silylated isobenzofuran 13, with little if any unsilylated 11 present. The conversion of 13 (m at δ 6.7–6.9, 2 H) to 14 (a single sharper downfield absorption, 4 H) was monitored by NMR and judged to be complete in ca. 6 h. Workup and chromatography as before gave 96 mg (52%) of 14 and 14 mg (11%) of 15.

Rate Constants for Intramolecular Cycloadditions. Two separate reactions were carried out in which solutions of 9 in ether were treated with 0.1 equiv of diisopropylamine followed by 2.4 equiv of MeLi. The concentration of 9 after addition of these reagents was 0.24 M.

In the first run, an aliquot examined by NMR after 15 min exhibited a pattern in the aromatic region attributed to cycloadduct 15 (ca. 38%) and lithiated isobenzofuran 12 (62%). After 37 min, *tert*-butyl alcohol was added, and this caused the appearance of a singlet at δ 7.9, the furan proton of 11. This signal disappeared with a half-life of ca. 9 min, corresponding to a rate constant (11 → 15) of $k_a = 1.3 \times 10^{-3}$ s^{-1} (ca. 32 °C). This experiment was repeated to confirm the stability of 12. Substrate 9 was added to MeLi (4.5 equiv)/LDA (0.1 equiv), and no change in the NMR spectrum of 12 was observed over a period of 3 h. Addition of *tert*-butyl alcohol gave 11 as before.

In the second reaction, the solution of 12 (m at δ 6.3–6.45, 2 H) was allowed to stand for 0.5 h (no change in the spectrum was seen), before being treated with 2.4 equiv of Me_3SiCl. This gave a spectrum attributed to a mixture of 15 and the silylated isobenzofuran 13; the m at δ 6.7–6.9 for the latter was integrated vs. total aromatic absorption to obtain the rate constant for the process (13 → 14), $k_b = 1.4 \times 10^{-4}$ s^{-1} (ca. 32 °C). Repetition of this experiment at a controlled NMR probe temperature gave $k_b = 6.5 \times 10^{-5}$ s^{-1} (25 °C).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

A New Synthetic Approach to 1-(Hydroxymethyl)-8-methoxy-1,2,3,4-tetrahydroisoquinolin-4-one

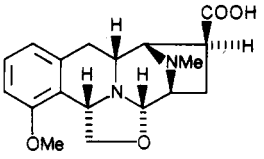
Robert M. Williams,*† Paul P. Ehrlich, Weixu Zhai, and James Hendrix

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523

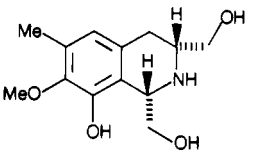
Received October 21, 1986

The tetrahydroisoquinoline moiety occurs as the structural nucleus of a wide variety of naturally occurring alkaloids.[1] As a result, numerous methods[2] have been developed and employed in the construction of natural alkaloids constituted of this ring system. Perhaps the most widely used synthetic construction is the classic Pictet–Spengler isoquinoline synthesis,[1] which involves the condensation of β-arylethylamines and carbonyl compounds. Cyclization occurs via the intermediacy of the putative Schiff base, furnishing the tetrahydroisoquinoline. The related Bischler–Napieralski reaction furnishes the corresponding 3,4-dihydroisoquinolines through an electronically similar electrophilic aromatic substitution. In both instances, rate-accelerating electron-releasing substituents generally induce cyclization to occur (ortho/para) at the less hindered (para) position to a significant extent. In the case of a *m*-methoxy-substituted β-arylamine, cyclization occurs to give the 6-methoxy regioisomer as the major and, often times, exclusive product.[1]

As part of a program to construct and study the rare tetrahydroisoquinoline antitumor alkaloid quinocarcin (DC-52, 1)[3] and the β-adrenergic receptor antagonist MY



1, quinocarcin



2, MY 336-a

336-a,[4] we needed a reliable and unambiguous synthetic protocol that would embrace the 8-oxygenated 1,2,3,4-tetrahydroisoquinoline nucleus.[5] Our approach is related to the classic Pomeranz–Fritsch reactions, wherein an appropriately substituted benzylic amine serves as the template for the penultimate C-4a/C-4 bond construction.[6]

2-Bromoanisole is lithiated (*n*-BuLi, THF) and condensed with the *N*-methoxy-*N*-methylamide[7] of (benzyloxy)acetic acid[8] (4) to furnish the ketone 5 in 90% yield (Scheme I). This coupling proved to be significantly superior to condensations of 3 with (benzyloxy)acetyl chloride,[8] the corresponding tertiary alcohol resulting from further reaction of 5 and 3 being the predominant product. However, preparatively useful quantities of 5 could also be obtained by coupling (benzyloxy)acetyl chloride and 3 in the presence of $CdCl_2$.[9]

Reductive amination of the ketone using the Borch[10] procedure (65%) followed by hydrogenolytic removal of the benzyl ether furnished the amino alcohol 7 (81%). Alkylation of the amine with ethyl bromoacetate (8; 95%) and formation of the cyclic urethane furnished the ethyl ester 9 (77%). Selective basic hydrolysis of the ethyl ester furnished the crystalline acid (75%; mp 165–166 °C), which was converted to the acid chloride with thionyl chloride. The crucial intramolecular Friedel–Crafts acylation proved to be extremely difficult and required extensive experimentation. Low yields (<10%) were obtained under classical conditions (hot CS_2, $AlCl_3$), but eventually the conditions reported by Uggeri[11] ($AlCl_3$, $Cl_2CH_2CH_2Cl_2$, 25

† Fellow of the Alfred P. Sloan Foundation 1986–1988. NIH Research Career Development Awardee 1984–1989. Eli Lilly Grantee 1986–1988.

(1) For reviews, see: (a) Adams, R., Ed. *Organic Reactions*; Wiley: New York; 1951; Vol. VI, pp 74–206. (b) Grethe, G., Ed. *Heterocyclic Compounds*, Part 1; Wiley: New York, 1981; Vol. 38.

(2) Miscellaneous approaches: (a) Venkov, A. P.; Mollov, N. M. *Synthesis* **1982**, 216. (b) Danishefsky, S.; Berman, E. *Tetrahedron Lett.* **1980**, *21*, 4819. (c) Kano, S.; Yuasa, Y.; Shibuya, S. *Heterocycles* **1984**, *22*, 2327. (d) Liu, J.-M.; Young, J.-J.; Li, Y.-J.; Sha, C.-K. *J. Org. Chem.* **1986**, *51*, 1120. (e) Otomasu, H.; Higashiyama, K.; Honda, T.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1982**, 2399. (f) Mendelson, W. L.; Spainhour, C. B.; Jones, S. S.; Lam, B. L.; Wert, K. L. *Tetrahedron Lett.* **1980**, *21*, 1393. (g) Deady, L. W.; Pirzada, N.; Topsom, R. D. *J. Chem. Soc. D* **1971**, 799. (h) Tamura, Y.; Uenishi, J.; Maeda, H.; Choi, H.; Ishibashi, H. *Synthesis* **1981**, 534.

(3) (a) Tomita, F.; Takahashi, K.; Shimizu, K. *J. Antibiot.* **1983**, *36*, 463. (b) Takahashi, K.; Tomita, F. *Ibid.* **1983**, *36*, 468.

(4) Kase, H.; Fujita, H.; Nakamura, J.; Hashizume, K.; Goto, J.; Kubo, K.; Shuto, K. *J. Antibiot.* **1986**, *39*, 354.

(5) An approach from isoquinoline involving selective electrophilic aromatic substitution has been reported: Rey, M.; Vergnani, T.; Dreiding, A. S. *Helv. Chim. Acta* **1985**, *68*, 1828.

(6) A completely different approach to this ring system that adequately (though not completely) addresses the 1,2,3-substitution pattern in this 8-methoxytetrahydroisoquinoline ring system has been reported: Danishefsky, S.; Harrison, P. J.; Webb, R. R.; O'Neill, B. T. *J. Am. Chem. Soc.* **1985**, *107*, 1421 and references cited therein.

(7) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.

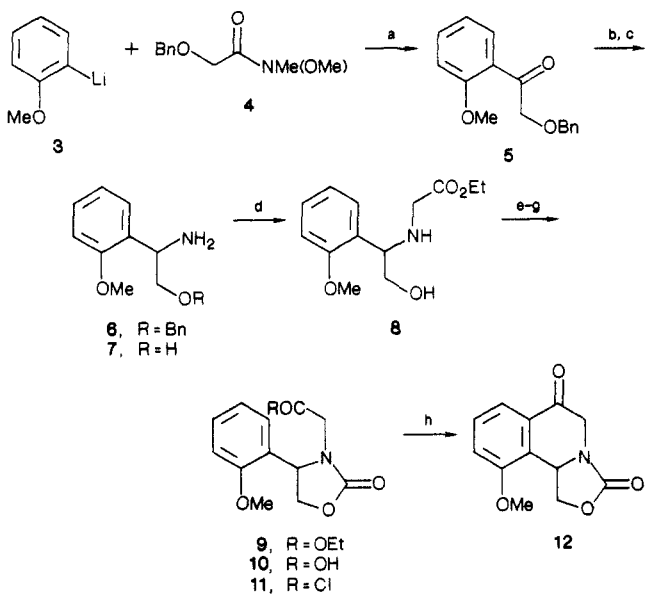
(8) Manhas, M. S.; Amin, S. G.; Chawla, H. P. S.; Bose, A. K. *J. Heterocycl. Chem.* **1978**, *15*, 601.

(9) (a) Cason, J. *Chem. Rev.* **1947**, *40*, 15. (b) Shirley, D. A. *Org. React. (N.Y.)* **1954**, *8*, 28. (c) Jones, P. R.; Desio, P. J. *Chem. Rev.* **1978**, *78*, 491. (d) Jones, P. R.; Shelnut, J. G. *J. Org. Chem.* **1979**, *44*, 696.

(10) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.

0022-3263/87/1952-2615$01.50/0

Scheme I[a]



[a] Reagents and conditions: (a) −15 °C, THF, 30 min, 5% HCl/EtOH, 90%; (b) $AcO^-N^+H_4$, $NaBH_3CN$, MeOH, 36 h, 65%; (c) 10% Pd/C, 0.5 M HCl/EtOH, 50 psi, 20 h, 81% (d) $BrCH_2CO_2Et$, Et_3N, THF, 20 h, 95%; (e) Im_2CO, THF, 2 h, 77%; (f) 1.0 M LiOH, EtOH, 1.5 h, 75%; (g) $SOCl_2$, C_6H_6, 80 °C, 3 h, 100%; (h) $AlCl_3$, $Cl_2HCCHCl_2$, 24 h, 65%.

°C; 65% yield) proved satisfactory to furnish the crystalline 1,2,3,4-tetrahydroisoquinoline **12**.

In a parallel series of experiments, the acid chloride corresponding to **11** prepared from phenylglycinol did *not* react intramolecularly to furnish the homologous tetrahydroisoquinoline. Instead, only *intermolecular* acylation products resulting from solvent incorporation or dimerization were obtained. Indeed, it seems that some electronic activation of the aromatic ring is required to effect closure in the modified Pomeranz–Fritsch approach.[12]

Experimental Section

(Benzyloxy)methyl 2-Methoxyphenyl Ketone (5). To a stirred solution of *o*-bromoanisole (1.28 mL, 10.0 mmol, 1.0 equiv) in dry pentane (15 mL) was added a 1.60 M solution of *n*-butyllithium in hexanes (6.25 mL, 10.0 mmol, 1.0 equiv) at room temperature in a nitrogen atmosphere. After 30 min, the solvent was removed in vacuo, and freshly distilled benzene (15 mL) was added immediately, followed by the addition of cadmium chloride (0.916 g, 5.0 mmol, 1.0 equiv) at room temperature. The resulting vigorously stirred suspension was heated to reflux in a nitrogen atmosphere for 6.5 h, at which time the mixture gave a negative Gilman's test. The mixture was allowed to cool to room temperature, (benzyloxy)acetyl chloride (1.845 g, 10.0 mmol, 1.0 equiv) was added, and the mixture was heated to reflux in a nitrogen atmosphere. After 2 h, the vigorously stirred mixture was cooled to room temperature, added to an equal volume of 10% HCl solution, and stirred for at least 30 min. The mixture was then separated, and the aqueous layer was washed with ether. The combined organic layers were then washed with 5% $NaHCO_3$ followed by saturated NaCl, dried over $MgSO_4$, concentrated, and separated by silica gel (eluted with 2.5% EtOAc/benzene) to afford 0.994 g (39%) of **5** as a yellow oil: ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.87 (3 H, s), 4.68 (2 H, s), 4.72 (2 H, s), 6.93 (2 H, m), 7.39 (6 H, m), 7.89 (1 H, dd, J = 7.73 Hz); IR (NaCl, neat) 3024, 2938, 1685, 1240, 1104 cm^{-1}.

(Note: The same procedure carried out with CdI_2 gave a 25% yield, and the same procedure carried out with the aryl Grignard reagent with $CdCl_2$ gave a 20% yield.)

***N*-Methoxy-*N*-methyl-2-(benzyloxy)acetamide (4).** To a stirred solution of (benzyloxy)acetyl chloride (3.226 g, 17.54 mmol, 1.0 equiv) and methoxymethylamine hydrochloride (1.93 g, 19.29 mmol, 1.1 equiv) in dry $CHCl_3$ (175 mL) cooled to 0 °C was added pyridine (3.12 mL, 38.58 mmol, 2.2 equiv). The resulting solution was stirred at room temperature for 12 h, when the $CHCl_3$ was evaporated, yielding a white residue. The residue was partitioned between brine and a 1:1 mixture of CH_2Cl_2/Et_2O. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated, yielding **4** (3.64 g, 99.5%) as a colorless oil: bp 132 °C (0.2 mmHg); ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.19 (3 H, s), 3.63 (3 H, s), 4.29 (2 H, s), 4.67 (2 H, s), 7.36 (5 H, m); IR (NaCl, neat) 3020, 3060, 2940, 1675, 1450, 1325, 1130, 1080, 980, 730, 690 cm^{-1}; mass spectrum, CI (NH_3) m/z 209.8 (M^+, 0.7%), 197 (3.1), 180 (9.0), 108 (5.8), 106 (10.4), 91 (2.4), 74 (5.9), 44 (4.5), 35 (100).

(Benzyloxy)methyl 2-Methoxyphenyl Ketone (5). To a stirred solution of *o*-bromoanisole (4.56 mL, 36.68 mmol, 3.0 equiv) in dry THF (12.5 mL) cooled to −15 °C was added *n*-BuLi (23.7 mL of a 1.54 M solution in hexanes, 3.0 equiv). The resulting solution was allowed to stir for 1 h at −15 °C, when it was added to a solution of **4** (2.55 g, 12.23 mmol, 1.0 equiv) in dry THF (125 mL), cooled to −15 °C, via cannula. The resulting solution was stirred for 30 min and poured into 50 mL of 5% HCl/EtOH at 0 °C. This solution was then partitioned between brine and a 1:1 mixture of CH_2Cl_2/Et_2O. The organic layer was separated, dried over Na_2SO_4, filtered, and evaporated, yielding **5** as a colorless oil (2.82 g, 90%): ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.87 (3 H, s), 4.68 (2 H, s), 4.72 (2 H, s), 6.93 (2 H, m), 7.39 (6 H, m), 7.89 (1 H, dd, J = 7.73 Hz); IR (NaCl, neat) 3020, 3060, 2930, 1680, 1595, 1480, 1280, 1235, 1100, 1010, 940, 740, 685 cm^{-1}; mass spectrum, CI (NH_3) m/z 257 (M^+, 14.5%), 151 (100), 135 (6.6), 106 (6.0), 91 (2.4), 35 (100).

***O*-Benzyl(2-methoxyphenyl)glycinol (6).** To a stirred solution of **5** (2.82 g, 11.029 mmol, 1.0 equiv) and ammonium acetate (8.50 g, 110.3 mmol, 10 equiv) in absolute methanol (35 mL) was added sodium cyanoborohydride (0.485 g, 7.72 mmol, 0.70 equiv) in one portion. The resulting solution was stirred at room temperature for 36 h. Concentrated HCl was added until pH <2. The MeOH was then evaporated, and the resulting white residue was dissolved in H_2O (10 mL) and washed with Et_2O (2 × 10 mL). The aqueous phase was then basified with powdered KOH to pH >10, saturated with NaCl, and extracted with CH_2Cl_2 (4 × 10 mL). The combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and evaporated to a colorless oil (1.832 g, 65%): ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 1.82 (2 H, br s), 3.45 (1 H, t, J = 8.52 Hz), 3.69 (1 H, dd, J = 9.24 Hz), 3.79 (3 H, s), 4.56 (3 H, m), 6.92 (2 H, m), 7.32 (7 H, m); IR (NaCl, neat) 3380, 3300, 3020, 3060, 2900, 2840, 1580, 1485, 1450, 1230, 1080, 1115, 850, 735, 680 cm^{-1}; mass spectrum, CI (NH_3) m/z 258 (M^+, 100), 256 (210), 241 (2.5), 228 (1.8), 150 (19.2), 136 (38.5), 106 (19.5), 91 (6.8), 35 (100).

(2-Methoxyphenyl)glycinol (7). To a solution of **6** (2.885 g, 11.21 mmol, 1.0 equiv) in 60 mL of 0.5 M HCl/EtOH contained in a Parr pressure vessel was added 10% Pd/C (2.98 g, 2.8 mmol, 0.25 equiv). The vessel was purged with hydrogen several times, charged to 50 psi, and hydrogenated for 20 h. The Pd/C was filtered off over Celite and the filtrate evaporated to a white solid. The solid was dissolved in water and washed once with Et_2O, basified to pH >10 with solid KOH, saturated with NaCl, and extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was then dried over $MgSO_4$, filtered, and evaporated, yielding **7** (1.52 g, 81%) as a colorless oil: ^1H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 2.57 (3 H, br s), 3.59 (1 H, m), 3.73 (1 H, m), 3.81 (3 H, s), 4.27 (1 H, m), 6.68 (1 H, d, J = 8.24 Hz), 6.91 (1 H, m), 7.23 (2 H, m); IR (NaCl, neat) 3360, 3280, 2920, 2830, 1590, 1490, 1235, 1140, 1120, 740 cm^{-1}; mass spectrum, CI (NH_3) m/z 168 (M^+, 5.8%), 151 (10.9), 136 (23.6), 44 (6.0), 35 (100).

***N*-(Carboxymethyl)(2-methoxyphenyl)glycinol (8).** To a stirred solution of **7** (1.16 g, 6.935 mmol, 1.0 equiv) and triethylamine (1.45 mL, 10.437 mmol, 1.5 equiv) in dry THF (60 mL) was added ethyl bromoacetate (1.00 mL, 9.04 mmol, 1.3 equiv). The reaction solution was stirred at room temperature for 20 h. The Et_3N·HBr was filtered off and washed with THF. The filtrate was evaporated to a clear residue, which was taken up in 70 mL of CH_2Cl_2, washed with H_2O (3 × 20 mL) and brine (1 × 20 mL), dried over $MgSO_4$, filtered, and evaporated to yield

(11) Uggeri, F.; Giordano, C.; Brambilla, A. *J. Org. Chem.* **1986**, *51*, 97.
(12) Some notable exceptions are included in ref 2f–h; see also ref 6.

8 (1.665 g, 95%) as a colorless oil: ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 1.23 (3 H, t, J = 7.45 Hz), 2.50 (2 H, br s), 3.35 (2 H, d, J = 5.43 Hz), 3.70 (2 H, m), 3.82 (3 H, s), 4.13 (3 H, m), 6.92 (2 H, m), 7.28 (2 H, m); IR (NaCl, neat) 3310, 2910, 1735, 1595, 1485, 1455, 1230, 1180, 1020, 740 cm^{-1}; mass spectrum, CI (NH_3) m/z 254 (M^+, 1.9), 236 (1.8), 208 (18.9), 168 (2.5), 150 (6.7), 130 (61.1), 104 (11.3), 72 (7.2), 55 (100).

Cyclic Urethane 9. To a stirred solution of 8 (1.665 g, 6.59 mmol, 1.0 equiv) in dry THF (60 mL) was added *N,N'*-carbonyldiimidazole (1.60 g, 9.87 mmol, 1.5 equiv). The resulting solution was stirred at room temperature for 2 h and evaporated to a white residue. The residue was taken up in CH_2Cl_2 (100 mL), washed with 1 M HCl (3 × 25 mL), H_2O (2 × 25 mL), and brine (1 × 25 mL), dried over $MgSO_4$, filtered, and evaporated, yielding 9 as a colorless oil (1.41 g, 77%): ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 1.25 (3 H, t, J = 7.03 Hz), 3.43 (1 H, d, J = 17.96 Hz), 3.82 (3 H, s), 4.16 (3 H, m), 4.34 (1 H, d, J = 17.98 Hz), 4.72 (1 H, t, J = 8.67 Hz), 5.35 (1 H, m), 6.97 (2 H, m), 7.27 (2 H, m); IR (NaCl, neat) 2960, 2920, 2820, 1750, 1600, 1580, 1485, 1460, 1415, 1240, 1195, 1080, 1115, 745 cm^{-1}. Mass spectrum, CI (NH_3) m/z 280 (M^+, 54.9%), 250 (3.1), 235 (1.2), 220 (1.4), 162 (1.8), 148 (1.7), 133 (2.0), 104 (1.7), 35 (100).

Carboxylic Acid 10. To a stirred solution of 9 (1.41 g, 5.059 mmol, 1.0 equiv) in 16 mL of absolute ethanol at −10 °C was added 6.7 mL of 1 M LiOH (6.7 mmol, 1.32 equiv). The reaction was allowed to stir for 1.5 h at −10 °C and was then neutralized with 6 M HCl (1.11 mL, 6.7 mmol, 1.32 equiv). The ethanol was evaporated, and the resulting residue was partitioned between 1 M HCl and CH_2Cl_2. The organic layer was separated, washed with H_2O (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered, and evaporated to a white solid. Recrystallization from EtOAc/hexanes afforded 957 mg of pure 10 (75%): mp 165–166 °C; ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.48 (1 H, d, J = 18.25 Hz), 3.83 (3 H, s), 4.19 (1 H, t, J = 8.02 Hz), 4.39 (1 H, d, J = 18.438 Hz), 4.73 (1 H, t, J = 9.174 Hz), 5.36 (1 H, m), 6.95 (2 H, m), 7.36 (2 H, m), 8.52 (1 H, br s); IR (NaCl, neat) 2900, 2810, 2700, 2585, 2500, 1750, 1675, 1595, 1580, 1450, 1240, 1200, 1190, 1110, 940, 850, 750, 735, 700, 630 cm^{-1}; mass spectrum, CI (NH_3) m/z 251 (M^+, 13.8%), 236 (3.5), 208 (7.9), 194 (6.6), 164 (2.5), 150 (5.5), 135 (4.1), 102 (3.7), 76 (3.2), 44 (8.1), 35 (100). Anal. ($C_{12}H_{13}NO_5$) C, H, N.

Acid Chloride 11. To a suspension of 10 (408 mg, 1.626 mmol, 1.0 equiv) in dry benzene (8 mL) was added $SOCl_2$ (0.36 mL, 4.91 mmol, 3.02 equiv). The suspension was then heated to mild reflux for 3 h, and the benzene and $SOCl_2$ were evaporated under reduced pressure. The resulting light amber residue (438 mg, 100%) was used directly for the next step without purification: ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.78 ($^1/_2$ H, s), 3.84 (3.5 H, s), 4.25 (1 H, dd, J = 8.63 Hz), 4.73 (2 H, m), 5.32 (1 H, dd, J = 9.02 Hz), 6.97 (2 H, m), 7.27 (2 H, m); IR (NaCl, neat) 3060, 3020, 2940, 2830, 1800, 1760, 1600, 1590, 1490, 1460, 1420, 1250, 1180, 1110, 1090, 1020, 950, 920, 850, 750, 670 cm^{-1}.

Isoquinolone 12. To a stirred solution of 11 (438 mg, 1.626 mmol, 1.0 equiv) in 16 mL of dry 1,1,2,2-tetrachloroethane was added $AlCl_3$ (867 mg, 6.5 mmol, 4.0 equiv). The reaction was stirred at room temperature for 24 h, when it was poured into 40 mL of ice water and acidified to pH <2 with concentrated HCl. The resulting slurry was extracted with CH_2Cl_2 (4 × 20 mL), and the combined organic extracts were washed with 1 M NaOH (1 × 10 mL) and brine (1 × 10 mL), dried over $MgSO_4$, filtered, and evaporated to an oil, which was separated by column chromatography (silica gel, 3:2 hexanes/EtOAc), yielding 12: 246 mg, 65%; mp 157–159 °C dec (recrystallized from EtOAc); ^{1}H NMR (270 MHz, $CDCl_3$, Me_4Si) δ 3.83 ($^1/_2$ H, s), 3.91 (3.5 H, s), 4.25 (1 H, t, J = 8.54 Hz), 4.67 (1 H, d, J = 18.15 Hz), 5.03 (1 H, t, J = 8.94 Hz), 5.23 (1 H, t, J = 8.61 Hz), 7.16 (1 H, dd, J = 8.28 Hz), 7.46 (1 H, t, J = 8.41 Hz), 7.73 (1 H, dd, J = 8.14 Hz); IR (NaCl, neat) 3080, 3020, 2940, 2870, 1765, 1695, 1595, 1580, 1430, 1280, 1250, 1120, 1030, 785, 740, 670 cm^{-1}; mass spectrum, CI (NH_3) m/z 233 (M^+, 16.9%), 219 (7.9), 189 (2.1), 174 (7.4), 159 (2.8), 132 (1.3), 35 (100). Anal. ($C_{12}H_{11}NO_4$) C, H, N.

Acknowledgment. We acknowledge The National Institutes of Health, The National Science Foundation, The Alfred P. Sloan Foundation, and Eli Lilly Corp. for their generous support of our programs.

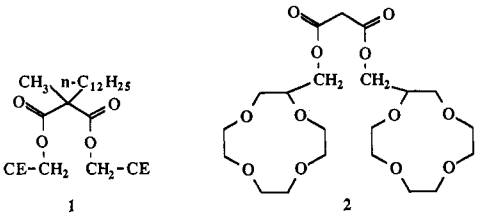
Lithium-Selective, Lipophilic, Small-Ring Bis(crown ethers)

Michael J. Pugia, Brian E. Knudsen, and Richard A. Bartsch*

Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79402-4260

Received December 23, 1986

Bis(crown ethers) may exhibit highly selective alkali metal cation complexation by formation of intramolecular complexes in which the cation is sandwiched between the two adjacent crown ether rings.[1] Ion-selective, bis(crown ether) esters derived from dodecylmethylmalonic acid and hydroxymethyl-substituted crown ethers have been found to be selective for the alkali metal cation that is slightly larger than the crown ether cavity. Thus, for bis(crown ether) esters 1 in which CE corresponds to 12-crown-4, 15-crown-5, and 18-crown-6 rings, selectivity for Na^+, K^+, and Cs^+, respectively, has been reported.[2-4] Similarly, the complex stability constants for interactions of Na^+ and K^+ with 1 where CE = 12-crown-4 in MeOH gave a Na^+/K^+ selectivity of 34.[5] Also, in extractions of aqueous Na^+, K^+, Rb^+, and Cs^+ picrate solutions with dichloromethane solutions of the malonate bis(12-crown-4) compound 2, the distribution ratios for Na^+ picrate were the highest by a considerable margin.[6]



1 2

By analogy, malonate-type bis(crown ethers) with very small crown ether rings might be expected to exhibit selectivity for complexation of Li^+. We now report the synthesis of new lipophilic bis(crown ethers) 3–5, which have 9-crown-3, 12-crown-4, and 14-crown-4 ring sizes, respectively, and comparison of their efficiencies for extraction of Li^+, Na^+, K^+, and Rb^+ picrates into deuteriochloroform. For 3 and 4, the crown ether rings are too small to accommodate even Li^+, whereas for 5, the crown ether ring size is appropriate for Li^+ complexation.[7-10]

Previously unreported (hydroxymethyl)-9-crown-3 (6) was prepared in high yield by an Okahara cyclization[11] of

(1) Takeda, Y. *Top. Curr. Chem.* **1984**, *121*, 1.
(2) Shono, T.; Okahara, M.; Ikeda, I.; Kimura, K.; Tamura, H. *J. Electroanal. Chem.* **1982**, *182*, 99.
(3) Kimura, K.; Tamura, H.; Shono, T. *J. Chem. Soc., Chem. Commun.* **1983**, 492.
(4) Kimura, K.; Ishikawa, A.; Tamura, H.; Shono, T. *J. Chem. Soc., Perkin Trans. 2* **1984**, 447.
(5) Ikeda, I.; Katazama, T.; Okahara, M.; Shono, T. *Tetrahedron Lett.* **1981**, *22*, 3615.
(6) Maeda, T.; Ouchi, M.; Kimura, K.; Shono, T. *Chem. Lett.* **1981**, 1573.
(7) Dalley, N. K. In *Synthetic Multidentate Macrocyclic Compounds*; Izatt, R. M., Christensen, J. J., Eds.; Academic Press: New York, 1978; Chapter 4.
(8) Lamb, J. D.; Izatt, R. M.; Christensen, J. J. In *Progress in Macrocyclic Chemistry*, Izatt, R. M., Christensen, J. J. Eds.; Wiley-Interscience: New York, 1981; Vol. 2, Chapter 2.
(9) Czech, B. P.; Babb, D. A.; Son, B.; Bartsch, R. A. *J. Org. Chem.* **1984**, *49*, 4805.
(10) Bartsch, R. A.; Czech, B. P.; Kang, S. I.; Stewart, L. E.; Walkowiak, W.; Charewicz, W. A.; Heo, G. S.; Son, B. *J. Am. Chem. Soc.* **1985**, *107*, 4997.

0022-3263/87/1952-2617$01.50/0