C, 47.31; H, 5.46. Found: C, 47.36; H, 5.31.

**Syntheses of 3-Methyleneoxolanes (2). Typical Procedure.** To a solution of bromide **1b** (2.53 g, 10 mmol) in 50 mL of ethanol were added 1.0 mL of 10 N aqueous NaOH and sodium borohydride (380 mg, 10 mmol). The solution was warmed to 50 °C under a nitrogen atmosphere, and powdered chlorocobaloxime(III)[5] (240 mg, 0.6 mmol) was added in portions over a period of 1 h. The temperature of the reaction mixture was kept between 50 and 60 °C. After the completion of the addition, the reaction mixture was further stirred for 30 min at the same temperature. Most of the ethanol was removed under reduced pressure, and after the addition of 50 mL of saturated aqueous NaCl, the mixture was extracted with pentane–ether (4:1) several times. The extracts were washed with saturated aqueous NaCl and dried over sodium sulfate. After the evaporation of the solvents, the residue was distilled under reduced pressure to give oxolane **2b**: 1.27 g (73%); bp 62–63 °C (0.5 mm); IR ($CCl_4$) 1671, 1044, 884, 700 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.48 (s, 3 H), 2.70 (diffused d, 1 H, $J$ = 16 Hz), 2.91 (diffused d, 1 H, $J$ = 16 Hz), 4.42 (diffused t, 2 H, $J$ = 15 Hz), 4.87 (t, 1 H, $J$ = 2 Hz), 4.97 (t, 1 H, $J$ = 2 Hz), 7.20–7.50 (m, 5 H); mass spectrum, $m/e$ 174.1041 ($M^+$) (Calcd for $C_{12}H_{14}O$ 174.1043).

The same procedure gave oxolanes **2c–e**, and chromatography on silica gel instead of distillation gave **2a** in the yield listed in Table I.

**2a**: mp 51–51.5 °C; IR ($CCl_4$) 1670, 1046, 883, 698 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 3.10–3.20 (m, 2 H), 4.27–4.36 (m, 2 H), 4.72–4.80 (m, 1 H), 4.85–4.96 (m, 1 H), 7.00–7.40 (m, 10 H). Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.21; H, 6.80.

**2c**: mp 94 °C (7.0 mm); IR ($CCl_4$) 1670, 1054, 883, 695 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 2.24 (diffused dd, 1 H, $J$ = 7, 16 Hz), 2.85 (diffused dd, 1 H, $J$ = 6, 16 Hz), 4.23 (diffused d, 1 H, $J$ = 13 Hz), 4.42 (diffused d, 1 H, $J$ = 13 Hz), 4.71–5.00 (m, 3 H), 7.23 (m, 5 H); mass spectrum, $m/e$ 160 ($M^+$). Hydrogenolysis of **2c** over Pd/C in ethanol gave 2-methyl-4-phenylbutanol which was identified by comparison with an authentic sample.[9]

**2d**: bp 95–100 °C (85 mm); IR ($CCl_4$) 1669, 1032, 885 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.20–2.00 (m, 8 H), 2.49 (br s, 1 H), 3.85–4.01 (m, 1 H), 4.25 (diffused d, 1 H, $J$ = 14 Hz), 4.46 (diffused d, 1 H, $J$ = 14 Hz), 4.86–5.01 (m, 2 H); mass spectrum, $m/e$ 138.1049 ($M^+$) (calcd for $C_9H_{14}O$ 138.1045).

**2e**: bp 90–95 °C (101 mm); IR ($CCl_4$) 1670, 1060, 887 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.47–2.03 (m, 6 H), 3.02 (br s, 1 H), 4.17 (diffused d, 1 H, $J$ = 14 Hz), 4.34 (diffused d, 1 H, $J$ = 14 Hz), 4.46–4.62 (m, 1 H), 4.93–5.00 (m, 2 H); mass spectrum, $m/e$ 124.0881 ($M^+$) (calcd for $C_8H_{12}O$ 124.0887).

**Syntheses of α-Methylene-γ-butyrolactones (4). Typical Procedure.** Chromium trioxide (12.0 g, 120 mmol) was added to a mixture of pyridine (12 mL) and dichloromethane (methanol free, 120 mL),[6] and the resulting solution was stirred for 20 min. To the mixture was added 5 mL of a dichloromethane solution of 3-methyleneoxolane **2b** (1.04 g, 6 mmol), and the reaction mixture was refluxed for 1 h. The solution part of the mixture was separated by decantation, and the residue was washed with dichloromethane. The dichloromethane solution was washed with saturated aqueous $NaHCO_3$. The solid residue of the reaction mixture was dissolved in a large amount (ca. 300 mL) of saturated aqueous $NaHCO_3$ and extracted with dichloromethane. The combined dichloromethane extracts were washed with 2 N aqueous HCl, passed through a short column of silica gel (1 cm i.d. × 10 cm) to remove the chromium compound, and condensed under reduced pressure. Distillation of the condensate gave γ-methyl-α-methylene-γ-phenyl-γ-butyrolactone (**4b**):[10] 6.77 g (60%); bp 94–97 °C (0.25 mm); IR ($CCl_4$) 1779, 1674, 702 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.68 (s, 3 H), 3.05 (t, 2 H, $J$ = 3 Hz), 5.46 (t, 1 H, $J$ = 3 Hz), 6.06 (t, 1 H, $J$ = 3 Hz), 7.10–7.35 (m, 5 H).

The same procedure gave α-methylene-γ-butyrolactones **4d** and **4e**, and recrystallization instead of distillation at the last stage gave lactones **4a** (methanol) and **4c** (hexane) in the yields listed in Table I. All α-methylene-γ-butyrolactones obtained in this work are identical with the reported ones in boiling and melting points and in spectroscopic properties.

(9) Brawn, J. V.; Kirschbaum, G. K. *Chem. Ber.* **1914**, *47*, 264.

(10) Hegedus, L. S.; Wagner, S. D.; Waterman, E. L.; Siirala-Hansen, K. *J. Org. Chem.* **1975**, *40*, 593.

**4a**:[11] mp 101–103 °C; IR ($CCl_4$) 1777, 1672, 698 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 3.64 (t, 2 H, $J$ = 3 Hz), 5.66 (t, 1 H, $J$ = 3 Hz), 6.28 (t, 1 H, $J$ = 3 Hz), 7.22–7.67 (m, 10 H).

**4c**:[10] mp 52–53.5 °C; IR ($CCl_4$) 1800, 1674, 700 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 2.65–2.96 (m, 1 H), 3.22–3.53 (m, 1 H), 5.44 (t, 1 H, $J$ = 8 Hz), 5.61 (t, 1 H, $J$ = 3 Hz), 6.22 (t, 1 H, $J$ = 3 Hz), 7.27–7.43 (m, 5 H).

**4d**:[7] bp 95–99 °C (4.0 mm); IR ($CCl_4$) 1778, 1672 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.25–2.10 (m, 8 H), 2.86–3.09 (m, 1 H), 4.44 (q, 1 H, $J$ = 6 Hz), 5.42 (d, 1 H, $J$ = 3 Hz), 6.07 (d, 1 H, $J$ = 3 Hz).

**4e**:[8] bp 135–139 °C (31 mm); IR ($CCl_4$) 1770, 1669 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.56–2.18 (m, 6 H), 3.25–3.49 (m, 1 H), 4.82–4.99 (m, 1 H), 5.54 (d, 1 H, $J$ = 3 Hz), 6.12 (d, 1 H, $J$ = 3 Hz).

**Registry No. 1a**, 81011-48-5; **1b**, 80997-76-8; **1c**, 80997-77-9; **1d**, 71960-57-1; **1e**, 80997-78-0; **2a**, 77862-49-8; **2b**, 81011-49-6; **2c**, 80997-79-1; **2d**, 75681-59-3; **2e**, 80997-80-4; **4a**, 29043-99-0; **4b**, 29043-98-9; **4c**, 26613-71-8; **4d**, 16822-06-3; **4e**, 61747-55-5; cobaloxime (I), 36451-60-2; 2-propynol, 107-19-7; 2-phenylpropene, 98-83-9; chlorocobaloxime (III), 59692-12-5; 2-methyl-4-phenylbutanol, 3023-61-8; 1,1'-ethylidenebis[benzene], 530-48-3; ethenylbenzene, 100-42-5; cyclohexene, 110-83-8; cyclopentene, 142-29-0.

(11) Oehler, E.; Reiniger, K.; Schmidt, U. *Angew. Chem.* **1970**, *82*, 480.

## Unusual Cyclization of Amidine Salts in the Formation of Quinazolones

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When an aromatic amine, **1**, reacts with a benzoxazinone, **2** (i.e., acylanthranil), to give a quinazolone, **5**, it can do so by two pathways (Scheme I).[1] Pathway A involves formation of an intermediate *o*-(acylamido)benzamide, **3**, which cyclizes at temperatures above 200 °C. Pathway B involves the formation of an amidine salt **4** which undergoes facile cyclization to yield the quinazolone even at room temperature.[1d] In the examples presented by Errede and co-workers,[1] the oxazine (**2**) had no substituents at the 5- or 8-position, and cyclization of the intermediate amidine salt (**4**) presented no complications. However, while preparing various substituted quinazolone derivatives, we have observed that certain substituents can alter the course of amidine salt cyclodehydration.

In our study, 2-acetamido-3-(carbomethoxy)-5,6-dimethylbenzoic acid (**6**)[2] was converted to the acylanthranil **7** by refluxing with phosphorus oxychloride in toluene[3] (Scheme II). The acylanthranil was treated with aniline derivatives **8** in anticipation of the preparation of the substituted quinazolone derivatives **9**. However, acidic substances were isolated and subsequently assigned structure **10**.

Although the benzoic acid **6** was recovered unchanged after heating with the aromatic amines **8**, addition of trace amounts of acetic acid led to the formation of *o*-acetamidobenzamido acids **11** (Scheme II). Acids **11b** and **11c**

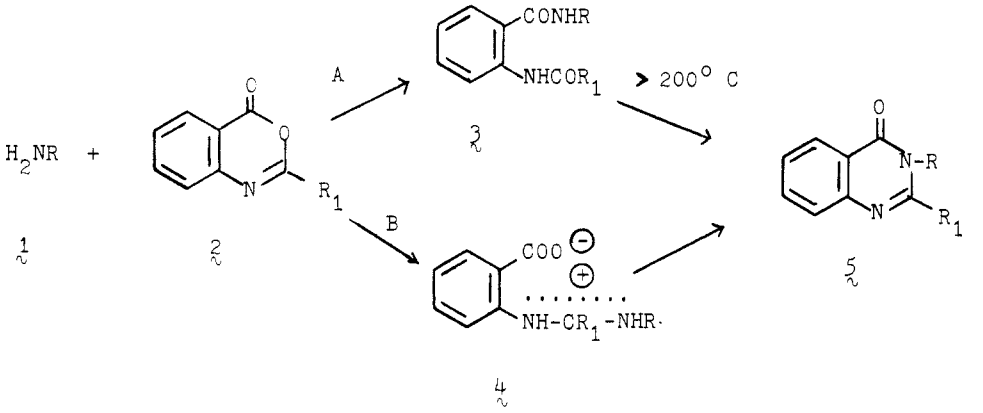
(1) (a) Errede, L. A. *J. Org. Chem.* **1976**, *41*, 1763. (b) Errede, L. A.; McBrady, J. J.; Oien, H. T. *J. Org. Chem.* **1976**, *41*, 1765. (c) Errede, L. A.; Oien, H. T.; Yarian, D. R. *J. Org. Chem.* **1977**, *42*, 12. (d) Errede, L. A.; McBrady, J. J.; Oien, H. T. *J. Org. Chem.* **1977**, *42*, 656.

(2) Nixon, W. J., Jr.; Garland, J. T.; Blanton, C. D., Jr. *Synthesis* **1980**, 56.

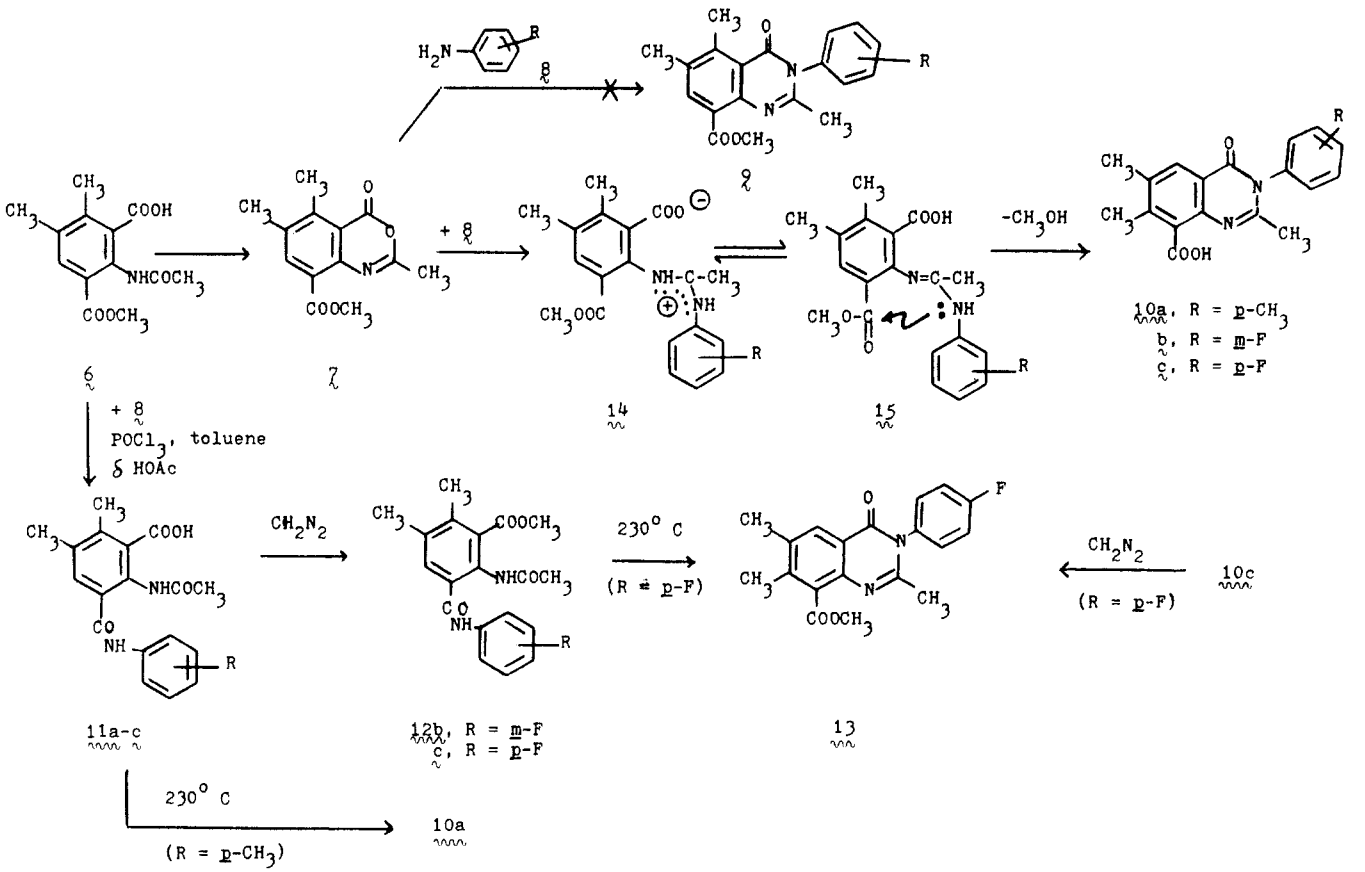
(3) Grimmel, H. W.; Guenther, A.; Morgan, J. R. *J. Am. Chem. Soc.* **1946**, *68*, 542.

0022-3263/82/1947-1777$01.25/0 

**Scheme I**



**Scheme II**

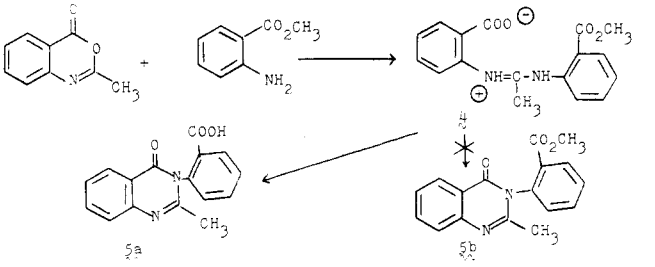


were esterified by diazomethane to yield **12b** and **12c**, respectively. When the acetamidobenzamido acid **11a** or ester **12c** was heated above 200 °C in diphenyl ether, the quinazolone acid **10a** or ester **13** was obtained in 64–88% yields. Esterification of a sample of **10c** obtained from the benzoxazinone (**7**) gave a product identical with **13** obtained from the acetamidobenzamido ester **12c**.

The quinazolone acids **10** obtained from **6** by using phosphorus oxychloride can be explained by the mechanism proposed by Scheme II. Under these conditions, the amine reacts with the benzoxazinone **7** by pathway B (Scheme I) to give amidine salts **14**.[4] One can consider the amidine salts to be in equilibrium with the corresponding neutral species **15** in which the terminal nitrogen attacks the ester moiety in preference to the carboxy moiety.[5] The presence of trace amounts of acetic acid appears to inhibit benzoxazinone formation while catalyzing formation of the acetamidobenzamido acids **11** as

(4) Errede, L. A.; Martinucci, P. D.; McBrady, J. J. *J. Org. Chem.* **1980**, *45*, 3009.

(5) In a private communication from Dr. L. A. Errede, we have been cautioned that ring closure via the $CO_2R$ group may be universally more facile than via the $CO_2H$ group, and the presence of ring substituents merely enhance the difference in a quantitative way rather than qualitatively. On the basis of personal observations not yet published, Dr. Errede has studied the kinetics of the reaction of acetylanthranil with methyl anthranilate, and the major product of cyclodehydration is **5a**:



these were not obtained when 6 and aromatic amines were heated alone in toluene.

## Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Melting points over 300 °C were determined on a Mel-Temp capillary melting point apparatus. The infrared spectra were recorded on a Perkin-Elmer 467 grating spectrophotometer. The NMR spectra were obtained on a 60 MHz Hitachi Perkin-Elmer R20A high-resolution spectrometer using $Me_4Si$ as an internal standard. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, GA. TLC was performed on Eastman chromatogram sheets coated with silica gel.

**8-(Carbomethoxy)-2,5,6-trimethyl-4*H*-3,1-benzoxazin-4-one (7).** In a round-bottomed flask were placed 2.0 g (7.5 mmol) of 2-acetamido-3-(carbomethoxy)-5,6-dimethylbenzoic acid (**6**)[2] and 1.2 g of phosphorus oxychloride in 60 mL of toluene. The mixture was refluxed for 3 h. After concentration in vacuo, cold absolute methanol was added to the gummy residue. A solid precipitate was collected by filtration and recrystallized from acetonitrile to yield 0.5 g (27%) of **7**: mp 258–260 °C; IR (KBr) 2950, 1730, 1670, 1600 $cm^{-1}$; NMR ($Me_2SO$-$d_6$, acetone-$d_6$) δ 7.6 (s, 1 H), 3.75 (s, 3 H), 2.2–2.3 (3 s, 9 H).

Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 63.12; H, 5.34; N, 5.62.

**2,6,7-Trimethyl-3-*p*-tolyl-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (10a).** To a 100-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and heating mantle were added 2.6 g (9.8 mmol) of **6**, 1.5 g (14 mmol) of *p*-toluidine, and 0.5 g of phosphorus oxychloride in 60 mL of toluene. The mixture was refluxed for 3.5 h and concentrated in vacuo. Treating the gum with ether yielded a white solid. After recrystallization from methanol, 1.5 g (47%) of **10a** was obtained: mp 249.5–251 °C; IR (KBr) 3300, 2950, 1720, 1685, 1620 $cm^{-1}$; NMR ($CDCl_3$) δ 8.1 (s, 1 H), 7.1–7.5 (m, 4 H), 2.75 (s, 3 H), 2.45 (s, 3 H), 2.4 (s, 3 H), 2.3 (s, 3 H).

Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.57; H, 5.66; N, 8.65.

**2,6,7-Trimethyl-3-(*m*-fluorophenyl)-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (10b).** The title compound was prepared as above from *m*-fluoroaniline and **6** in 32% yield (acetonitrile): mp 298–300 °C; IR (KBr) 3400, 1710, 1680, 1600 $cm^{-1}$; NMR ($CD_3CN$, TFA) δ 8.45 (s, 1 H), 7.2–7.5 (m, 4 H), 2.8 (s, 3 H), 2.6 (s, 3 H), 2.5 (s, 3 H).

Anal. Calcd for $C_{18}H_{15}N_2O_3F$: C, 66.25; H, 4.63; N, 8.58. Found: C, 66.21; H, 4.65; N, 8.58.

**2,6,7-Trimethyl-3-(*p*-fluorophenyl)-3,4-dihydro-4-oxoquinazoline-8-carboxylic Acid (10c).** The title compound was prepared as above from *p*-fluoroaniline and **6** in 37% yield (methanol): mp 311–313 °C; IR (KBr) 1710, 1680, 1610 $cm^{-1}$; NMR (pyridine-$d_5$, TFA) δ 8.7 (s, 1 H), 7.4–8.4 (m, 4 H), 2.7 (s, 3 H), 2.3 (s, 3 H), 2.25 (s, 3 H).

Anal. Calcd for $C_{18}H_{15}N_2O_3F$: C, 66.25; H, 4.63; N, 8.58. Found: C, 66.03; H, 4.68; N, 8.46.

**2,6,7-Trimethyl-3-(*p*-fluorophenyl)-3,4-dihydro-4-oxo-8-(carbomethoxy)quinazoline (13).** In a 250-mL Erlenmeyer flask was placed 3.5 g (0.01 mol) of **10c** dissolved in 50 mL of methylene chloride and 50 mL of absolute methanol. The flask was placed in an ice bath on a magnetic stirrer. The mixture was stirred as an excess of ethereal diazomethane solution was added. After 2 h the solvents were evaporated in vacuo. The solid residue was recrystallized from aqueous methanol to give 2.6 g (71%) of **13**: mp 237–239 °C; IR (KBr) 2980, 1730, 1690, 1620 $cm^{-1}$; NMR ($CDCl_3$, $Me_2SO$-$d_6$, TFA) δ 8.0 (s, 1 H), 7.2–7.5 (m, 4 H), 3.8 (s, 3 H), 2.8 (m, 6 H), 2.4 (s, 3 H).

Anal. Calcd for $C_{19}H_{17}N_2O_3F$: C, 67.05; H, 5.03; N, 8.23. Found: C, 66.94; H, 5.05; N, 8.18.

***N*-*p*-Tolyl-2-acetamido-3-carboxy-4,5-dimethylbenzamide (11a).** To a 250-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and heating mantle were added 2.6 g (9.8 mmol) of **6**, 1.5 g (14 mmol) of *p*-toluidine, 0.5 g of phosphorus oxychloride, and 0.5 mL of acetic acid in 60 mL of toluene. After refluxing the mixture for 3.5 h, the solvent was removed in vacuo. The white precipitate was recrystallized from acetonitrile to yield 1.7 g (51%) of **11a**: mp 253–255 °C; IR (KBr) 3280, 2940, 1710, 1660, 1640, 1600 $cm^{-1}$; NMR (TFA) δ 8.05 (s, 1 H), 7.25–7.60 (m, 4 H), 2.6 (s, 3 H), 2.4 (2 s, 6 H), 2.25 (s, 3 H).

Anal. Calcd for $C_{19}H_{20}N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.27; H, 6.00; N, 8.15.

***N*-(*m*-Fluorophenyl)-2-acetamido-3-(carbomethoxy)-4,5-dimethylbenzamide (12b).** To a 250-mL round-bottomed flask equipped with a magnetic stirrer, reflux condenser, and heating mantle were added 5.2 g (0.02 mol) of **6**, 2.0 mL of *m*-fluoroaniline, 1.0 g of phosphorus oxychloride, and 0.5 mL of acetic acid in 100 mL of toluene. The mixture was refluxed for 4 h, the solvent was removed in vacuo, and the solid residue was recrystallized from aqueous methanol to yield 2.3 g (34%) of **11b**: mp 219–221 °C; IR (KBr) 3240, 3020, 2940, 1725, 1640, 1600 $cm^{-1}$. This acid was treated with excess ethereal diazomethane in methylene chloride. The solvent was evaporated in vacuo, and the solid residue was recrystallized from absolute methanol to yield 2.1 g (87%) of **12b**: mp 209–211 °C; IR (KBr) 3260, 2960, 1730, 1660, 1600 $cm^{-1}$; NMR ($CDCl_3$, TFA) δ 9.4 (s, 1 H), 9.15 (s, 1 H), 8.0 (s, 1 H), 7.25–7.70 (m, 4 H), 4.0 (s, 3 H), 2.4 (2 s, 6 H), 2.3 (s, 3 H).

Anal. Calcd for $C_{19}H_{19}N_2O_4F$: C, 63.68; H, 5.34; N, 7.82. Found: C, 63.75; H, 5.38; N, 7.80.

***N*-(*p*-Fluorophenyl)-2-acetamido-3-(carbomethoxy)-4,5-dimethylbenzamide (12c).** The title compound was prepared as above from **6** and *p*-fluoroaniline. The intermediate acetamidobenzamido acid (**11c**) was obtained in 41% yield (acetonitrile): mp 224–226 °C; IR (KBr) 3280, 2960, 1710, 1660, 1650, 1610 $cm^{-1}$. Treatment of the acid with diazomethane gave an 88% yield (methanol–ether) of **12c**: mp 236–238 °C; IR (KBr) 3280, 2980, 1720, 1670, 1660, 1620 $cm^{-1}$; NMR ($CDCl_3$, $Me_2SO$-$d_6$, TFA) δ 9.4 (s, 1 H), 9.15 (s, 1 H), 8.0 (s, 1 H), 7.1–7.7 (m, 4 H), 3.95 (s, 3 H), 2.4 (2 s, 6 H), 2.3 (s, 3 H).

Anal. Calcd for $C_{19}H_{19}N_2O_4F$: C, 63.68; H, 5.34; N, 7.82. Found: C, 63.61; H, 5.40; N, 7.79.

**Thermal Cyclodehydration in Diphenyl Ethers. (A) Preparation of 10a.** In a 250-mL round-bottomed flask were heated 2.4 g (7 mmol) of **11a** and 40 mL of diphenyl ether in an oil bath at 230–40 °C for 15 min. The mixture was cooled, petroleum ether (bp 30–60 °C) was added, an the solid precipitate was collected by filtration. After recrystallization from methanol, **10a** was obtained: 2.0 g (88%); mp 249–251 °C. The IR and NMR spectra and $R_f$ values were identical with those of **10a** obtained from the benzoxazinone (Scheme II).

**(B) Preparation of 13.** The acetamidobenzamide ester **12c** (2.0 g, 5.5 mmol) was taken up in 40 mL of diphenyl ether and heated in an oil bath at 230–240 °C with vigorous stirring for 25 min. The reaction mixture was cooled, and petroleum ether was added. Recrystallization of the solid precipitate from methyl acetate gave **13**: 1.2 (64%); mp 237–238 °C. The IR and NMR spectra and $R_f$ values were identical with those of **13** obtained by esterification of **10c** (Scheme II).

**Acknowledgment.** This research was supported in part by National Institute of Neurological and Communicative Disorders and Stroke (Grant 5RO1NS16988).

**Registry No. 6**, 73318-18-0; **7**, 81045-03-6; **8** (R = *p*-Me), 106-49-0; **8** (R = *m*-F), 372-19-0; **8** (R = *p*-F), 371-40-4; **10a**, 81045-04-7; **10b**, 81045-05-8; **10c**, 81045-06-9; **11a**, 81045-07-0; **11b**, 81045-08-1; **11c**, 81045-09-2; **12b**, 81045-10-5; **12c**, 81045-11-6; **13**, 81045-12-7.

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# Retinoic Acid Metabolites. 2.[1] Total Synthesis of *rac*-(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-(6-carboxy-2,6-dimethyl-3-oxo-1-cyclohexen-1-yl)-2,4,6,8-nonatetraenoic Acid and *rac*-(2*E*,4*E*,6*E*,8*E*)-3,7-Dimethyl-9-[2,6-dimethyl-6-(hydroxymethyl)-3-oxo-1-cyclohexen-1-yl]-2,4,6,8-nonatetraenoic Acid

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Retinoic acid has numerous essential functions in the body[2] and is very rapidly excreted from the system as the

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