to the residue. This solution was then stirred for 16 hr at room temperature. Water (10 ml) was added, and the solution was stirred for 15 min, then extracted with benzene. The extracts were dried and evaporated to give a semisolid which was recrystallized from benzene to give 192 mg (75%) of **7**: mp 125–126.5°; ir (Nujol) 1775, 1670 cm^{-1}; uv max (95% EtOH) 328 nm (ϵ 6000); nmr ($CDCl_3$) δ 5.21 (m, 4), 6.57 (d, 1), 7.33 (s, 5), 7.47 (d, 1); mass spectrum *m/e* (rel intensity) 241 (44, M^+), 91 (100), 65 (13).

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.23; H, 4.45; N, 5.74.

1-Benzyl-3-hydroxymethyl-4-carbethoxy-2(1*H*)-pyridone (6).—A solution of 215 mg (3.44 mmol) of sodium cyanohydridoborate in 10 ml of dry tetrahydrofuran was added to 510 mg (1.7 mmol) of acid chloride prepared as above. The resulting solution was stirred for 16 hr. After cooling in an ice bath, the solution was added quickly to an ice-cold, rapidly stirred solution of 50 ml of 10% aqueous phosphate buffer at pH 4.9. Stirring was continued for 1 min, and the solution was rapidly extracted with four 50-ml portions of benzene. The combined extracts were washed with cold water, dried, and evaporated *in vacuo* (bath temperature below 20°) to give 490 mg of **6** as a thick oil: ir (liquid) 3430, 1730, 1665, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (t, 3), 4.37 (q, 2), 4.87 (s, 2), 5.15 (s, 2), 6.49 (d, 1), 7.31 (s, 5), 7.35 (d, 1).

A sample of hydroxy ester **6** was converted quantitatively to the lactone **7**, mp 124–125°, by refluxing for 2 hr with a catalytic amount of *p*-toluenesulfonic acid in tetrahydrofuran.

Methyl 2-Carbomethoxy-3-carbethoxy-5-dimethylamino-5-(3-pyridyl)penta-2,4-dienoate (3c).—A solution of 397 mg (2.65 mmol) of *N,N*-dimethylnicotinamide in 1 ml of thionyl chloride was stirred for 2 hr at 70°. Excess thionyl chloride was removed *in vacuo*, and the residue was dissolved in 1 ml of fresh thionyl chloride. After stirring at 70° for 21 hr, the excess thionyl chloride was again removed *in vacuo*. The residual solid was dissolved in 2 ml of methylene chloride, and to this stirred solution at 0° was added 4.5 ml (11.5 mmol) of 2.56 *N* ethanolic sodium ethoxide. This suspension was stirred for 10 min, diluted with 20 ml of benzene, stirred for an additional 10 min, then filtered through Celite under a dry nitrogen atmosphere. The solvent was evaporated from the filtrate *in vacuo*, and the resulting oil was dissolved in 3 ml of benzene and filtered through Celite under a dry nitrogen atmosphere. The solvent was removed *in vacuo* to give 600 mg of crude product which contained 50 mol % amide acetal[13] **2b** by nmr analysis: nmr ($CDCl_3$) 1.23 (t, 6), 2.12 (s, 6), 3.48 (m, 4), 7.50 (m, 2), and 8.66 (m, 2). This material was used without further purification.

To the crude acetal prepared above was added 450 mg (1.95 mmol) of triester **1b**; the solution was stirred for 20 hr at 88° under a nitrogen atmosphere. The reaction mixture was purified by preparative tlc (five 20 × 20 cm plates, PF_{254} silica gel, eluted with 1:1 ethyl acetate–benzene). The yellow band of R_f 0.2 was removed from the plate and the product was extracted from the silica gel with 4:1 chloroform–methanol to give 127 mg (14%) of enamine **3c** as an unstable yellow oil: ir (liquid) 1735, 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.03 (t, 3), 2.87 (s, 6), 3.37 (q, 2), 3.64 (s, 3), 3.80 (s, 3), 5.97 (s, 1), 7.40 (m, 2) and 8.55 (m, 2); mass spectrum *m/e* 362 (M^+).

1-Benzyl-3-carbomethoxy-4-carbethoxy-6-(3-pyridyl)-2(1*H*)-pyridone (4c).—To a solution of 84 mg (0.23 mmol) of enamine **3c** in 1 ml of absolute ethanol was added 48 mg (0.44 mmol) of benzylamine; the resulting solution was refluxed for 108 hr. The solvent was removed *in vacuo* and the product was purified by preparative tlc (silica gel PF_{254}, eluted with ethyl acetate) to give 24 mg (26%) of colorless oil which crystallized from ethyl acetate–benzene to give **4c**: mp 130–133°; ir (Nujol) 1730, 1710, 1670, 1630 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (t, 3), 3.98 (s, 3), 4.33 (q, 2), 5.18 (s, 2), 6.53 (s, 1), 6.90 (m, 2), 7.23 (m, 5), 8.57 (m, 2); mass spectrum *m/e* 392 (M^+).

Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.36; H, 4.92. Found: C, 67.33; H, 5.14.

***o*-Cyano-*N,N*-dimethylbenzamide (9a).**—To a solution of methyl *o*-cyanobenzoate[11] (2.42 g, 15 mmol) in 15 ml of ethanol was added 21 ml (16 mmol) of 0.75 *N* ethanolic potassium hydroxide. The resulting mixture was stirred for 48 hr, and the potassium salt was collected by filtration of the ethanolic suspension. The white solid was dried at 25° *in vacuo* for 2 hr to give 2.69 g (98%) of potassium *o*-cyanobenzoate. This product was ground to a fine powder and suspended in 50 ml of methylene chloride. Oxalyl chloride (2.0 ml, 20 mmol) was added to the suspension, and then 10 drops of pyridine was *cautiously* added. The resulting suspension was stirred for 3 hr at room temperature and then was transferred to an addition funnel and added dropwise with stirring over 30 min to 50 ml of 25% aqueous dimethylamine at 0°. The mixture was stirred for an additional 15 min at room temperature, the layers were separated, and the aqueous layer was extracted with three 25-ml portions of methylene chloride. Water (20 ml) was added to the combined extracts, and portions of 12 *N* hydrochloric acid were added with intermittent shaking until the aqueous layer remained acidic. The extracts were dried and evaporated to give 2.58 g of impure cyanoamide **9a**. This product was dissolved in 40 ml of 1:1 ether–benzene, and the resulting solution was washed with three 10-ml portions of 0.5 *N* hydrochloric acid. The combined washings were extracted with 10 ml of ether, and the combined extracts were dried and evaporated to give 2.21 g (88%) of gas chromatographically pure amide **9a**: ir (liquid) 2210, 1640 cm^{-1}; nmr (CCl_4) δ 2.86 (s, 3), 3.05 (s, 3), 7.55 (m, 5).

Methyl 2-Carbomethoxy-3-carbethoxy-5-dimethylamino-5-(2-cyanophenyl)penta-2,4-dienoate (3d). Procedure A.—To a solution of 1.33 g (7.0 mmol) of triethyloxonium fluoroborate[14] in 2 ml of methylene chloride was added a solution of 1.13 g (6.5 mmol) of cyanoamide **9a**. The solution was stirred for 23 hr at room temperature and cooled to 0°, and 2.83 ml (7.0 mmol) of 2.47 *N* ethanolic sodium ethoxide was added. The resulting suspension was stirred for 5 min, diluted with 10 ml of petroleum ether, and filtered through Celite under an atmosphere of dry nitrogen. The solvent was removed *in vacuo* to give 1.58 g of an oil which was >95% amide acetal **2c**:[13] nmr ($CDCl_3$) δ 1.27 (t, 6), 2.28 (s, 6), 3.50 (m, 4), 7.58 (m, 4).

To the acetal was added 1.64 g (27.1 mmol) of triester **1b**, and the resulting solution was stirred at 90° for 70 hr under nitrogen. The crude reaction product was dissolved in 1 ml of carbon tetrachloride and transferred to a Morton flask. Petroleum ether (9 ml) was added, and the mixture was stirred vigorously for 15 min. The solution was decanted from the red oil and discarded, and this extraction process was repeated. The red oil (2.2 g) was chromatographed *via* the dry column technique[15] on a 1.5 × 36 in. nylon column packed with Baker silica gel which had been preequilibrated with 1:9 ethyl acetate–benzene. The yellow band was cut from the column, and the product was isolated by extraction from the silica gel to give 800 mg (30% from amide) of **3d** as a dark oil. Crystallization from ethyl acetate–cyclohexane afforded 610 mg (23%) of product, mp 135–138°. Two recrystallizations afforded 360 mg of analytically pure **3d**: mp 138–139°; uv max (95% EtOH) 401 nm (ϵ 27,000); ir (Nujol) 2210, 1740, 1720, 1690 cm^{-1}; nmr ($CDCl_3$) δ 1.06 (t, 3), 2.88 (s, 6), 3.38 (q, 2), 3.62 (s, 3), 3.78 (s, 3), 6.02 (s, 1), 7.50 (m, 4); mass spectrum *m/e* 386 (M^+).

Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.61; H, 5.83; N, 6.95.

Procedure B.—A solution of 1.11 g (6.4 mmol) of amide **9a** and 1.33 g (7.0 mmol) of triethyloxonium fluoroborate[14] in 4 ml of methylene chloride was stirred for 48 hr at 25°. A solution of triester anion was prepared by adding 1.61 g (7.0 mmol) of triester dropwise to a suspension of sodium hydride (340 mg of 50% dispersion, 7.1 mmol) in 4 ml of dimethylformamide at 0°. This solution was then added under nitrogen to the cooled methylene chloride solution in small portions over 3 min. The reaction mixture was allowed to come to room temperature and was stirred under nitrogen for 5 hr. Methylene chloride (25 ml) was added, and the resulting solution was washed with three 25-ml portions of water. The organic layer was dried and evaporated to give 2.48 g of red oil. The product was crystallized from ethyl acetate–cyclohexane to give 790 mg (32%) of **3d**, mp 136–137°.

6-Oxo-7-carbomethoxy-8-carbethoxy-10(*H*)-pyrido[1,2-*a*]isoindole (11).—To a solution of 700 mg (1.75 mmol) of **3d** in 40 ml of ethanol was added 10 ml of W-2 Raney nickel. The resulting suspension was hydrogenated at atmospheric pressure, and the reduction was monitored by observing the decrease in the 401-nm absorption of **3d**. After 17 hr, the catalyst was removed by filtration through Celite, and the ethanol was evaporated. The crude product was purified by dry column[15] chromatography on a

(12) Available from Alfa Inorganics, Beverly, Mass.

(13) The remainder of the material was a mixture of the corresponding ester and dimethylamide.

(14) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(15) B. Loev and M. M. Goodman, *Chem. Ind.* (*London*), 2026 (1967).

1 × 25 in. silica gel column, eluting with ethyl acetate. The resulting material (450 mg) was further purified by preparative tlc (silica gel PF_{254}, using 97:3 chloroform–methanol to elute) and the product was recrystallized to give 230 mg (42%) of **11**: mp 159–162° (analytical sample mp 161.5–163°); ir (Nujol) 1725, 1710, 1640 cm^{-1}; uv max (95% EtOH) 366 nm (ε 14,300); nmr ($CDCl_3$) δ 1.37 (t, 3), 3.95 (s, 3), 4.35 (q, 2), 5.15 (s, 2), 7.10 (s, 1), 7.60 (m, 4); mass spectrum *m/e* 313 (M^+).

Anal. Calcd from $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.20; H, 4.73; N, 4.29.

***N*,*N*-Dimethyl-3-cyanoquinaldamide (9b).**—To a suspension of 10.12 g (62.1 mmol) of the sodium enolate of ethyl 3-cyanopyruvate was added 40 ml (86.8 mmol) of 2.17 *N* methanolic hydrochloric acid. The suspension was stirred for 15 min and the solvent was removed *in vacuo*. The resulting mixture was suspended in 80 ml of chloroform and filtered, and the solvent was removed *in vacuo* to give an orange oil. This crude cyano keto ester was dissolved in 200 ml of absolute ethanol containing a catalytic quantity of HCl, and a solution of 10.97 g (91 mmol) of *o*-aminobenzaldehyde in 50 ml of absolute ethanol was added. The reaction mixture was stirred at 25° for 7 days. The solution was made basic with ethanolic sodium ethoxide, and the solvent was removed *in vacuo*. The residue was stirred three times with 250-ml portions of ether, the suspensions being filtered each time. The combined ether extracts were evaporated, and the semisolid residue was crystallized from ether to give 4.40 g (32%) of ethyl 3-cyanoquinaldate: mp 130–132°; ir (Nujol) 2220, 1720 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 69.24; H, 4.52; N, 12.60.

A solution of ethyl 3-cyanoquinaldate (967 mg, 4.28 mmol) in 4 ml of dimethylamine was stirred with a Dry Ice–acetone condenser for 1 hr and then diluted with 15 ml of absolute ethanol. The reaction mixture was stirred for 16 hr at 25°. The solvent was removed *in vacuo* and the resulting solid was recrystallized from ethyl acetate to give 645 mg (67%) of **9b**: mp 139–141; ir (Nujol) 2220, 1655 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.55; H, 5.04; N, 18.25.

Methyl 2-Carbomethoxy-3-carbethoxy-5-(*N*,*N*-dimethylamino)-5-(3-cyano-2-quinolyl)penta-2,4-dienoate (3e).—A solution of 555 mg (2.92 mmol) of triethyloxonium fluoroborate and 553 mg (2.38 mmol) of amide **9b** in 7 ml of methylene chloride was stirred for 48 hr at 25°. A solution of the triester anion was prepared by adding 876 mg (3.81 mmol) of triester **1b** dropwise to a suspension of sodium hydride (213 mg of 50% dispersion, 4.44 mmol) in 2 ml of dimethylformamide at 25° and then stirring for 30 min. This solution was then added at 0° to the methylene chloride solution prepared above. After stirring for 5 min, methylene chloride (*ca.* 25 ml) was added and the solution was washed with four 25-ml portions of water. The organic layer was dried and evaporated to give 1.3 g of crude product. Purification by preparative tlc (silica gel PF_{254}, eluting with 1:1 ethyl acetate–benzene) afforded 539 mg (52%) of **3e** as an unstable oil: ir (liquid) 2220, 1730, 1690 cm^{-1}; uv max (95% EtOH) 425 nm (ε 27,000); nmr ($CDCl_3$) δ 0.80 (t, 3), 2.88 (q, 2), 2.92 (s, 6), 3.57 (s, 3), 3.78 (s, 3), 6.13 (s, 1), 7.93 (m, 4), 8.67 (s, 1); mass spectrum *m/e* 437 (M^+).

7-Carbethoxy-8-carbomethoxy-9-oxo-11(*H*)-indolizino[1,2-6]-quinoline (13).—To 340 mg (0.78 mmol) of **3a** was added 5 ml of ethanolic W-2 Raney nickel, and the suspension was hydrogenated at atmospheric pressure for 15 hr. The reaction mixture was filtered through Celite and the solvent was removed *in vacuo* to give 216 mg of crude material. The product was purified by preparative tlc (silica gel PF_{254}, eluted with ethyl acetate) to give 30 mg (11%) of an insoluble solid: mp 280–284°; ir (Nujol) 1730, 1720, 1660, 1620, 1610 cm^{-1}; uv max (95% EtOH) 372 nm (ε 9700).

Anal. Calcd for $C_{20}H_{16}N_2O_5$: mol wt, 364.10592. Found:[16] mol wt, 364.10593.

Registry No.—**3a**, 33707-20-9; **3b**, 33707-21-0; **3c**, 33707-22-1; **3d**, 33703-23-2; **3e**, 33666-43-2; **4a**, 33707-24-3; **4b**, 33707-25-4; **4c**, 33707-26-5; **5a**, 33707-27-6; **5b**, 33707-28-7; **6**, 33707-29-8; **7**, 33707-30-1; **9a**, 26487-08-1; **9b**, 33707-32-3; **11**, 33707-33-4; **13**, 33707-34-5; ethyl 3-cyanoquinaldate, 33707-35-6.

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(16) We thank R. Graham Cooks, Purdue University, for this measurement.

Synthesis of *N*-Alkyl-3-carboxy-4-pyridones

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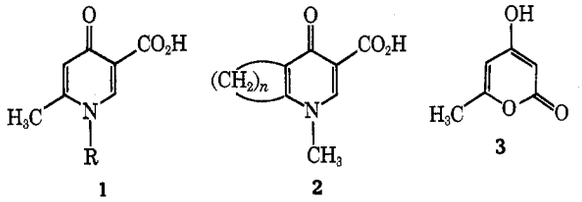
The synthesis of several *N*-alkyl-3-carboxy-4-pyridones is described beginning with substituted 4-hydroxy-2-pyrones. Several of the pyrones are prepared by a new synthesis involving the condensation of a morpholine enamine with carboethoxyacetyl chloride to give a diketo ester. The diketo ester is cyclized with sodium methoxide in dimethylformamide to afford the 4-hydroxy-2-pyrone. The 4-hydroxy-2-pyrones react with the dimethyl acetal of dimethylformamide in a new reaction to introduce a 3-dimethylaminomethylene moiety. Rearrangement of this intermediate with primary amines leads to the title compounds.

In this paper we report the synthesis of several *N*-alkyl-3-carboxy-4-pyridones of types **1** and **2**. A convenient starting material for the preparation of **1** should be **3**. We planned to introduce an aldehyde or related functionality in position **3** after which rearrangement with ammonia or primary amines should yield **1**.

This type of rearrangement has been done with ammonia and dehydroacetic acid (**4** to **6**) when the temperature of the reaction did not exceed 100°.[1] A side product was the decarboxylated pyridone. According to Schut and coworkers[2] only the decarboxylated compound is isolated when dehydroacetic acid is treated with primary amines. In our case the major product was always the pyridonecarboxylic acid.



R = H, alkyl

Introduction of the aminomethylene functionality into the 3 position of a 4-hydroxy-2-pyrone was accomplished by using the dimethyl acetal of dimethylformamide, a compound known to react with active methy-

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(2) R. N. Schut, W. G. Stryeker, and T. M. H. Lin, *J. Org. Chem.*, **28**, 3046 (1963).