

spectrum was taken 30 min after addition of the Hex₃B; in no case was there a signal corresponding to a vinylborane or a vinylborate complex. To effect protonolysis, the flask was warmed to 0 °C after 30 min or kept at 0 °C for 30 min, and 1 equiv of HOAc was added. The contents were analyzed by GC, and no 2-methyl-2-nonene was detected.

Competitive Reaction. *cis*-1-Chloro-1-butene and 1-pentyne (10.0 mmol each) were added via syringe to a round-bottom flask containing *n*-nonane (4 mmol) and THF (10 mL) and equipped with a magnetic stirring bar. The flask was then cooled to -110 °C, and *sec*-BuLi (10.0 mmol) was slowly added via syringe. After 30 min of stirring at low temperature, the reaction mixture at -110 °C was quenched with MeI. The contents of the flask were then warmed to room temperature and analyzed by GC for residual reactants. The relative reactivities were calculated by using the Ingold-Shaw equation.¹⁵

Instrumentation. All products were identified by GC coinjection with an authentic sample using a variety of columns and by GC/MS. GC data was obtained by using a Varian 1200 instrument equipped with a 1/8 in. column. Columns used were as follows: 6 ft 10% SP2100 on 100/120 Supelcoport, 18 ft 30% adiponitrile on 60/80 mesh Firebrick, 6 ft 0.15% picric acid on 80/100 Carboxpack in series with 9 ft 30% adiponitrile on 60/80 mesh Firebrick. Mass spectra data were obtained with a Finnigan 4000 GC/MS equipped with a 6 ft × 1/4 in. 3% OV-1 on 80/100 mesh Chromosorb W or an 18 ft × 1/8 in. 30% adiponitrile column. ¹¹B NMR spectra were obtained with a Varian FT80A.

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Registry No. 1, 513-37-1; 2a, 16136-85-9; 2b, 7611-87-2; 3a, 16136-84-8; 3b, 7611-86-1; *n*-BuLi, 109-72-8; *sec*-BuLi, 598-30-1; 2-methyl-2-heptene, 627-97-4; 2-butyne, 503-17-3; 2-pentyne, 627-21-4.

(15) Ingold, C. K.; Shaw, F. R. *J. Chem. Soc.* 1927, 2918.

Preparation of Oxygenated Phenylacetic Acids

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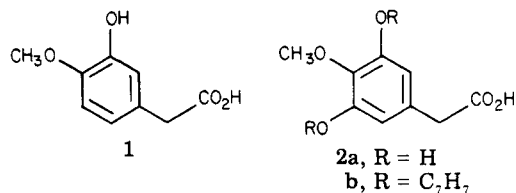
Oxygen-substituted phenylacetic acids have been employed in the synthesis of a wide variety of natural products, embracing such diverse species as flavonoids and alkaloids.^{1,2} One especially important area is their use in the synthesis of the opiate alkaloids.^{3,4} Rice has employed (3-hydroxy-4-methoxyphenyl)acetic acid (1, homoisovanillic acid) in a concise synthesis of the opiate precursor dihydrothebaine.^{3a,d} In a related approach to the synthesis of the opiate skeleton, Beyerman employed [3,5-bis(benzyloxy)-4-methoxyphenyl]acetic acid (2b).^{4a-c}

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(2) For an example of the use of (3-hydroxy-4-methoxyphenyl)acetic acid (1) in simple alkaloid synthesis, see: Kametani, T.; Takemura, M.; Ogasawara, K.; Fukumoto, K. *J. Heterocycl. Chem.* 1974, 11, 179.

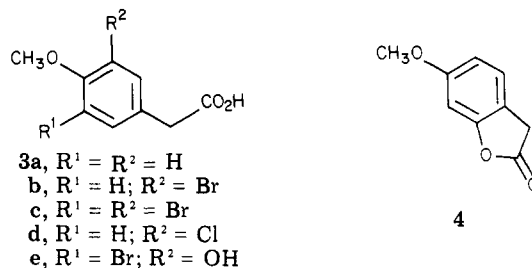
(3) (a) Rice, K. C. *J. Org. Chem.* 1980, 45, 3135. (b) Grewe, R.; Friedrichsen, W. *Chem. Ber.* 1967, 100, 1550. (c) Morrison, G. C.; Waite, R. R.; Shavel, J., Jr. *Tetrahedron Lett.* 1967, 4055. (d) Rice, K. C.; Brossi, A. *J. Org. Chem.* 1980, 45, 592.

(4) (a) Beyerman, H. C.; Lie, T. S.; Maat, L.; Bosman, H. H.; Buurman, E.; Bijsterveld, E. J. M.; Sinnige, H. J. M. *Recl. Trav. Chim. Pays-Bas.* 1976, 95, 24. (b) Beyerman, H. C.; van Berkel, J.; Kie, T. S.; Maat, L.; Wessels, J. C. M.; Bosman, H. H.; Buurman, E.; Bijsterveld, E. J. M.; Sinnige, H. J. M. *Ibid.* 1978, 97, 127. (c) Lie, T. S.; Maat, L.; Beyerman, H. C. *Ibid.* 1979, 98, 419.



Finally, Schwartz demonstrated the utility of 2b for the synthesis of thebaine using the phenolic oxidative coupling approach.⁵ Due to the importance of 1 and 2a as codeine precursors, much attention has been given to their preparation.⁶ In general, the synthesis of these compounds involves the one-carbon homologation of a benzyl derivative and then manipulation of the aromatic functionality. The most convenient preparations of 1 use isovanillin as the starting material. This strategy was demonstrated by Grewe and Fischer^{6f} wherein isovanillin was converted to the cyanohydrin, which was then successively hydrolyzed and reductively dehydroxylated to give 1 in greater than 80% yield. This preparation of 1, while affording a good yield of material, suffers in that it is experimentally tedious and involves procedures during which hydrogen cyanide is evolved. To date, only one synthesis of an analogue of 2a has been reported.⁷ Gallic acid was esterified and then selectively methylated in poor yield at the 4-hydroxyl group. Benzoylation of the remaining free phenols and homologation by the Arndt-Eistert procedure⁸ gave 2b.

The disadvantages noted above prompted us to devise a general method of preparation of 1 and 2a from a common starting material. An excellent candidate for the initiation of this strategy is the relatively inexpensive and readily available (4-methoxyphenyl)acetic acid 3.⁹ Our proposed synthesis of 1 and 2a required bromination of 3a to 3b and 3c followed by displacement of the halides by hydroxide in a copper-catalyzed reaction. A previous attempt to employ this general strategy for the synthesis of 1 was performed by Hrothama.¹⁰ In that report, the necessary ipso substitution of the halogen atom in 3d was not observed. This compound was found to be relatively unreactive to reagents such as aqueous barium hydroxide at 170 °C and reacted via aryne mechanisms (3d → 4) at higher temperatures. However the recent report of the facile substitution of 4-bromoanisole by methoxide using cuprous oxide catalysis¹¹ and our own success in the synthesis of catechols from *o*-bromophenols prompted us to explore the applicability of 3b and 3c.¹²



(5) Schwartz, M. A.; Zoda, M. F. *J. Org. Chem.* 1981, 46, 4623.

(6) (a) Spath, E.; Lang, N. *Monatsh. Chem.* 1921, 42, 273. (b) Hahn, G.; Schulz, H. *J. Chem. Ber.* 1939, 72, 1302. (c) Bersch, H. W. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* 1939, 277, 271. (d) Kindler, K.; Metzendorf, W.; Dschi-yin-kwok *Chem. Ber.* 1943, 76, 308. (e) Fischer, H. E.; Hibbert, H. *J. Am. Chem. Soc.* 1947, 69, 1208. (f) Grewe, R.; Fischer, H. *Chem. Ber.* 1963, 96, 1520.

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(8) Bachmann, W. E.; Struve, W. S. *Org. React. (N.Y.)* 1942, 1, 38.

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(10) Hrothama, O. *Chem. Ber.* 1942, 75, 123.

(11) (a) Bacon, R. G. R.; Rennison, S. C. *J. Chem. Soc. C* 1969, 312.

(b) Bacon, R. G. R.; Stewart, O. J. *Ibid.* 1969, 301.

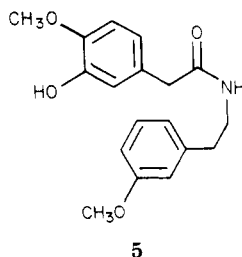
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Table I. Dehalohydroxylation of 3c

| run | scale (%) ^a | temp, °C | time, days | % yield | product, % 1/ % 2a ^b |
|-----|------------------------|----------|------------|---------|------------------------------------|
| 1 | 1.47 (1) | 150 | 2.5 | 80 | 10/90 |
| 2 | 3.0 (3) | 160 | 2 | 81 | 10/80 |
| 3 | 5.0 (5) | 160 | 2 | 100 | 38/62 |
| 4 | 3.0 (4) | 110 | 7 | 86.5 | 25/75 |
| 5 | 2.6 (4) | 110 | 5 | 78 | 15/85 |
| 6 | 20.0 (5) | 110 | 9 | 90 | 35/65 |

^aScale is in grams. Concentration (g/100 mL of H₂O) is given in parentheses. ^bDetermined by ¹H NMR.

The preparation of 3b was easily accomplished in greater than 95% yield by monobromination of 3a with bromine in either chloroform or glacial acetic acid.¹³ Dibromination of 3a in chloroform or 1,2-dichloroethane to give 3c required a large excess of bromine and the presence of ferric bromide catalyst. While in the former reaction there was no trace of dibrominated products even when a large excess of bromine was used, the latter preparation required careful monitoring to insure that no trace of monohalogenated product remained. The dehalohydroxylation reactions were performed in a stainless steel Parr reaction vessel. Before each run the bomb was cleaned by filling the vessel with 6 M nitric acid, rinsing, and then filling again with concentrated ammonia. Without this cleansing, the reaction results were extremely variable, especially for the reaction of 3c. The reactions were performed at 1–5% concentrations of the halide in deaerated 10% aqueous sodium hydroxide containing a catalytic amount of cupric sulfate. Heating 3b for 36 h at 150 °C gave excellent yields of 1. Small-scale reactions (5 g) usually provided material having a narrow melting point range. A large-scale reaction of 3b (25 g) afforded a 97% yield of 1 but with a slightly lower purity. The reaction product showed essentially one spot that moved by silica gel TLC, with the presence of some very polar material that remained at the origin. In contrast, Rice reported that the homoisovanillic acid prepared via the cyanohydrin contained several impurities that were removed with difficulty.^{3d} In order to determine the viability of using 1 directly without further purification, the crude product was reacted with *m*-methoxyphenethylamine to afford amide 5.^{3a} The yield of 5 was comparable to that obtained by Rice using rigorously purified 1.¹⁴



Dehalohydroxylation of the dibromo compound 3c gave variable results (Table I). The desired product 2a was the major component of the reaction mixture, but an additional component (10–40%) was also found. After esterification of the crude reaction product,¹⁵ the minor

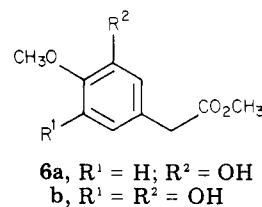
(13) Coutts, I. G. C.; Durbin, A. K.; Schofield, K. *Aust. J. Chem.* **1970**, *23*, 791.

(14) Rice obtained the purified free acid 1 in 67% yield from isovanillin and converted this into amide 5 in 95% yield^{3a} (64% overall). Our yield for 5 from 1 is 81% (80% overall from 3a).

(15) Durham, L. J.; McLeod, D. J.; Cason, J. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 635.

component was identified as the methyl ester of 1,^{6f} which resulted from a reductive removal of bromine. In order to determine at what step the reduction had occurred, a dehalohydroxylation reaction was interrupted prior to completion. ¹H NMR analysis showed the presence of 3c, 1, and 2a in minor amounts and an additional component which was identified as (3-bromo-5-hydroxy-4-methoxyphenyl)acetic acid (3e). No monobromo derivative 3b was detected. When 3e was resubjected to the reaction conditions for the conversion of 3c to 2a, similar product compositions were obtained as from the complete reaction of 3c.¹⁶

Several attempts at modification of reaction conditions to limit the amount of reduction failed to afford any results consistently superior to our initial conditions (Table I). All attempts to fractionally recrystallize 2a failed, as did trituration to remove 1. Due to their carboxyl moieties, 1 and 2a exhibited poor chromatographic behavior. The combined extracts from the hydroxylation reaction (run 6) were esterified,¹⁵ and chromatography of the mixture on silica gel afforded 6a in 18% and 6b in 40% yields.



Saponification of 6b gave the free acid 2a. After two recrystallizations from chloroform, 2a possessed a melting point of 181–182 °C. The reported value for the melting point of (3,5-dihydroxy-4-methoxyphenyl)acetic acid, however, was 130 °C.^{17b} The ¹H NMR and ¹³C NMR spectra of our 2a were found to be consistent for the symmetrical structure. The cause of this discrepancy is unknown.

In conclusion, the preparation of 1 from 3a using a bromination, dehalohydroxylation sequence, is rapid, gives a product of high purity, and is amenable to large-scale preparations. While less attractive for the preparation of 2a, this method does rival the known method in yield and is a much shorter procedure.

Experimental Section¹⁸

(3-Bromo-4-methoxyphenyl)acetic Acid (3b). This was prepared by direct bromination of 3a in ethanol-free chloroform or acetic acid as per the literature.¹³ The crude product (98% yield) was used directly. The recrystallized material had mp

(16) The presence of a meta or para hydroxy substituent in the aryl bromide has been previously noted to lower the yields of substitution of products.^{11a} The mechanism of reduction as proposed by Bacon^{11b} involves hydrogen atom donation from a phenol to an aryl radical (formed from the halide and the copper catalyst). Bacon, while stating that phenols were generally converted into resins (as in our case), isolated several oxidatively coupled phenolic products to support his claim.^{11b} Additionally the direct conversion of 3c into 2b fails due to the facile reduction of aryl halides by benzylic alkoxide under the conditions required for substitution.^{11a}

(17) (a) Karnal, A.; Qureshi, A. A.; Richards, R. W. *Tetrahedron* **1965**, *21*, 1411 and references contained therein. (b) Recrystallization from ether^{17a} also gave mp 181–182 °C.

(18) Low-resolution mass spectrometry was performed on a Varian MAT CH-7 or a Finnigan 3500 instrument. Infrared Spectra were recorded on Perkin-Elmer spectrophotometers, Models 727B and 137. Melting points were determined on a Büchi capillary melting point apparatus and are uncorrected. ¹H NMR analyses were performed on Varian spectrometers, Model FT-80 or Model EM-360. Chemical shifts (δ) are reported as parts per million downfield from tetramethylsilane as internal standard. High-resolution mass spectra were obtained on a CEC-1038 mass spectrometer by Richard Wielesek at the University of Oregon Micro-Analytical Lab. Combustion analyses were performed by MicAnal, Tucson, AZ.

113–115 °C (lit.¹³ mp 112–115 °C).

(3-Hydroxy-4-methoxyphenyl)acetic Acid (1). Into a stainless steel bomb was placed 5.05 g (20.6 mmol) of **3b**. A degassed¹⁹ solution of 45 g (1.1 mol) of NaOH in 450 mL of H₂O containing a catalytic amount of CuSO₄ (1 g) was then added. The bomb was sealed, heated to 150 °C for 1.5 days, and cooled. The solution was acidified and extracted manually with ether and then continuously extracted overnight with ether.²⁰ The combined ethereal solutions were evaporated to dryness to afford 3.72 g (99%) of **1**, mp 127–129 °C (lit.^{3d} mp 128.5–130.5 °C). Further purification was effected by recrystallization of the crude product with 20% 2-propanol/CHCl₃; mp 128–130 °C; ¹H NMR (CDCl₃) δ 6.87 (2 H, br s), 6.79 (1 H, br s), 3.87 (3 H, s), 3.55 (2 H, s).

N-[2-(3-Methoxyphenyl)ethyl](3-hydroxy-4-methoxyphenyl)acetamide (5). Bromide **3b** (25 g, 102 mmol) was converted into crude **1** (16.42 g, 97%) by the method above. The melting point of the crude acid was 123–127 °C. A round-bottom flask containing 0.394 g (2.16 mmol) of this acid was reacted with *m*-methoxyphenethylamine by thoroughly mixing the components at 80 °C and then heating at 200 °C for 2 h. The resultant glass was dissolved in benzene and precipitated with hexane, and the crude product was recrystallized from toluene, mp 100–101 °C (lit.^{8b} mp 101 °C). The yield of **5** was 0.576 g (84%).

(3,5-Dibromo-4-methoxyphenyl)acetic Acid (3c). To a solution of 20.09 g (120 mmol) of **3a** in 220 mL of anhydrous CHCl₃ (P₂O₅) was added 4.28 g (14.4 mmol) of FeBr₂. A solution of 18.5 mL (360 mmol) of Br₂ in 30 mL of CHCl₃ was added dropwise to the reaction vessel. After the mixture was stirred for 42 h at room temperature, an additional 10 mL of Br₂ (190 mmol) and 1.04 g (4.8 mmol) of FeBr₂ were added. The solution was stirred for 18 h, then poured carefully into an excess of 5% aqueous NaHSO₃, and extracted with ether. The combined ethereal extracts were washed with H₂O and brine and then dried (Na₂SO₄). Removal of the solvent afforded 37.76 g (96%) of dibromo **3c**, in greater than 98% purity, as determined by ¹H NMR. The crude solid was routinely used directly. Recrystallization from toluene/hexane gave **3c** with the following: mp 132–134 °C; MS, *m/z* (relative intensity) 322 (M⁺, 48), 324 (91), 326 (44), 281, 279 (100), 277; IR (KBr) 3200–2600, 1710 cm⁻¹; ¹H NMR (acetone-*d*₆) δ 8.85 (COOH, br s), 7.47 (2 H, s), 3.77 (3 H, s), 3.58 (2 H, s); ¹³C NMR (acetone-*d*₆) δ 171, 152, 133, 116, 59, 38.

Anal. Calcd for C₉H₈Br₂O₃: C, 33.37; H, 2.49. Found: C, 33.24; H, 2.47.

(3,5-Dihydroxy-4-methoxyphenyl)acetic Acid (2a). Into a stainless steel bomb was placed 20.00 g (61.6 mmol) of **3c**. A degassed¹⁹ solution of 47.0 g (1.18 mol) of NaOH in 470 mL of H₂O containing a catalytic amount of CuSO₄ (1.0 g) was added to the bomb. The bomb was sealed, heated to 110 °C for 9 days, cooled, and then worked up as for **1** to give 9.55 g (78%, based on conversion of **3c** to **2a**) of a 1.7/1 mixture of **2a** and **1**. The continuous extraction afforded 1.50 g (12%) of a 3/1 mixture of **2a** and **1**. Following the method of Cason,¹⁵ the mixture of **1** and **2a** from the dehalohydroxylation reaction (10.89 g) was esterified with methanol and sulfuric acid to give 9.31 g of a 1.6/1 mixture of **6b** and **6a**. A portion of this product (1.58 g) was column chromatographed on silica gel, eluting with 20% acetone in CHCl₃. This returned 0.39 g (18.7% from **3c**) of **6a** as an oil^{6f} and 0.90 g (40.0% from **3c**) of **6b** as a solid. Recrystallization from toluene gave **6b**, mp 116–117 °C. An analytical sample of **6b** was prepared by sublimation (0.1 torr, 100 °C): MS, *m/z* (relative intensity) 212 (M⁺), 153 (100); IR (KBr) 3300, 1720, 1200, 1160, 1040 cm⁻¹; ¹H NMR (CDCl₃) δ 7.45 (2 H, s), 6.32 (2 H, s), 3.84 (3 H, s), 3.56 (3 H, s), 3.40 (2 H, s).

Anal. Calcd for C₁₀H₁₂O₅: C, 56.60; H, 5.70. Found: C, 56.61; H, 5.66.

To 0.106 g (0.50 mmol) of the methyl ester **6b** was added 1.1 mL of 10% aqueous NaOH. The solution was stirred for 30 min at room temperature and then acidified with 4 N HCl. The resulting aqueous solution was extracted with EtOAc. The

(19) Degassing was performed by stirring the aqueous solution under aspirator vacuum for 2 h.

(20) Four hand extractions with ether, in the preparation of **1**, generally recovered greater than 90% of the hydroxylated product. In the case of **2a**, these were much less efficient. In the latter case, ethyl acetate is a much superior extraction solvent.

combined organic extracts were washed with brine and then dried over Na₂SO₄. Evaporation afforded 0.10 g (100%) of **2a** as a solid, which was recrystallized from CHCl₃; mp 181–182 °C; MS, *m/z* (relative intensity) 198 (M⁺), 197 (100), 153; IR (KBr) 3490, 3300–2700, 1705, 1600, 1505 cm⁻¹; ¹H NMR (acetone-*d*₆) δ 8.40 (CO₂H, OH, br s), 6.36 (2 H, s), 3.76 (3 H, s), 3.42 (2 H, s); ¹³C NMR (acetone-*d*₆) δ 174, 157, 135, 131, 109, 60, 41.

Anal. Calcd for C₉H₁₀O₅: C, 54.55; H, 5.09. Found: C, 54.11; H, 4.94. Calcd *M_r* = 198.053. Found *M_r* = 198.053.

(3-Bromo-5-hydroxy-4-methoxyphenyl)acetic Acid (3e). Via the above methods, **3e** was obtained by interruption of the dehalohydroxylation of **3c** prior to completion. Subsequent esterification, chromatography, and saponification afforded **3e**, which was recrystallized from toluene: mp 159.5–160.5 °C; MS, *m/z* (relative intensity) 260 (M⁺, 100), 262 (99), 247, 245, 217, 215; IR (KBr) 3500–2800, 1715, 1570, 1490 cm⁻¹; ¹H NMR (CDCl₃) δ 7.58 (1 H, d, *J* = 2 Hz), 7.21 (1 H, d, *J* = 2 Hz), 3.75 (3 H, s), 3.34 (2 H, s).

Anal. Calcd for C₉H₉BrO₄: C, 41.41; H, 3.48. Found: C, 41.43; H, 3.34.

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Registry No. **1**, 1131-94-8; **2a**, 34021-73-3; **3a**, 104-01-8; **3b**, 774-81-2; **3c**, 89936-29-8; **3e**, 89936-30-1; **5**, 74007-21-9; **6a**, 15964-81-5; **6b**, 89936-31-2; *m*-MeOC₆H₄CH₂CH₂NH₂, 2039-67-0; CuSO₄, 7758-98-7.

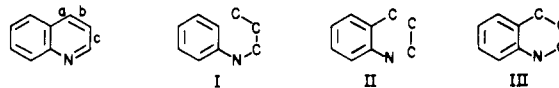
Cyclodehydration of *o*-Vinyl Anilides. A General Synthesis of Substituted Quinolines

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The quinoline ring system is usually synthesized from readily available aromatic amine derivatives.² The large number of reactions of this type can be classified according to the mode of final bond closure to form the heterocyclic ring. Important name reactions based on bond "a" formation include the Skraup and Doebner–von Miller synthesis of quinolines and the Combes, Conrad–Limpach, and Knorr synthesis of quinolones (see I). The Friedlander and Pfitzinger reactions are examples of final closure of bond "b" (see II). Most surprisingly, methods based on final closure of bond "c" are sparse³ and usually highly specialized.^{4,5} We now outline a general two-step preparation of substituted quinolines based on bond "c" formation via cyclization of in situ generated *o*-vinyl anilides (see III).



(1) Recipient of a Camille and Henry Dreyfus Grant for Newly Appointed Young Faculty in Chemistry.

(2) (a) Jones, G. "The Quinolines"; Wiley-Interscience: London, 1977; pp 93–318. (b) "Comprehensive Organic Chemistry"; Barton, D., Ollis, G., Eds.; Pergamon Press: New York, 1979; Vol. 4.

(3) For a related cyclization involving *o*-phenyl anilides, see: (a) Boyer, J. H.; Patel, J. R. *Synthesis* 1978, 205. (b) *o*-Phenyl isocyanides. Boyer, J. H.; Patel, J. R. *J. Chem. Soc., Chem. Commun.* 1977, 855.

(4) The Camps reaction forms quinolones via bond "c" closure. Mixtures of regioisomers are often possible. See: Camps, R. *Chem. Ber.* 1899, 32, 3228. Also see ref 2a, pp 191–197.

(5) For recent examples of bond c closure, see: DeMayo, P.; Sydnes, L. K.; Wenska, G. *J. Chem. Soc., Chem. Commun.* 1979, 499. Hull, R. *J. Chem. Soc., Perkin Trans. 1* 1973, 2911. Künzle, F.; Schmutz, J. *Helv. Chim. Acta* 1970, 53, 798. Yanagisawa, H.; Nakao, H.; Ando, A. *Chem. Pharm. Bull.* 1973, 21, 1080.