(Tosyloxy)anthraquinones: Versatile Synthons for the Preparation of Various Aminoanthraquinones[1]

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Various aminoanthraquinones can be easily prepared from (tosyloxy)anthraquinone precursors. Unsymmetrical 1,4-diaminoanthraquinones are prepared via the intermediate monoamino mono(tosyloxy)anthraquinones derived from 1,4-bis(tosyloxy)anthraquinone. The ability to remove tosylate groups sequentially is controlled by the proper selection of solvent and temperature. Hindered 1,4-diamino and 1-aminoanthraquinones are prepared from their corresponding tosyl derivatives, and the amount of steric hindrance present can be successfully correlated with spectral and color data. The methods described offer advantages over the literature preparations of these compounds.

Introduction

As part of our interest in specialty dyes, we needed to prepare unsymmetrically substituted 1,4-diaminoanthraquinones, 1,4-diaminoanthraquinones hindered at positions 2 and 3, and various 1-aminoanthraquinones. The literature methods were lengthy or tedious or at times gave very low or no yields.[2-4] The (tosyloxy)anthraquinone compounds **1**, **2**, **4**, and **6** were prepared as starting materials that would enable us to achieve the desired objectives.

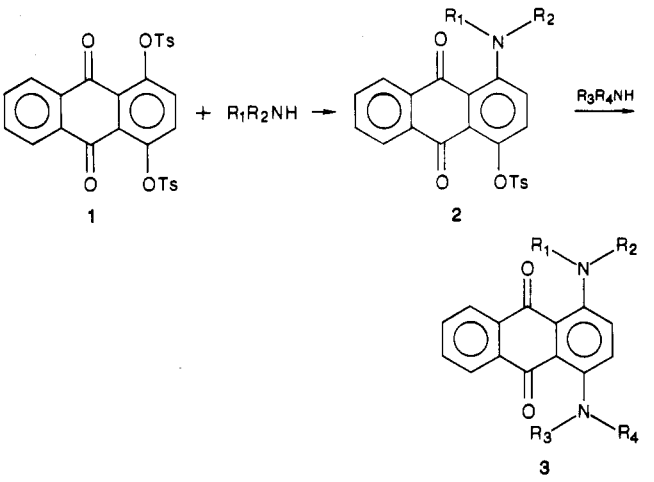
Results and Discussion

Unsymmetrical 1,4-Diaminoanthraquinones. During an attempt to make a symmetrically 1,4-disubstituted aminoanthraquinone from 1,4-bis(tosyloxy)anthraquinone, the latter was treated with excess amine by using mild reaction conditions. Instead of the expected blue product, indicative of 1,4-diamino substitution, a red product, indicative of 1-amino substitution, was obtained. Analysis showed that this red product was the 1-amino-4-(tosyloxy)anthraquinone. Obviously isolation of such intermediates in good yield could provide a general method for the rational preparation of mixed amino compounds. Thus treatment of the intermediate with a second amine, using harsher conditions, should result in replacement of the remaining tosyloxy group and formation of the mixed aminoanthraquinone. This potential was realized and the initial work was expanded to the general procedure outlined below.

The 1,4-bis(tosyloxy)anthraquinone was conveniently prepared from readily available reagents by modification of a known procedure[5] and could be stored at room temperature for long periods with no apparent decomposition.

The general method is outlined in Scheme I. The key to success was the ability to synthesize and isolate the intermediate monoaminomono(tosyloxy)anthraquinone

Scheme I



derivatives readily and in good yield. By choosing the correct solvent and temperature, the reaction could be stopped at this intermediate stage. We found that refluxing methylene chloride (40 °C) gave good yields of the intermediate monoaminomono(tosyloxy)anthraquinones if the amine was alkyl-substituted (**2a,b**). Treatment of these intermediates in pyridine solvent (60–110 °C) with a second alkylamine gave good yields of the unsymmetrical 1,4-bis(alkylamino)anthraquinones (**3a,b**). For aromatic amines (poor nucleophiles) it was necessary to use Me_2SO, known to increase the basicity of amines,[6] at 150 °C for attachment of the first arylamino group to form the mono(arylamino)mono(tosyloxy)anthraquinone (**2c**). Treatment of this intermediate with Me_2SO, now at 180 °C, and a second aromatic amine gave the mixed 1,4-bis(arylamino)anthraquinone in moderate yield (**3d**).

1,4-Bis(tosyloxy)anthraquinone could also be used to make symmetrical diaminoanthraquinones (**3c**). Pyridine (or Me_2SO for aromatic amines) was used as solvent, but the intermediate monoaminomono(tosyloxy)anthraquinone was not isolated. An excess of the desired amine was used with the appropriate solvent and only the final 1,4-diaminoanthraquinone was isolated.

Some problems were encountered in our attempts to prepare mixed N-disubstituted, N′-monosubstituted diaminoanthraquinones. For example, 1-(diethylamino)-4-(tosyloxy)anthraquinone (**2b**) could be prepared in good yield with the low temperature sufficient to add only the first amine to the anthraquinone ring. However subse-

(1) The work on unsymmetrical aminoanthraquinones was presented at the 188th National Meeting of American Chemical Society, Philadelphia, PA, August 1984; Medicinal Chemistry Section, Poster Session, paper 56.

(2) (a) Simon, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 1974. (b) McSheehy, J. A. U.S. Patent 2 727 045, 1955. (c) James, G. A. W. G.B. Patent 1 504 137, 1978. (d) Brendle, R. N. U.S. Patent 4 170 564, 1979. (e) Ludwigshafen, F. G.; Mannheim, G. R. U.S. Patent 3 597 254, 1971. (f) Gutzwiller, E. U.S. Patent 2 448 094, 1948.

(3) (a) Basel, P. A. U.S. Patent 2 121 928, 1938. (b) Wick, A. U.S. Patent 3 927 043, 1975. (c) Lord, W. M.; Peters, A. T. *J. Appl. Chem. Biotech.* **1977**, *27*, 362. (d) Allen, C. F. H.; Frame, G. F.; Wilson, C. V. *J. Org. Chem.* **1941**, *6*, 732. (e) Allen, C. F. H.; Frame, G. F.; Wilson, C. V. *J. Org. Chem.* **1942**, *7*, 63.

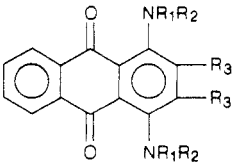
(4) (a) Adam, J. M. G.B. Patent 2 019 870, 1979. (b) Adam, J. M. G.B. Patent 2 014 178, 1979.

(5) Kurita, K. *Chem. Ind. (London)* **1974**, 345.

(6) Reyes, A.; Scott, R. M. *J. Phys. Chem.* **1980**, *84*, 3600.

0022-3263/87/1952-1305$01.50/0

Table I. Change in Spectral Properties with Increasing Steric Hindrance



compd	R_1	R_2	R_3	^1H NMR δ_{NH}	UV ϵ	UV λ, nm	color
3c	H	*n*-butyl	H	10.76	17300	648	blue
5c	H	neopentyl	methyl	9.97	8120	594	blue
5b	H	isopropyl	methyl	9.06, 8.96	6940	570	violet-blue
5a	H	*tert*-butyl	methyl	7.33	3540	526	violet-red
5d	methyl	methyl	methyl		2400	494	red

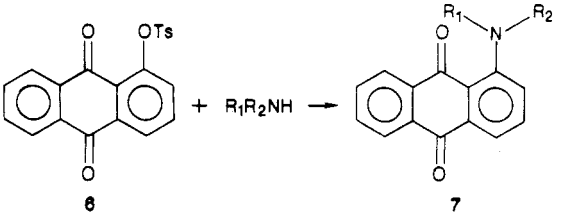
quent treatment with *n*-propylamine at the higher temperatures necessary to attach a second amine group to the same anthraquinone ring gave the 1-(ethylamino)-4-(*n*-propylamino)anthraquinone (**3b**). Even when we started with 1-(*n*-propylamino)-4-(tosyloxy)anthraquinone and added diethylamine last in the sequence, the final product was the same compound, **3b**. Instances of N-disubstituted aminoanthraquinones readily reverting to N-monosubstituted aminoanthraquinones have been previously reported in the literature.[7] The de-alkylation apparently results from a complex series of rearrangements involving a reduced (leuco) ring species and an oxidation step to the final product which now contains an intramolecular H-bonded six-membered ring.[8] The reaction could also be driven by evaporative loss of the acetaldehyde (bp 21 °C) byproduct.[9]

Hindered Aminoanthraquinones. We also wished to prepare anthraquinone dyes with methyl groups at positions 2 and 3 and alkylamino groups at positions 1 and 4. Because of our success with the previously prepared 1,4-bis(tosyloxy)anthraquinone we felt that 1,4-bis(tosyloxy)-2,3-dimethylanthraquinone (**4**) could be used for the preparation of aminoanthraquinones containing methyls at positions 2 and 3.

The methyl groups were added to quinizarin by means of the Marschalk alkylation.[10] Attempts to prepare the corresponding ditosylate from this compound by the previously described procedure gave low yields. When 2,3-dimethylquinizarin was treated with *p*-toluenesulfonyl chloride and sodium hydroxide under phase-transfer catalysis,[11] a good yield of 1,4-bis(tosyloxy)- 2,3-dimethylanthraquinone (**4**) was obtained.

1-Aminoanthraquinones. Procedures beginning with 1-chloroanthraquinone[12] sometimes took several days to give good yields and often involved sealed-tube reactions. Those starting with 1-nitroanthraquinone[13] gave, in our hands, product mixtures that were difficult to purify. A photochemical method beginning with 1-methoxyanthraquinone[14] was successful only with primary aliphatic amines. Because of these drawbacks and with the success of 1,4-bis(tosyloxy)anthraquinone as precursor to 1,4-diaminoanthraquinones, we decided to investigate the use of 1-(tosyloxy)anthraquinone (**6**) for the preparation of 1-aminoanthraquinone derivatives. The tosyloxy compound was prepared by adaptation of our original procedure. Treatment of this compound with excess amine (pyridine solvent) easily gave the corresponding 1-aminoanthraquinones **7** (Scheme II). For preparation of phenylamino derivatives, Me_2SO was the solvent of choice.

Scheme II



6 **7**

Spectral Data: Correlation with Structure. The amount of steric hindrance present in each molecule can be judged by an examination of the molar absorptivity in the visible region and by an examination of chemical shift (NMR) of the proton attached to nitrogen. The correlation of structure to spectral properties is shown in Table I. It is known that hydrogen bonding shifts the proton NMR absorption to lower field.[15] It has been established that in 1-aminoanthraquinones the proton on nitrogen is intramolecularly hydrogen bonded to the carbonyl oxygen.[16] Thus the proton absorption at δ 10.76 for 1,4-bis(*n*-butylamino)anthraquinone represents the "normal" situation. As the steric crowding around nitrogen becomes more severe (moving downward in Table I) the proton absorption gradually moves upfield, toward the non-H-bonded position (δ 3–5).[17] With *tert*-butyl groups on nitrogen, the upfield shift of the proton becomes so large that it approaches the non-H-bonded region.

Examination of the molar absorptivities (Table I) shows that they correlate well with the NMR data. Since molar absorptivity is a measure of the conjugation between the electrons on nitrogen and the aromatic ring,[18] 1,4-bis(*n*-

(7) (a) Lord, W. M.; Peters, A. T. *J. Chem. Soc. C* **1968**, 784. (b) Lord, W. M.; Peters, A. T. *Chem. Ind. (London) 1973*, 227. (c) Lynch, J.; Meth-Cohn, O. *J. Chem. Soc., Perkin Trans. 1* **1973**, 920. (d) Ruediger, E. H.; Kaldas, M. D.; Gandhi, S. S.; Fedryna, C.; Gibson, M. S. *J. Org. Chem.* **1980**, *45*, 1974.

(8) (a) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211. (b) See ref 7c.

(9) Suggested by a referee.

(10) Marschalk, C.; Koenig, F.; Ouroussoff, N. *Bull. Soc. Chem. Fr.* **1936**, 1545.

(11) (a) Dockx, J. *Synthesis* **1973**, 450. (b) Foglia, T. A.; Barr, P. A.; Mallory, A. M. *J. Am. Oil Chem. Assoc.* **1977**, *54*, 858A.

(12) (a) Wood, G. D.; Peters, A. T. *J. Chem. Soc.* **1962**, 3373. (b) Lord, W. M.; Peters, A. T. *J. Chem. Soc.* **1968**, 783.

(13) Slavik, V.; Arient, J. *Collect. Czech. Chem. Commun.* **1975**, *40*, 1193.

(14) Griffiths, J.; Hawkins, C. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2283.

(15) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; Wiley: New York, 1981; p 194.

(16) (a) Simon, M. S. *J. Am. Chem. Soc.* **1963**, *85*, 1974. (b) Peters, R. H.; Summer, H. H. *J. Chem. Soc.* **1953**, 2101. (c) Egerton, G. S.; Roach, A. G. *J. Soc. Dyers Colour.* **1958**, *74*, 405. (d) Allen, C. F. H.; Wilson, C. V.; Frame, G. F. *J. Org. Chem.* **1942**, *7*, 169. (e) Yoshida, Z.; Takalayashi, F. *Tetrahedron* **1968**, *24*, 933.

(17) See ref 15, p 198.

(18) See ref 15, p 321.

butylamino)anthraquinone again represents conjugation in a "normal" situation. From molecular models, it is clear that when the internal H-bond is present, the electron pair on nitrogen is held orthogonal to the aromatic ring in a very favorable position for full conjugation. As the steric crowding around nitrogen increases, the C–N bond is twisted such that less than full conjugation is possible. This is shown by the decreasing value of ϵ as one moves down Table I. With the *N,N*-dimethyl compound (no H-bonding possible), molecular models show that the preferred conformation is one where the electron pair on nitrogen is almost in the plane of the aromatic ring (little conjugation). Since the ϵ of the 1,4-bis(*tert*-butylamino) compound is closer to that of the *N,N*-dimethyl compound, it argues that the electron pair of 1,4-bis(*tert*-butylamino)anthraquinone is similarly positioned, indicating a large amount of hindrance present and correlating well with the NMR chemical shift data. The movement of λ_{max} to shorter wavelength is also consistent with the diminished conjugation of the more hindered compounds. Finally, the color of the compounds changed drastically from a bright blue in the "normal" situation to red for the very hindered compounds (**5a,d**).

The use of hindered (alkylamino)anthraquinones and (*N*-phenylamino)anthraquinones as dyes in a hypochlorite color-stable product is outlined in our patent.[19]

Experimental Section

Melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. NMR spectra were recorded on a JEOL-FX90Q spectrometer operating in the FT mode with Me_4Si as internal standard. UV–vis spectra were recorded on a Cary Model 219 spectrophotometer, IR spectra on a Beckmann Acculab 2 or a Perkin-Elmer 283B, and mass spectra on a LKB 9000 instrument (SRI International). Elemental analyses were performed by Galbraith Laboratories. TLC was performed on either Analtech silica gel F or alumina F plates, and spots were detected either by use of UV lamp (254 nm) or by direct visual inspection. Column chromatography was carried out on EM-60 silica gel (70–230 mesh) or EM-90 alumina (activity II-III, 70–230 mesh).

1,4-Bis(tosyloxy)anthraquinone (1). To quinizarin (5.0 g, 21 mmol, Aldrich Chemical Co.) suspended in MeCN (150 mL) at reflux was added Et_3N (15 mL, 107 mmol) and *p*-toluenesulfonyl chloride (9.6 g, 50 mmol). The resulting solution was stirred at reflux for 5 h, and the course of reaction was followed by TLC (SiO_2, CH_2Cl_2). The MeCN was removed by rotary evaporator, and CH_2Cl_2 (250 mL) was added. This mixture was washed with water (3 × 150 mL), and the CH_2Cl_2 layer was dried over $MgSO_4$. Filtration and solvent removal gave **1** as a yellow-brown solid (11.9 g). This was dissolved in hot $CHCl_3$ (185 mL), petroleum ether (200 mL, bp 30–60 °C) was added, and the mixture was cooled in an ice bath. Filtration of the resulting slurry gave a bright yellow solid, dried to yield 10.0 g (87%): mp 225–226 °C; mass spectrum, *m/e* 548 (M^+), 394 ($M - C_7H_7SO_2 + H$), 239 ($M - 2C_7H_7SO_2 + H$), 155 ($C_7H_7SO_2$), 91 (C_7H_7); ^1H NMR (CD_2Cl_2) δ 8.02–7.94 (m, 2 H), 7.91–7.69 (m, 6 H), 7.45 (s, 2 H), 7.33–7.24 (m, 4 H), 2.35 (s, 6 H); IR (Nujol) 1680 (C=O), 1310 (asymmetrical SO_2 stretch), 1175, 1190 (symmetrical SO_2 stretch), 920, 895, 860, 810, 795, 780, 745 cm^{-1} (S–O–C stretch); UV–vis max (CH_2Cl_2) 331 nm (ϵ 4820).

Anal. Calcd for $C_{28}H_{20}S_2O_8$: C, 61.31; H, 3.65; S, 11.68. Found: C, 61.10; H, 3.81; S, 11.54.

Preparation of the 1-Amino-4-(tosyloxy)anthraquinones (2a–c). The general method for the preparation of these compounds is given followed by the yield, mp, and spectral data for each specific compound.

1-(Alkylamino)-4-(tosyloxy)anthraquinones 2a,b. The 1,4-bis(tosyloxy)anthraquinone was dissolved in CH_2Cl_2 and amine added (~250 molar excess) and then refluxed from 5–24 h. The reaction could be followed by TLC (SiO_2; Hex/EtOAc, 70:30). The starting materials gave R_f ~0.40 region (dark spot under UV light), the monoaminomono(tosyloxy)anthraquinones were bright red, R_f ~0.65 region, and there was usually a faint blue spot present at R_f ~0.80 region (the 1,4-diaminoanthraquinone). When the reaction was complete as judged by TLC, the liquids were removed by evaporation, CCl_4 was added to the residue, and the slurry was filtered. The red filtrate was placed on a column of silica gel, the column eluted with Hex/EtOAc (70:30), and the red band collected. Further purification could be achieved, especially if any phenolic material (violet) is present by chromatography through a short alumina column or by preparative TLC.

1-(Arylamino)-4-(tosyloxy)anthraquinone 2c. The 1,4-bis(tosyloxy)anthraquinone was dissolved in Me_2SO, the aromatic amine added (~250 molar excess), and the solution heated at 150 °C for 2 h. The reaction was followed by TLC as described above. When reaction was complete, the solution was cooled, poured into 10% aqueous HCl, and extracted with CH_2Cl_2 and the CH_2Cl_2 washed with water and dried over $MgSO_4$. After filtration, the solvent was evaporated and the residue dissolved in CCl_4. Purification is as described above.

1-(Isopropylamino)-4-(tosyloxy)anthraquinone (2a) was prepared from **1** and isopropylamine. The yield was 76% and the mp 164–165.5 °C: mass spectrum, *m/e* 435 (M^+), 420 ($M - CH_3$), 280 ($M - C_7H_7SO_2$), 238 ($280 - C_3H_7 + H$), 210 ($238 - CO$), 182 ($210 - CO$), 155 ($C_7H_7SO_2$), 91 (C_7H_7); ^1H NMR (CD_2Cl_2) δ 9.97 (br s, 1 H), 8.19–8.10 (m, 2 H), 7.85–7.67 (m, 4 H), 7.27–6.97 (m, 4 H), 4.02–3.68 (m, 1 H), 2.30 (s, 3 H), 1.38, 1.31 (d, 6 H); IR (Nujol) 1180 (symmetrical SO_2 stretch), 890, 860, 820, 780 cm^{-1} (S–O–C stretch); UV–vis max (xylenes) 500 nm (ϵ 6660).

Anal. Calcd for $C_{24}H_{21}NSO_5$: C, 66.21, H, 4.83; N, 3.22; S, 7.36. Found: C, 66.35, H, 4.75; N, 3.25; S, 7.38.

1-(Diethylamino)-4-(tosyloxy)anthraquinone (2b) was prepared from **1** and diethylamine. The yield was 91% and the mp 140–141 °C: mass spectrum, *m/e* 449 (M^+), 434 ($M - CH_3$), 420 ($M - C_2H_5$), 294 ($M - C_7H_7SO_2$), 266 ($294 - CO$), 155 ($C_7H_7SO_2$), 91 (C_7H_7); ^1H NMR (CD_2Cl_2) δ 8.19–8.13 (m, 2 H), 7.97–7.68 (m, 4 H), 7.30–7.15 (m, 4 H), 3.48–3.24 (q, 4 H), 2.26 (s, 3 H), 1.22–1.06 (t, 6 H); IR (Nujol) 1172 (symmetrical SO_2 stretch), 945, 872, 830, 820, 800, 785, 765 cm^{-1} (S–O–C stretch); UV–vis max (xylenes) 506 nm (ϵ 3650).

Anal. Calcd. for $C_{25}H_{23}NSO_5$: C, 66.82; H, 5.12; N, 3.12; S, 7.13. Found: C, 66.86; H, 5.08; N, 3.04; S, 7.00.

1-Anilino-4-(tosyloxy)anthraquinone (2c) was prepared from **1** and aniline. The yield was 79% and the mp 185–186 °C: mass spectrum, *m/e* 469 (M^+), 314 ($M - C_7H_7SO_2$), 155 ($C_7H_7SO_2$), 91 (C_7H_7); ^1H NMR (CD_2Cl_2) δ 11.50 (br s, 1 H), 8.26–8.12 (m, 2 H), 8.02–7.87 (m, 2 H), 7.79–7.62 (m, 4 H), 7.54–7.13 (m, 7 H), 2.31 (s, 3 H); IR (Nujol) 1355 (asymmetrical SO_2 stretch), 1184 (symmetrical SO_2 stretch), 945, 872, 840, 822, 810, 800, 788, 755 cm^{-1} (S–O–C stretch); UV–vis max (xylenes) 500 nm (ϵ 7000).

Anal. Calcd for $C_{27}H_{19}NSO_5$: C, 69.08; H, 4.05; N, 2.98; S, 6.82. Found: C, 68.82; H, 4.11; N, 2.85; S, 7.04.

Preparation of 1,4-Diaminoanthraquinones (Unsymmetrical or Symmetrical, 3a–d). The general method for the preparation of these compounds is given.

1,4-Bis(alkylamino)anthraquinones 3a–c. The appropriate 1-amino-4-(tosyloxy)anthraquinone was dissolved in pyridine, amine (~800 molar excess) added, and the solution heated between 60 and 100 °C for 3–24 h. The reaction was conveniently followed by TLC (SiO_2; Hex/EtOAc, 90:10). The starting material gave a red spot (R_f ~0.20) and the product a blue spot (R_f ~ 0.60–0.70). When reaction was complete, as judged by TLC, the liquids were removed by evaporation; CCl_4 added to the residue and the slurry filtered. The blue filtrate was placed on a column of silica gel, the column eluted with Hex/EtOAc (90:10) and the blue band collected. Further purification was achieved, especially if any phenolic material (violet) was present, by chromatography through a short alumina column or by preparative TLC. The compounds could be purified by recrystallization ($EtOH/H_2O$).

1,4-Bis(arylamino)anthraquinone 3d. The appropriate 1-(arylamino)-4-(tosyloxy)anthraquinone was dissolved in Me_2SO, the aromatic amine added (~2000 molar excess), and the solution heated at 180 °C for 3 h. The reaction was followed by TLC as described above. When reaction was complete, the solution was cooled, poured into 10% aqueous HCl, extracted with CH_2Cl_2 and

(19) Sudbury, B. A.; Zielske, A. G. U.S. Patent 4 457 855, 1984.

the CH_2Cl_2 washed with water and dried over $MgSO_4$. After filtration, the solvent was evaporated and the residue dissolved in CCl_4. Purification proceeded as described above.

1-(Isopropylamino)-4-(*n*-propylamino)anthraquinone (3a) was prepared from **2a** and *n*-propylamine. The yield was 67% and the mp 120–121 °C: mass spectrum, *m/e* 322 (M^+), 307 (M – CH_3), 293 (M – C_2H_5), 279 (307 – CO), 251 (M – 2CO); ^1H NMR (CD_2Cl_2) δ 10.99 (br s, 1 H), 10.88 (br s, 1 H), 8.39–8.22 (m, 2 H), 7.77–7.59 (m, 2 H), 7.27 (s, 2 H), 3.90 (m, 1 H), 3.46–3.28 (m, 2 H), 1.81–1.58 (m, 2 H), 1.39, 1.32 (d, 6 H), 1.26–1.07 (t, 3 H); vis max (xylenes) 598 nm (ε 14 100), 646 (16 200).

Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.53; H, 6.83; N, 8.70. Found: C, 74.55; H, 6.92; N, 8.80.

1-(Ethylamino)-4-(*n*-propylamino)anthraquinone (3b) was prepared from **2b** and *n*-propylamine. The yield was 65% and the mp 152–153.5 °C: mass spectrum, *m/e* 308 (M^+), 293 (M – CH_3), 279 (M – C_2H_5); ^1H NMR (CD_2Cl_2) δ 10.70 (br s, 2 H), 8.37–8.23 (m, 2 H), 7.75–7.38 (m, 2 H), 7.20 (s, 2 H) 3.56–3.24 (m, 4 H), 1.97–1.58 (m, 2 H), 1.44–1.29 (t, 3 H), 1.14–0.98 (t, 3 H); vis max (xylenes) 598 nm (ε 15 100), 646 (17 300).

Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 74.02; H, 6.49; N, 9.09. Found: C, 73.99; H, 6.52; N, 9.06.

1,4-Bis(*n*-butylamino)anthraquinone (3c) was prepared from 1 and *n*-butylamine. The yield was 68% and mp 120–121 °C: mass spectrum, *m/e* 350 (M^+), 307 (M – C_3H_7); ^1H NMR (CD_2Cl_2) δ 10.76 (br s, 2 H), 8.34–8.19 (m, 2 H), 7.74–7.57 (m, 2 H), 7.20 (s, 2 H), 3.48–3.27 (m, 4 H), 1.88–1.30 (m, 8 H), 1.06–0.91 (t, 6 H); vis max (xylenes) 600 nm (ε 15 000), 648 (17 300).

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.50; H, 7.42; N, 7.84.

1-Anilino-4-(3,5-dimethylanilino)anthraquinone (3d) was prepared from **2c** and 3,5-dimethylaniline. The yield was 56% and mp 219.5–220.5 °C: mass spectrum, *m/e* 418 (M^+); ^1H NMR (CD_2Cl_2) δ 12.20 (br s, 2 H), 8.41–8.30 (m, 2 H), 7.80–7.69 (m, 2 H), 7.52–7.34 (m, 7 H), 6.90 (br s, 3 H), 2.32 (s, 6 H); UV–vis max (xylenes) 404 nm (ε 6600), 600 (13 400), 641 (14 400).

Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.38; H, 5.26; N, 6.70. Found: C, 80.11; H, 5.14; N, 6.54.

1,4-Bis(tosyloxy)-2,3-dimethylanthraquinone (4). Application of the method (MeCN, Et_3N) described for 1,4-bis(tosyloxy)anthraquinone gave dark material that needed column chromatography treatment (76% yield) before being recrystallized (65% yield). A better procedure follows. *p*-toluenesulfonyl chloride (4.38 g, 23 mmol) and 2,3-dimethylquinizarin[9] (1.2 g, 4.5 mmol) were dissolved in CH_2Cl_2 (360 mL) and combined with aqueous sodium hydroxide (0.25%, 620 mL, 38 mmol), to which tetrabutylammonium bromide (TBAB, 7.5 g, 23 mmol) had been added. The two-phase system was stirred rapidly, in a Morton flask, for 2 days at room temperature. The course of the reaction could be followed by TLC (SiO_2, CH_2Cl_2). The CH_2Cl_2 layer was separated, washed with water, and dried over $MgSO_4$. After filtration, the solvent was removed by evaporation and the residue stirred with CCl_4 (100 mL) for 1 h. Filtration of the slurry gave an orange solid. The dried solid (2.40 g, 95%) had mp 220–223 °C. Recrystallization ($CHCl_3$–petroleum ether) gave a yellow solid of mp 228–229 °C: mass spectrum, *m/e* 576 (M^+), 421 (M – $C_7H_7SO_2$), 267 (M – $2C_7H_7SO_2$ + H), 155 ($C_7H_7SO_2$), 91 (C_7H_7); ^1H NMR (CD_2Cl_2) δ 7.86–7.65 (m, 10 H), 7.33–7.24 (m, 2 H), 2.36 (s, 6 H), 2.08 (s, 6 H); IR (Nujol) 1310 cm^{-1} (asymmetrical SO_2 stretch), 1170 cm^{-1} (symmetrical SO_2 stretch), 905, 745 cm^{-1} (S–O–C stretch); UV–vis max (CH_2Cl_2) 332 nm (ε 4210).

Anal. Calcd for $C_{30}H_{24}S_2O_8$: C, 62.50; H, 4.17; S, 11.11. Found: C, 62.28; H, 4.32; S, 11.07.

Preparation of Sterically Hindered Aminoanthraquinones 5a–d. General Method. The 1,4-bis(tosyloxy)-2,3-dimethylanthraquinone was dissolved in pyridine, the appropriate amine added (600 molar excess), and the solution heated between 60 and 180 °C for various time periods. For low-boiling amines a Parr bomb was used. The reaction was conveniently followed by TLC (SiO_2; Hex/EtOAc, 90:10). When reaction was complete, as judged by TLC, the liquids were removed by evaporation, CCl_4 (or Hex) was added to the residue, and the slurry was filtered. The filtrate was placed on a column of silica gel and eluted with Hex/EtOAc (90:10) and the appropriate band collected. Further purification could be achieved, especially if any phenol material (violet) is present by chromatography through a short alumina column or by preparative TLC (silica gel). The compounds could also be recrystallized ($EtOH/H_2O$).

1,4-Bis(*tert*-butylamino)-2,3-dimethylanthraquinone (5a) was prepared from 4 and *tert*-butylamine at 180 °C for 18 h (Parr bomb). The yield was 77% of red solid with mp 171–173 °C: mass spectrum, *m/e* 378 (M^+), 363 (M – CH_3), 266 (M – $2C_4H_9$ + 2H), 238 (266 – CO); ^1H NMR (CD_2Cl_2) δ 8.19–8.05 (m, 2 H), 7.81–7.65 (m, 2 H), 7.33 (br s, 2 H), 2.41 (s, 6 H), 1.09 (s, 18 H); vis max (xylenes) 526 nm (ε 3540).

Anal. Calcd for $C_{24}H_{30}N_2O_2$: C, 76.19; H, 7.94; N, 7.41. Found: C, 76.03; H, 7.81; N, 7.31.

1,4-Bis(isopropylamino)-2,3-dimethylanthraquinone (5b) was prepared from 4 and isopropylamine at 60 °C for 5 days. The yield was 81.6% of violet-blue solid with mp 117.5–118.5 °C: mass spectrum, *m/e* 350 (M^+), 335 (M – CH_3), 333 (M – OH), 307 (335 – CO); ^1H NMR (CD_2Cl_2) δ 9.06, 8.96 (br d, 2 H), 8.29–8.19 (m, 2 H), 7.79–7.65 (m, 2 H), 3.48 (m, 2 H), 2.33 (s, 6 H), 1.18, 1.11 (d, 12 H); vis max (xylenes) 570 nm (ε 6940).

Anal. Calcd for $C_{22}H_{26}N_2O_2$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.32; H, 7.51; N, 7.95.

1,4-Bis(neopentylamino)-2,3-dimethylanthraquinone (5c) was prepared from 4 and neopentylamine at 90 °C for 24 h. The yield was 82% of blue solid with mp 108–110 °C: mass spectrum, *m/e* 406 (M^+), 349 (M – C_4H_9) 292 (M – $2C_4H_9$); ^1H NMR (CD_2Cl_2) δ 9.97 (br s, 2 H), 8.35–8.21 (m, 2 H), 7.78–7.63 (m, 2 H), 3.00 (br s, 4 H), 2.33 (s, 6 H), 0.96 (s, 18 H); vis max (xylenes) 594 (ε 8120).

Anal. Calcd for $C_{26}H_{34}N_2O_2$: C, 76.85; H, 8.37; N, 6.90. Found: C, 76.60; H, 8.41; N, 6.84.

1,4-Bis(dimethylamino)-2,3-dimethylanthraquinone (5d) was prepared from 4 and dimethylamine at 100 °C for 22 h (Parr bomb). The yield was 55% of red solid with mp 127–128 °C: mass spectrum, *m/e* 322 (M^+), 305 (M – OH); ^1H NMR (CD_2Cl_2) δ 8.17–8.06 (m, 2 H), 7.74–7.64 (m, 2 H), 2.78 (s, 12 H), 2.34 (s, 6 H); vis max (xylene) 494 nm (ε 2400).

Anal. Calcd for $C_{20}H_{22}O_2$: C, 74.53; H, 6.83; N, 8.70. Found: C, 74.34; H, 6.96; N, 8.43.

1-(Tosyloxy)anthraquinone (6). The 1-hydroxyanthraquinone (2.5 g, 11 mmol; Aldrich Chemical Co.) was suspended in hot MeCN (200 mL); to this was added Et_3N (10 mL, 71 mmol) and *p*-toluenesulfonyl chloride (4.0 g, 21 mmol). This solution was heated at reflux for 5 h with stirring, following the course of reaction by TLC (SiO_2; CH_2Cl_2). The solvents were removed via rotary evaporator, CH_2Cl_2 (150 mL) was added, and the CH_2Cl_2 was washed with water (3 × 80 mL) and dried over $MgSO_4$. After filtration, the solvent was removed by evaporation to give an orange/brown solid (4.0 g). The solid was dissolved in hot $CHCl_3$ (15 mL) and petroleum ether (bp 30–60 °C, 35 mL) added and then cooled in an ice bath to give a yellow solid suspended in an orange/brown solution. The yellow solid was isolated by filtration and upon drying gave 3.4 g (81% yield) of a solid with mp 148–149 °C: mass spectrum, *m/e* 378 (M^+), 155 ($C_7H_7SO_2$), 91 (C_7H_7); ^1H NMR (CD_2Cl_2) δ 8.33–7.98 (m, 2 H), 7.88–7.43 (m, 7 H), 7.34–7.24 (m, 2 H), 2.36 (s, 3 H); IR (Nujol) 1680 (C=O), 1325 (asymmetrical SO_2 stretch), 1178 (symmetrical SO_2 stretch), 875, 835, 802, 750 cm^{-1} (S–O–C stretch); UV–vis max (CH_2Cl_2) 328 nm (ε 4800).

Anal. Calcd for $C_{21}H_{14}SO_5$: C, 66.67; H, 3.70; S, 8.46. Found: C, 66.45; H, 3.90; S, 8.38.

Preparation of 1-Aminoanthraquinones 7a,b. General Method. 1-(Tosyloxy)anthraquinone (6) was dissolved in pyridine, the appropriate amine (200 molar excess) added, and the solution heated between 60–180 °C for 2–18 h. For low-boiling amines a Parr bomb was used. The reaction was conveniently followed by TLC (SiO_2; Hex/EtOAc, 80:20). The 1-aminoanthraquinone products gave a bright red spot on TLC. When reaction was complete, as judged by TLC, the liquids were removed by means of a rotary evaporator; CCl_4 was added to the residue and the slurry filtered. The filtrate was placed on a column of silica gel, the column eluted with Hex/EtOAc (90:10), and the red band collected. Further purification can be achieved, especially if phenolic material is present, by chromatography through a short alumina column or by preparative TLC (silica gel). Purification can also be achieved by recrystallization ($ETOH/H_2O$).

1-(*n*-Propylamino)anthraquinone (7a) was prepared from 6 and *n*-propylamine at 60–70 °C for 3 h. The yield of red solid was 77% and the mp 149–150.5 °C: mass spectrum, *m/e* 265 (M^+)

236 ($M - C_2H_5$), 208 (236 – CO), 180 (208 – CO); ^1H NMR (CD_2Cl_2) δ 9.72 (br s, 1 H), 8.30–8.14 (m, 2 H), 7.84–7.61 (m, 2 H), 7.56–7.46 (m, 2 H), 7.15–7.01 (m, 1 H), 3.41–3.20 (m, 2 H), 1.91–1.56 (m, 2 H), 1.16–1.00 (t, 3 H); vis max (xylenes) 502 nm (ε 6760).

Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.98; H, 5.66; N, 5.28. Found: C, 76.86; H, 5.72; N, 5.22.

1-Anilinoanthraquinone (7b) was prepared from **6** and aniline in Me_2SO at 180 °C for 2 h. The yield of red solid was 77% with mp 136–138 °C: mass spectrum, *m/e* 299 (M^+); ^1H NMR (CD_2Cl_2) δ 11.32 (br s, 1 H), 8.33–8.16 (m, 2 H), 7.86–7.65 (m, 2 H), 7.61–7.12 (m, 8 H); vis max (xylenes) 501 nm (ε 6200).

Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.27; H, 4.35; N, 4.68. Found: C, 80.42; H, 4.35; N, 4.69.

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Stereospecific Synthesis of the Enantiomers of Verapamil and Gallopamil

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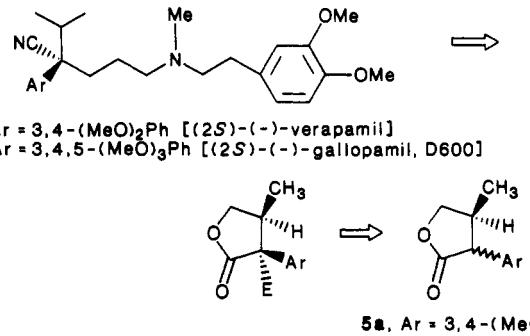
Stereospecific synthesis of the title compounds has been achieved in >95% ee by use of optically active 1,2-propanediols. Nucleophilic displacement of the chiral secondary mesylate **4a**, derived in one step from (2*S*)-(+)-1,2-propanediol (**3a**), with the dianion of 3,4-dimethoxyphenylacetic acid, proceeded with Walden inversion. Subsequent hydrolysis of the trityl protecting group afforded a mixture of (2*R*,3*S*)- and (2*S*,3*S*)-butyrolactones **5a** that, upon alkylation of their sodium enolates with allyl bromide, gave (2*S*,3*S*)-butyrolactone **6a**. Further elaboration afforded (2*S*)-(–)-verapamil (**1a**) in 45% overall yield. Its antipode, **1b**, was synthesized from (2*R*)-(–)-1,2-propanediol (**3b**), and the enantiomers of gallopamil (**2a**, **2b**) were prepared in analogous fashion.

Verapamil and gallopamil are important calcium slow-channel antagonists, useful in the treatment of a variety of cardiovascular disorders. Verapamil, the first calcium channel blocking agent approved in the United States, is used as a racemate orally for the treatment of vasospastic and classical angina pectoris and parenterally for the treatment of superventricular tachycardia. Use in other cardiovascular diseases is under study.

The pharmacological properties of the (–) and (+) enantiomers of verapamil and of gallopamil appear to be quite different. Highly stereoselective effects on the fast sodium ion current and the slow calcium ion current have been noted.[1-6] The (–) enantiomer of each of these agents has greater effects on the slow calcium ion current. In dogs and rabbits, differential pharmacological effects of the enantiomers on the myocardium are noted. Stereoselective metabolism also occurs with substantial "first-pass" metabolism of the more active (–) enantiomer.[7,8] These observations may account for the poor ability to correlate plasma concentration of the racemic drug to cardiovascular measurements and effects.[9-13] Thus, there exists a significant need for methods to obtain the individual enantiomers to allow for further pharmacological and metabolic study.

Scheme I



To date, the only methods available for obtaining the enantiomers of these compounds involve the tedious resolution of diastereomeric salts.[14-16] We herein report the first stereoselective synthesis of the enantiomers of verapamil and gallopamil via a route that should also be applicable to the preparation of analogues containing a quaternary carbon.

In planning a synthetic route toward (2*S*)-(–)-verapamil (**1a**), we chose (3*S*)-methyl-2-(3,4-dimethoxyphenyl)-butyrolactone (**5a**) as our more immediate target (Scheme I). With **5a** in hand, alkylation of its enolate with an

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