The Regiospecific Synthesis of the A and B Rings of Phomazarin

Vincent Guay and Paul Brassard*

Département de chimie, Université Laval,
Québec (Québec) Canada G1K 7P4

Received August 4, 1986

Elaboration of the A ring of phomazarin by the Conrad-Limpach approach has been shown to be possible in the case of a protected hydroquinone substrate. However similar condensations using a suitably substituted naphthoquinone gave a lactam instead of the expected benzoquinolone. Attempts to annulate simplified models of the A-B rings with the appropriate diene have also been successful albeit in low yield.

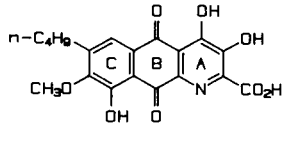
J. Heterocyclic Chem., **24**, 1649 (1987).

We have recently completed a regiospecific synthesis of the B and C rings of phomazarin (**1**) [1]. However, in spite of extensive data on the Conrad-Limpach process of heteroannulation [2], we have experienced considerable difficulty in incorporating the A ring into an appropriate substrate. In fact not only do many reagents provide consistent low yields, a well known drawback of this approach, but the required intermediates also seem to show an unexpected dichotomous behavior.

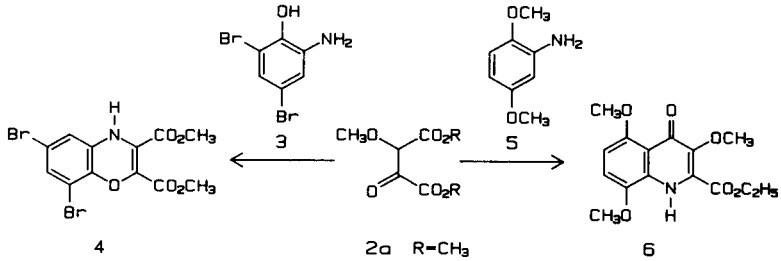
The ambident reactivity of compounds such as 6-amino-1,3-dimethyluracil in Gould-Jacobs [3,4] or Doebner-Miller [5] reactions has previously been recorded and rationalized. Even aniline shows some tendency to react similarly in analogous circumstances [6]. However, aminoquinones [7,8] are considered to give "normal" products and the fact that they can behave as enamines does not seem to have previously been observed.

Notwithstanding the poor results [9] obtained earlier with their use, dialkyl 3-methoxy-2-oxo-1,4-butanedioates (**2**) [9,10] were judged to be among the most convenient reagents for elaborating phomazarin by this approach, since all the functionalities could then in principle be introduced in a simple two-step process. *o*-Hydroxyanilines such as 2-amino-4,6-dibromophenol (**3**) were not expected to be ideal substrates and were indeed found to be quite unsuitable as they readily lead to benzoxazine derivatives (*i.e.* **4**). Protecting the phenol in the form of a mesylate as in 2-amino-6-bromo-4-methoxyphenol methanesulfonate (**15a**) did not much improve the process since only 10% of an unidentified enamine-like product was obtained and no attempt was made to cyclize it.

Turning to aminohydroquinone dimethyl ethers as proposed earlier by Baxter, *et al.* [11] in the case of oxosuccinates, 2,5-dimethoxyaniline (**5**) was condensed with diester **2b** and after cyclization afforded the expected quinolone **6** in rather low yield (23%) (Scheme I). Reductive methylation of the previously prepared 3-acetamido-7-butyl-5-hydroxy-6-methoxynaphthoquinone (**7**) [1] under phase transfer conditions gave an excellent yield of the corresponding tetramethyl ether **8**. However hydrolysis of the amide and reaction of the free amine **9** with diester **2a** in refluxing toluene followed by heating in diphenyl ether at 250° gave



1

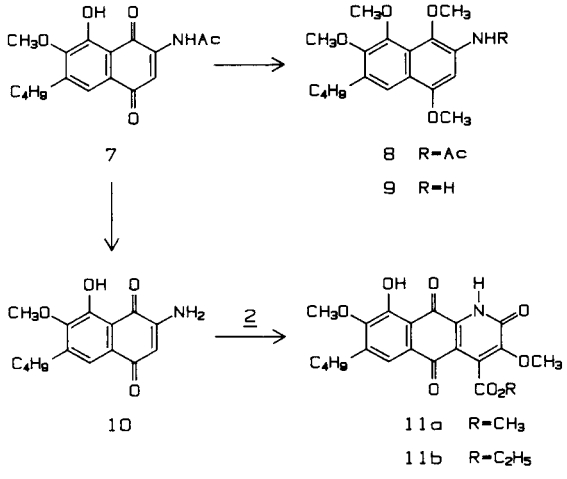


4 2a R=CH3 2b R=C2H5 6

SCHEME I

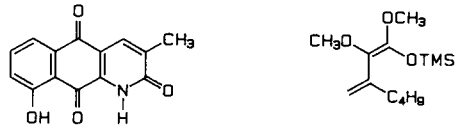
a complex mixture from which the expected product could not be isolated.

On the other hand, there are several claims to the effect that certain aminoquinones [7,8] can be cyclized to the corresponding quinolonequinones. In an experiment conducted with 3-amino-7-butyl-6-methoxyjuglone (**10**) [1] and the usual diester **2a**, a 40% yield was obtained of a red product which quite definitely was not the expected derivative of phomazarin. The nmr spectrum [12] of the latter shows signals at 13.15, 12.85, 4.15, 4.15, 4.08 and 3.98 ppm for two intramolecularly bonded hydroxyls and three methoxyl groups whereas the corresponding chemical shifts for the synthetic material occurred at 11.70, 9.86, 4.19, 4.04 and 4.03 ppm. The infra-red spectra were also very different; the authentic substance revealed bands at 1748 and 1637 cm^{-1} while our compound gave a more complex pattern with absorptions at 3250, 1740, 1685, 1653 and 1635 cm^{-1}. These data suggest a lactam structure for this product and the infra-red spectrum of amide **12** [13] derived from lambertellin provided a close parallel of it with bands at 3270, 1680, 1650 and 1640 cm^{-1}. Confirmation of structure **11a** was sought by carrying out a similar reaction using diester **2b** and the analogous product **11b**, obtained in very low yield, nevertheless established by the presence of two methoxyl and one ethoxyl groups the expected course of the reaction (Scheme II).

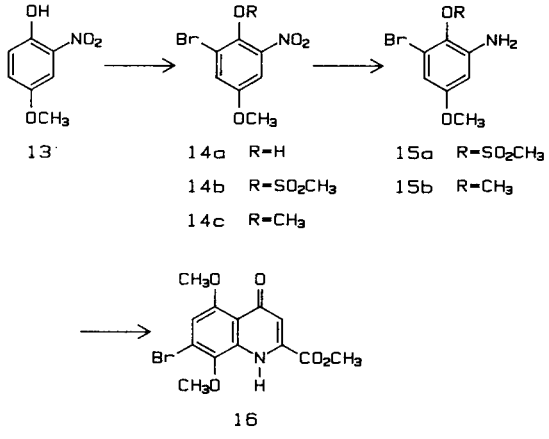


SCHEME II

Since formation of the A ring of phomazarin as a last step in an eventual synthesis seemed to provide little promise, the possibility was also explored of carrying out this step at the outset and completing the process by an annulation involving a previously prepared diene [1]. In a preliminary test, the cycloaddition of diene **19** to Baxter's 6-chloroquinolonequinone **17** [11] followed by aromatization of the adduct proceeded only in low yield (11%) and yielded azaanthraquinone **20** having the "wrong" orientation of the substituents. In order to obtain an appropriate substrate (*i.e.* **18**) 4-methoxy-2-nitrophenol (**13**) [14] was brominated and methylated to give 2-bromo-6-nitrohydroquinone dimethyl ether (**14c**) (a previous preparation [15]

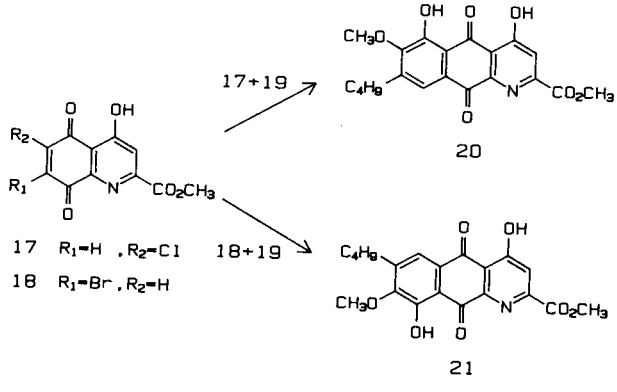


of this compound by bromination of nitrohydroquinone dimethyl ether was found in fact to yield the 2,5-isomer). Reduction of the nitro-compound with iron gave amine **15b** to which was added dimethyl acetylenedicarboxylate. The resultant enaminone could be cyclized in the usual



SCHEME III

way to 7-bromoquinolone **16** (Scheme III). Oxidation of this 5,8-dimethyl ether with ceric ammonium nitrate afforded the highly insoluble quinone **18** in overall very high yield. Finally cycloaddition of diene **19** to this quinone followed by aromatization provided a 3-deoxyphomazarin derivative **21** (Scheme IV). This result in spite of the inefficiency of the last step, illustrates the usefulness of the approach in a eventual synthesis of the natural product.



SCHEME IV

EXPERIMENTAL

All melting points were taken for samples in capillary tubes with a Thomas-Hoover Apparatus and are not corrected. The uv spectra were determined on a Hewlett-Packard 8450A spectrophotometer and the ir spectra on a Beckman Model IR-4520 instrument calibrated with a film of polystyrene. The ^{1}H nmr spectra were recorded with a Varian XL-200 spectrometer using tetramethylsilane as internal standard. Mass spectra were obtained with a Hewlett-Packard 5995A spectrometer. Merck silica gel $60F_{254}$ for dry column chromatography, was used throughout in a product to absorbent ratio of 1:50-100. Elemental anlayses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Exact masses were provided by the Laboratoire de spectrométrie de masse, Université de Sherbrooke, Sherbrooke, Québec.

6,8-Dibromo-2,3-dimethoxycarbonyl-4*H*-1,4-benzoxazine (**4**).

A mixture of 2-amino-4,6-dibromophenol (**3**) (10.1 g, 38 moles) [16], dimethyl 3-methoxy-2-oxo-1,4-butanedioate (**2a**) (7.2 g, 38 mmoles) [10] and *p*-toluenesulfonic acid (100 mg) in benzene (300 ml) was heated to reflux for 24 hours under a Dean-Stark apparatus, then cooled and evaporated. The residue triturated in carbon tetrachloride (50 ml) gave benzoxazine **4** (5.3 g, 34%), mp 206.0-206.5° (chloroform-methanol): ir (potassium bromide): ν max 1780, 1660, 1603, 1595 and 1579 cm^{-1}; uv (methanol): λ max 242 sh (log ϵ 4.06), 302 sh (3.99) and 330 (4.09) nm; ^{1}H nmr (deuteriochloroform): δ 3.74 and 3.90 (2 x 3H, 2s, 2,3-CO_2CH_3), 6.99 (1H, d, J = 1.9 Hz, 5-H), 7.29 (1H, d, J = 1.9 Hz, 7-H) and 10.48 (1H, br s, 4-H); ms: m/z 405/407/409 (M)$^+$.

Anal. Calcd. for $C_{12}H_9Br_2NO_5$: C, 35.41; H, 2.23; Br, 39.26; N, 3.43. Found: C, 35.36; H, 2.29; Br, 39.45; N, 3.28.

2-Ethoxycarbonyl-3,5,8-trimethoxy-4-quinolone (**6**).

A solution of 2,5-dimethoxyaniline (**5**) (1.532 g, 10.00 mmoles) [17] and diethyl 3-methoxy-2-oxo-1,4-butanedioate (**2b**) (2.182 g, 10.00 mmoles) [9] in toluene (60 ml) was heated to reflux (Dean-Stark apparatus) for 40 hours, cooled and evaporated. The residue was added to diphenyl ether (50 ml) at 250°; the mixture was refluxed for 30 minutes then cooled and poured on a column of silica gel (70 g). Elution with benzene and then benzene-acetone (1:1) gave quinolone **6** (710 mg, 23%), mp 119.5-120.0° (benzene-hexane); ir (potassium bromide): ν max 3405, 1695, 1620, 1583 and 1530 cm^{-1}; uv (methanol): λ max 220 (log ϵ 4.23), 238 (4.35), 303 (3.76), 315 (3.81), 325 (3.79) and 362 (3.72) nm; ^{1}H nmr (deuteriochloroform): δ 1.46 (3H, t, J = 7.1 Hz, 2-$CO_2CH_2CH_3$), 3.93, 3.97 and 4.00 (3 x 3H, 3s, 3,5,8-OCH_3), 4.50 (2H, q, J = 7.1 Hz, 2-$CO_2CH_2CH_3$), 6.53 (1H, d, J = 8.8 Hz, 7-H), 6.92 (1H, d, J = 8.8 Hz, 6-H) and 9.08 (1H, br s, 1-H); ms: m/z 307 (M)$^+$.

Anal. Calcd. for $C_{15}H_{17}NO_6$: C, 58.63; H, 5.58; N, 4.56. Found: C, 58.65; H, 5.68; N, 4.50.

3-Acetamido-7-butyl-5,6-dimethoxynaphthoquinone (5-Methyl Ether of **7**).

a) A mixture of acetamidonaphthoquinone **7** (807 mg, 2.54 mmoles) [1], dimethyl sulfate (2.52 g, 20 mmoles), anhydrous potassium carbonate (3.04 g, 22 mmoles) and dry acetone (100 ml) was refluxed for 1.5 hour, cooled, filtered, evaporated, diluted with ethyl acetate (100 ml), washed with water, dried and again evaporated. Purification of the residue by chromatography (benzene-ethyl acetate 5:1) gave the dimethyl ether (491 mg, 58%), mp 126.5-127.0° (ethanol); ir (potassium bromide): ν max 3266, 1690, 1666, 1645, 1620, 1584 and 1500 cm^{-1}; uv (methanol): λ max 225 sh (log ϵ 4.30), 263 (4.46), 302 (4.18) and 368 (3.63) nm; ^{1}H nmr (deuteriochloroform): δ 0.95 (3H, br t, J = 7.1 Hz, 4'-H), 1.40 (2H, m, 3'-H), 1.61 (2H, m, 2'-H), 2.27 (3H, s, 3-NHCOCH_3), 2.71 (2H, br t, J = 7.6 Hz, 1'-H), 3.92 and 3.95 (2 x 3H, 2s, 5,6-OCH_3), 7.74 and 7.77 (2 x 1H, 2s, 2,8-H) and 8.44 (1H, br s, 3-N*H*$COCH_3$); ms: m/z 331 (M)$^+$.

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.53; H, 6.44; N, 4.06.

A second zone afforded a small amount (~6%) of a by-product which is probably the corresponding *N*-methylacetamide.

b) A mixture of quinone **7** (1.740 g, 5.49 mmoles), methyl iodide (10 ml) silver (I) oxide (10 g) and dry chloroform (150 ml) was stirred at 25° for 24 hours, filtered and evaporated. Chromatography (hexane-ethyl acetate 2:1) of the residue gave the 5-methyl ether of **7** (1.020 g, 56%). A by-product (~7%) thought to be 6-butyl-4,7,8-trimethoxy-1,2-naphthoquinone monoacetimide was also isolated.

3-Acetamido-7-butyl-1,4,5,6-tetramethoxynaphtalene (**8**).

A mixture of acetamidonaphthoquinone **7** (635 mg, 2.00 mmoles) in methylene chloride (30 ml), sodium hydrosulfite (4.40 g, 25.0 mmoles) in water (30 ml) and cetyltrimethylammonium bromide (10 mg) was shaken vigorously for 5 minutes. The phases were separated and the aqueous solution extracted with methylene chloride (2 x 25 ml). To the organic extracts were added cetyltrimethylammonium bromide (72 mg, 0.20 mmole) and , under nitrogen, dimethyl sulfate (6 ml) then sodium hydroxide (6.0 g) in water (30 ml). After shaking vigorously for 9 hours, the phases were separated, the aqueous solution extracted with methylene chloride (2 x 100 ml) and the combined organic phases washed with water (3 x 200 ml). Purification of the crude product by chromatography (methylene chloride-ethyl acetate 5:1) gave tetramethyl ether **8** (647 mg, 90%), mp 149.5-150.0° (hexane); ir (potassium bromide): ν max 3300, 1660, 1622, 1607 and 1510 cm^{-1}; uv (methanol): λ max 236 (log ϵ 4.53), 254 (4.65) and 313 (3.95) nm; ^{1}H nmr (deuteriochloroform): δ 0.96 (3H, br t, J = 7.0 Hz, 4'-H), 1.43 (2H, m, 3'-H), 1.65 (2H, m, 2'-H), 2.26 (3H, s, 3-NHCOCH_3), 2.74 (2H, br t, J = 7.6 Hz, 1'-H), 3.83, 3.86 and 3.99 (3H, 3H, 6H, 3s, 1,4,5,6-OCH_3), 7.79 (1H, s, 8-H), 7.98 (1H, s, 2-H) and 8.06 (1H, br s, 3-N*H*$COCH_3$); ms: m/z 361 (M)$^+$.

Anal. Calcd. for $C_{20}H_{27}NO_5$: C, 66.46; H, 7.53; N, 3.88. Found: C, 66.70; H, 7.53; N, 3.81.

7-Butyl-9-hydroxy-3,8-dimethoxy-4-methoxycarbonyl-1*H*-benzo[*g*]quinoline-2,5,10-trione (**11a**).

A solution of 3-amino-7-butyl-5-hydroxy-6-methoxynaphthoquinone (**10**) (207 mg, 0.75 mmole) [1] and diester **2a** (150 mg, 0.80 mmole) in dry toluene (12 ml) was heated to reflux for 24 hours in a flask fitted with a receiver "for heavy entrainers" containing 3Å molecular sieves (10 g). The solvent was replaced by diphenyl ether (5 ml), the mixture was refluxed for 30 minutes and separated by chromatography (hexane then methylene chloride-ethyl acetate 3:1) to give quinolinetrione **11a** (125 mg, 40%), mp 206.0-206.5° (methanol); ir (potassium bromide): ν max 3250, 1740, 1685, 1653, 1635 and 1595 cm^{-1}; uv (methanol): λ max 222 (log ϵ 4.26), 274 (4.32), 312 (4.20), 320 sh (4.19) and 432 (3.79) nm; ^{1}H nmr (deuteriochloroform): δ 0.94 (3H, br t, J = 7.1 Hz, 4'-H), 1.37 (2H, m, 3'-H), 1.58 (2H, m, 2'-H), 2.70 (2H, br t, J = 7.8 Hz, 1'-H), 4.03 and 4.04 (2 x 3H, 2s, 4-CO_2CH_3 and 8-OCH_3), 4.19 (3H, s, 3-OCH_3), 7.58 (1H, s, 6-H), 9.86 (1H, br s, 1-H) and 11.70 (1H, s, 9-OH); ms: m/z 415 (M)$^+$.

Anal. Calcd. for $C_{21}H_{21}NO_8$: C, 60.72; H, 5.10; N, 3.37. Found: C, 60.79; H, 4.92; N, 3.50.

7-Butyl-4-ethoxycarbonyl-9-hydroxy-3,8-dimethoxy-1*H*-benzo[*g*]quinoline-2,5,10-trione (**11b**).

A reaction similar to the foregoing with naphthoquinone **10** and diester **2b** (175 mg, 0.80 mmole) gave quinolinetrione **11b** (25 mg, 8%), mp 198.0-198.5° (ethanol); ir (potassium bromide): ν max 3255, 1740, 1690, 1656, 1638 and 1595 cm^{-1}; uv (methanol): λ max 223 (log ϵ 4.29), 273 (4.33), 311 (4.23), 320 sh (4.20) and 432 (3.82) nm; ^{1}H nmr (deuteriochloroform): δ 0.94 (3H, br t, J = 7.1 Hz, 4'-H), 1.37 (2H, m, 3'-H), 1.44 (3H, t, J = 7.1 Hz, 4-$CO_2CH_2CH_3$), 1.59 (2H, m, 2'-H), 2.70 (2H, br t, J = 7.7 Hz, 1'-H), 4.03 (3H, s, 8-OCH_3), 4.20 (3H, s, 3-OCH_3), 4.53 (2H, q, J = 7.1 Hz, 4-$CO_2CH_2CH_3$), 7.58 (1H, s, 6-H), 10.30 (1H, br s, 1-H) and 11.72 (1H, s, 9-OH); ms: m/z 429 (M)$^+$.

Anal. Calcd. for $C_{22}H_{23}NO_8$: C, 61.53; H, 5.40; N, 3.26. Found: C, 62.02; H, 5.53; N, 3.21.

6-Bromo-4-methoxy-2-nitrophenol (**14a**).

Bromine (16.0 g, 0.10 mole) in acetic acid (20 ml) was added (45 minutes) at 25° to 4-methoxy-2-nitrophenol (**13**) (16.9 g, 0.10 mole) [14] and sodium acetate (16.4 g, 0.20 mole) in the same solvent (100 ml). The mixture was stirred at this temperature for 30 minutes and at 70° for 2

hours, then poured into water (1.5 l) containing concentrated hydrochloric acid (10 ml) to give bromonitrophenol **14a** (18.7 g, 75%), mp 117.2-117.7° (chloroform-hexane); ir (potassium bromide): ν max 3240 and 1523 cm^{-1}; uv (methanol): λ max 286 (log ϵ 3.65) and 394 (3.50) nm; ^1H nmr (deuteriochloroform): δ 3.83 (3H, s, 4-OCH_3), 7.53 (1H, d, J = 3.1 Hz, 5-H), 7.54 (1H, d, J = 3.1 Hz, 3-H) and 10.80 (1H, s, 1-OH).

Anal. Calcd. for $C_7H_6BrNO_4$: C, 33.90; H, 2.44; N, 5.65; Br, 32.22. Found: C, 33.96; H, 2.51; N, 5.40; Br, 32.22.

The mesylate **14b** (7.4 g, 76%) was obtained from phenol **14a** (7.44 g, 30.0 mmoles) and methanesulfonyl chloride (3.78 g, 33.0 mmoles) in pyridine (30 ml) at 25° (24 hours), mp 130.5-131.0° (chloroform-methanol); ir (potassium bromide): ν max 1607 and 1532 cm^{-1}; uv (methanol): λ max 240 sh (log ϵ 3.98) and 322 (3.37) nm; ^1H nmr (deuteriochloroform): δ 3.37 (3H, s, 1-OSO_2CH_3), 3.88 (3H, s, 4-OCH_3), 7.41 (1H, d, J = 3.3 Hz, 5-H) and 7.45 (1H, d, J = 3.3 Hz, 3-H); ms: m/z 325/327 $(M)^+$.

Anal. Calcd. for $C_8H_8BrNO_6S$: C, 29.46; H, 2.47; N, 4.29. Found: C, 29.47; H, 2.51; N, 4.18.

6-Bromo-1,4-dimethoxy-2-nitrobenzene (**14c**).

Methylation of phenol **14a** (2.480 g, 10.00 mmoles) with dimethyl sulfate (5.05 g, 40.0 mmoles) and potassium carbonate (6.91 g, 50.0 mmoles) in dry acetone (100 ml) at reflux (1.5 hour) gave the dimethyl ether **14c**, after chromatography (benzene) (2.529 g, 97%), mp 98.0-98.5° (benzene-hexane); ^1H nmr (deuteriochloroform): δ 3.83 (3H, s, 4-OCH_3), 3.96 (3H, s, 1-OCH_3), 7.27 (1H, d, J = 3.2 Hz, 5-H) and 7.35 (1H, d, J = 3.2 Hz, 3-H); ms: m/z 261/263 $(M)^+$.

Anal. Calcd. for $C_9H_8BrNO_4$: C, 36.67; H, 3.08; N, 5.34. Found: C, 36.55; H, 3.03; N, 5.28.

3-Bromo-2-mesyloxy-5-methoxyaniline (**15a**).

A mixture of mesylate **14b** (1.631 g, 5.00 mmoles), iron powder (100 mesh) (2.1 g, 37.6 mmoles) and concentrated hydrochloric acid (0.05 ml) in a mixture of ethanol, acetic acid and water (2:2:1) (50 ml) was refluxed for 2.5 hours, filtered, diluted with water (300 ml) and extracted with ethyl acetate (3 x 200 ml). The organic layer was washed with saturated aqueous sodium bicarbonate (250 ml) and water (2 x 200 ml). Evaporation of the dried solution gave amine **15a** (1.472 g; 99%), mp 144.5-145.0° (chloroform-methanol); ^1H nmr (deuteriochloroform): δ 3.43 (3H, s, 2-OSO_2CH_3), 3.73 (3H, s, 5-OCH_3), 4.26 (2H, br s, 1-NH_2), 6.26 (1H, d, J = 2.8 Hz, 6-H) and 6.52 (1H, d, J = 2.8 Hz, 4-H); ms: m/z 295/297 $(M)^+$, 216/218 $(M\text{-}SO_2CH_3)^+$.

Anal. Calcd. for $C_8H_{10}BrNO_4S$: C, 32.45; H, 3.40; N, 4.73. Found: C, 32.35; H, 3.43; N, 4.65.

3-Bromo-2,5-dimethoxyaniline (**15b**).

A mixture of nitro-compound **14b** (2.621 g, 10.00 mmoles), iron powder (100 mesh) (3.66 g), acetic acid (0.2 ml) and water (7.5 ml) was warmed at 90-100° for 1 hour. Aniline **15b**, an oil (2.233 g, 96%), was isolated as in the preceding paragraph and used without purification.

7-Bromo-5,8-dimethoxy-2-methoxycarbonyl-4-quinolone (**16**).

The foregoing amine **15b** (2.233 g, 9.62 mmoles) dimethyl acetylenedicarboxylate (1.387 g, 9.76 mmoles) and absolute methanol (25 ml) were refluxed for 19 hours. After evaporation of the solvent, the residue and diphenyl ether (10 ml) were refluxed for 20 minutes, cooled, diluted with hexane (50 ml) and filtered to give quinolone **16** (3.108 g, 91%), mp 166.0-166.5° (methanol); ir (potassium bromide): ν max 3400, 1725, 1631, 1594 and 1525 cm^{-1}; uv (methanol): λ max 226 (log ϵ 4.40), 244 (4.36), 281 (3.93), 290 (3.95) and 347 (3.83) nm; ^1H nmr (deuteriochloroform): δ 3.95, 3.98 and 4.03 (3 x 3H, 3s, 2-CO_2CH_3 and 5,8-OCH_3), 6.80 and 6.88 (2 x 1H, 2s, 3,6-H) and 9.09 (1H, br s, 1-H); ms: m/z 341/343 $(M)^+$.

Anal. Calcd. for $C_{13}H_{12}BrNO_5$: C, 45.64; H, 3.54; N, 4.09; Br, 23.38. Found: C, 45.80; H, 3.59; N, 4.08; Br, 23.20.

6-Butyl-4,8-dihydroxy-7-methoxy-2-methoxycarbonyl-1-azaanthraquinone (**21**).

To quinolone **16** (3.080 g, 9.00 mmoles) in acetonitrile (90 ml) at 0° was added ceric ammonium nitrate (14.80 g, 27.0 mmoles) in water (36 ml) over 3 minutes. The mixture was stirred at 0° for 10 minutes and diluted with water (550 ml) to give the insoluble quinolonequinone **18** (2.725 g, 97%). To this crude quinone (312 mg, 1.00 mole) in dichloromethane (2 ml) was added 3-butyl-1,2-dimethoxy-1-trimethylsiloxybutadiene (**19**) (388 mg, 1.50 mmoles) [1] and triethylamine (0.5 ml) in the same solvent (3 ml). The mixture was stirred for 5 days at 25° and after adding acetic acid (1 ml) was poured into water (50 ml) and extracted with dichloromethane (3 x 50 ml). The crude product was purified by chromatography on silica gel deactivated with 2% oxalic acid (benzene-ethyl acetate 10:1) to give the azaanthraquinone **21** (75 mg, 19%), mp 171.0-171.5° (methanol); ir (potassium bromide): ν max 1729, 1639, 1606, 1578 and 1562 cm^{-1}; uv (methanol): λ max 255 (log ϵ 4.42), 268 sh (4.40) and 424 (3.76) nm; ^1H nmr (deuteriochloroform): δ 0.97 (3H, br t, J = 7.3 Hz, 4'-H), 1.41 (2H, m, 3'-H), 1.63 (2H, m, 2'-H), 2.76 (2H, br t, J = 7.6 Hz, 1'-H), 4.06 (3H, s, 7-OCH_3), 4.11 (3H, s, 2-CO_2CH_3), 7.74 (1H, s, 5-H), 7.95 (1H, s, 2-H) and 12.82 and 12.94 (2H, 2s, 4,8-OH); ms: m/z 385.1152 (M^+, Calcd. 385.1161).

Anal. Calcd. for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63. Found: C, 62.37; H, 5.01; N, 3.68.

Acknowledgements.

We gratefully acknowledge financial support and bursaries (to VG) from the Natural Sciences and Engineering Research Council of Canada and the Fonds F.C.A.C. (Gouvernement du Québec).

REFERENCES AND NOTES

[1] V. Guay and P. Brassard, *Synthesis*, 294 (1987).

[2] G. Jones, "Quinolines" in "The Chemistry of Heterocyclic Compounds", G. Jones ed, Vol **32**, Tome I, John Wiley and Sons, New York, 1977, p 143.

[3] G. L. Anderson, J. L. Shim and A. D. Broom, *J. Org. Chem.*, **41**, 1095 (1976).

[4] G. L. Anderson, *J. Heterocyclic Chem.*, **22**, 1469 (1985).

[5] S. Wawzonek, *J. Org. Chem.*, **41**, 3149 (1976).

[6] J. Reisch, *Angew. Chem., Int. Ed. Engl.*, **2**, 741 (1963).

[7] K. H. Dudley and R. L. McKee, *J. Org. Chem.*, **32**, 3210 (1967).

[8] A. V. Pinto, V. F. Ferreira, M. C. F. R. Pinto and L. U. Meyer, *Synth. Commun.*, **15**, 1181 (1985).

[9] D. S. Breslow, M. S. Bloom, J. C. Shivers, J. T. Adams, M. J. Weiss, R. S. Yost and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1232 (1946).

[10] J. Pryde and R. T. Williams, *J. Chem. Soc.*, 1627 (1933).

[11] I. Baxter and W. R. Phillips, *J. Chem. Soc., Perkin Trans. I*, 2374 (1973).

[12] A. J. Birch, D. N. Butler, R. Effenberger, R. W. Rickards and T. J. Simpson, *J. Chem. Soc., Perkin Trans. I*, 807 (1979).

[13] T. B. Tjio, T. Sproston and H. Tomlinson, *Lloydia*, **28**, 359 (1965).

[14] R. Robinson and J. C. Smith, *J. Chem. Soc.*, 392 (1926).

[15] H. E. Ungnade and K. T. Zilch, *J. Org. Chem.*, **16**, 64 (1951).

[16] T. R. Kelly, A. Echavarren and M. Behforouz, *J. Org. Chem.*, **48**, 3849 (1983).

[17] J. M. Guillard, M. Robinson, J. Scott and S. Thornley, *J. Chem. Soc.*, 2924 (1929).