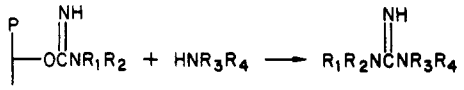
Table I. Synthesis and Properties of N^G-Alkylarginines

derivative[a] synthesized	ornithine or lysine bound,[b] μmol/g	release with amine[c] arginine derivative, μmol/g	release with amine[c] ornithine or lysine,[d] μmol/g	% yield of purified derivative	R_f on electrophoresis[e]	retention[f] time, min	$[\alpha]^{25}_D$[g]
Arg	74.3	49.5	6.9	66.4	1.00	50	+23
N^G-MeArg	72.8	48.2	7.5	66.2	0.95	48	+26
N^G,N^G-Me_2Arg	66.3	46.2	7.3	69.7	0.90	48	+24.8
N^G-EtArg	68.4	43.6	2.9	63.6	0.90	60	+23.8
N^G-BuArg	58.6	38.2	5.4	66.2	0.83	97	+24.2
N^G-HeArg	78.6	51.3	7.4	65.2	0.76	132	
HoArg	76.0	61.2	15.8	79.5	1.00	60	
N^G-MeHoArg	104.3	81.2	18.8	81.0	0.95	58	
N^G,N^G-Me_2HoArg	78.3	63.4	12.7	80.0	0.95	50	

[a] Abbreviation used: Me = methyl, Ho = homo, Et = ethyl, Bu = butyl, He = hexyl. [b] Each experiment was performed on ornithine or lysine newly coupled to cellulose. [c] Polymers containing ornithine or lysine were incubated with different amines for 24 h at 50 °C. [d] Products of hydrolysis. [e] The electrophoresis was performed in pyridine–acetate buffer, pH 3.5, for 35 min at 70 V/cm. [f] Amino acid analysis on the short column in sodium citrate buffer, pH 5.28.[6] [g] Cl, 1 N HCl.

Scheme I



R_1, R_2, R_3, and R_4 are either H or an alkyl group and P is a polysaccharide

cycle of reactions. We used the cellulose at least three times, without any loss of efficiency. The procedure described was also used to synthesize other guanidines including agmatine, creatin, and α-guanido amino acids.

Experimental Section

Cellulose was from Whatman. Sepharose and Sephadex were from Pharmacia. Alkylamines and cyanogen bromide were from Fluka AG. Amino acid analysis were performed on a Beckman 120 after acid hydrolysis (6 M HCl, 100 °C, 24 h).[6] The NMR spectra were measured on a Varian A60 spectrometer, using tetramethylsilane as an internal standard (δ 0) and D_2O as solvent. Silica gel was used for thin-layer chromatography. High-voltage electrophoresis on Whatman no. 3MM papers was run at pH 3.5 for 35 min at 70 V/cm.

Preparation of Lysine- or Ornithine-Copper Complex.[7] Lysine or ornithine (10 g) was dissolved in 100 mL of water and brought to boiling. $CuCO_3$ was slowly added, until no more $CuCO_3$ was solubilized (5 min). The mixture was filtered to remove excess $CuCO_3$ and the blue solution was brought to pH 10 with KOH and used for coupling.

Activation of Cellulose by Cyanogen Bromide. Cellulose (10 g) was suspended in 25 mL of 2 M K_2CO_3 and cooled to 4 °C. CNBr (15 g) dissolved in dimethylformamide or acetonitrile was added and the mixture was stirred vigorously for 10 min. The suspension was filtered and washed with cold water and sodium bicarbonate (0.2 M).

Binding of Lysine or Ornithine Complex. A solution of the copper complex (30 mL) was added to the filtered activated cellulose (10 g) at 4 °C and was stirred overnight. The reaction mixture was filtered to remove nonreacted complex and washed until the eluate was colorless. The blue cellulose cake was treated with 1 M HCl (30 mL) to destroy the copper complex; it was then filtered and washed with water. The amount of ornithine or lysine coupled (about 100 μmol/g) was determined by amino acid analysis after total hydrolysis.

Synthesis of N^G-Alkylarginines. All the N^G-alkylarginines were synthesized similarly. A typical example for the synthesis is the preparation of N^G-methylarginine. Ornithine–cellulose (20 g) was incubated for 24 h at 50 °C with a 20% solution of methylamine in water (60 mL). The suspension was filtered and washed. The filtrate, together with the washings, was concentrated to dryness in vacuo. The residue was dissolved again in water and concentrated to dryness. It was again dissolved in 5 mL water, brought to pH 5 with hydrochloric acid, and again concentrated to dryness. It was finally dissolved in 2 mL of water and crystallized by the addition of 30 mL of ethanol. Electrophoresis of the product revealed the presence of N^G-methylarginine (90%) and about 5% each of ornithine and methylcitrulline. The product was purified on a DOWEX 50(H^+) column, using a gradient of NH_4OH from 0.1–1.5 M, concentrated to dryness, and crystallized from water–ethanol; NMR δ 3.75 (α-CH), 3.26 (NCH_2), 1.75 (CH_2CH_2), 2.85 (N^G-CH_3). Thin-layer chromatography in several solvents showed one spot identical with an authentic commercial sample when sprayed with ninhydrin. The product was also coeluted with N^G-methylarginine from the amino acid analyzer. Details of other derivatives synthesized are given in Table I. All the derivatives synthesized had good C, H, N analyses.

Registry No. Lysine, 56-87-1; ornithine, 70-26-8; Arg, 74-79-3; N^G-MeArg, 17035-90-4; N^G,N^G-Me_2Arg, 30315-93-6; N^G-EtArg, 20933-81-7; N^G-BuArg, 75830-51-2; N^G-HeArg, 75830-52-3; HoArg, 156-86-5; N^G-MeHoArg, 75830-53-4; N^G,N^G-Me_2HoArg, 75830-54-5.

(6) D. H. Spackman, W. H. Stein, and S. Moore, *J. Biol. Chem.*, **235**, 648–659 (1960).
(7) R. L. M. Synge, *Biochem. J.*, **42**, 99–107 (1948).

Conversion of Alkoxy-9,10-anthraquinones to Alkoxyanthracenes

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Reduction of 9,10-anthraquinones is often required as a final step in the preparation of fully aromatic anthracenes. Although several reductive systems may be used for the parent compound[1] and its simple derivatives, efficient reductive aromatization methods are not available for *peri*-alkoxy-9,10-anthraquinones. Acidic reduction conditions are not compatible with the presence of *peri*-alkoxy groups.[2,3] The traditionally employed zinc–aqueous ammonia method failed in the case of 1,5-dimethoxyanthraquinone;[3] furthermore, this reductive system is often unreliable[1,4] and frequently experimentally difficult. A direct conversion to alkoxyanthracenes[5,6] observed during treatment of alkoxy-9,10-anthraquinones with cyclohexyl

(1) M. Konieczny and R. G. Harvey, *J. Org. Chem.*, **44**, 4813 (1979), and references cited therein.
(2) G. F. Attree and A. G. Perkin, *J. Chem. Soc.*, 144 (1931).
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(4) M.-J. Brienne and J. Jacques, *Bull. Chim. Soc. Fr.*, 190 (1973).
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(6) D. W. Cameron and P. E. Schütz, *J. Chem. Soc. C*, 2121 (1967).

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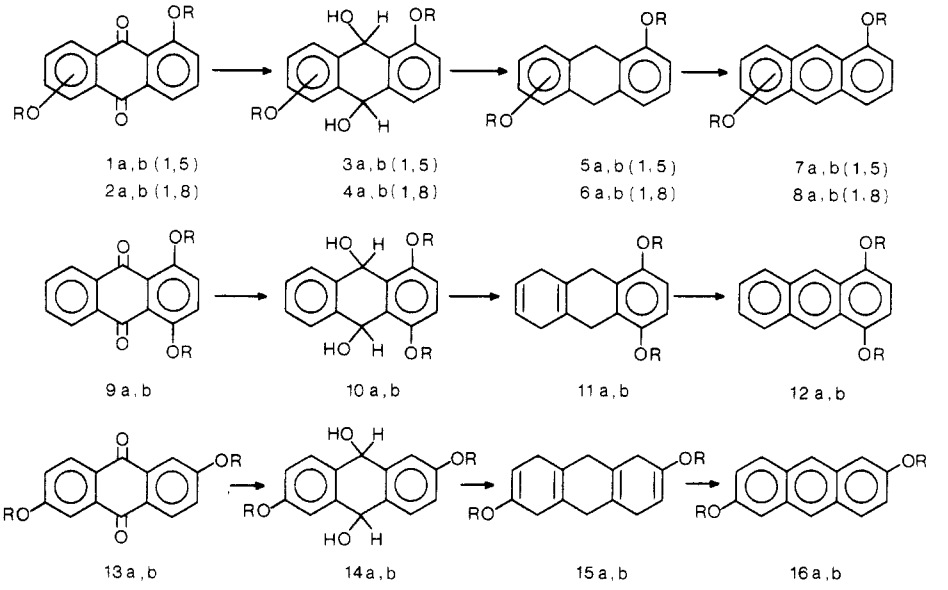
Scheme I[a]



[a] a, R = Me; b, R = Et.

Table I. Reduction-Dehydrogenation of Alkoxyanthraquinones. Yields, Melting Points, and Analytical Data of Isolated Compounds

		9,10-dihydro-9,10-anthracenediol			reduced anthracene			anthracene		
anthraquinone			% yield	mp,[a] °C		% yield	mp, °C		% yield	mp, °C
1,5-dimethoxy	1a	3a	90	235-238	5a[b]	90	141-142[c]	7a	85	229-230[d]
1,5-diethoxy	1b	3b	90	165-170	5b[b,e]	95	138-139	7b	90	179-180[f]
1,8-dimethoxy	2a	4a	95	190-196	6a[b,g]	95	111-112	8a	80	197[h]
1,8-diethoxy	2b	4b	90	170-175	6b[b,i]	90	108-109	8b	85	134-135[j]
1,4-dimethoxy	9a	10a	90	147-148[k]	11a[l,m]	95	95-96	12a	65	125-126[n]
1,4-diethoxy	9b	10b	90	112-114	11b[l,o]	90	122-123	12b[p]	60	86-88
2,6-dimethoxy	13a	14a	80	190-192	15a[q,r]	70	123-124	16a	65	260-262[s]
2,6-diethoxy	13b	14b	85	117-120	15b[q,t]	65	139-140	16b	60	227-228[u]

[a] Melting range is due to the presence of a mixture of cis-trans isomers. [b] 9,10-Dihydro derivative. [c] Lit.[3] mp 147-147.5 °C. [d] Lit.[6] mp 228 °C. [e] NMR δ 7.41-6.7 (aromatic protons, 6), 4.15 (q, 4, OCH_2), 4.05 (s, 2, H-9 and H-10), 1.45 (t, 6, CH_3); mass spectrum, *m/e* 268. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.80; H, 7.59. [f] Lit.[11] mp 179 °C. [g] NMR δ 7.46-6.7 (aromatic protons, 6), 4.03 (s, 4, H-9 and H-10), 3.95 (s, 6, OCH_3); mass spectrum, *m/e* 240. Anal. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 79.86; H, 6.87. [h] Lit.[6] mp 198 °C. [i] NMR δ 7.46-6.75 (aromatic protons, 6), 4.19 (q, 4, OCH_2), 4.05 (br s, 4, H-9 and H-10), 1.48 (t, 6, CH_3); mass spectrum, *m/e* 268. Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.47; H, 7.75. [j] Lit.[11] mp 139 °C. [k] Lit.[7] mp 141-143 °C. [l] 5,8,9,10-Tetrahydro derivative. [m] NMR δ 6.76 (s, 2, H-2 and H-3), 5.92 (s, 2, vinyl protons), 3.86 (s, 6, CH_3), 3.23 (s, 4, H-9 and H-10), 2.76 (s, 4, H-5 and H-8); mass spectrum, *m/e* 242. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.08; H, 7.71. [n] Lit.[7] mp 134-136 °C. [o] NMR δ 6.71 (s, 2, H-2 and H-3), 5.91 (s, 4, vinyl protons), 4.1 (q, 4, OCH_2), 3.23 (s, 4, H-9 and H-10), 2.75 (s, 4, H-5 and H-8), 1.53 (t, 6, CH_3); mass spectrum, *m/e* 270. Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.65; H, 8.56. [p] NMR δ 8.71 (s, 2, H-9 and H-10), 6.5 (s, 2, H-2 and H-3), 8.16-7.33 (4, remaining aromatic protons), 4.18 (q, 4, OCH_2), 1.53 (t, 6, CH_3); mass spectrum, *m/e* 266. [q] 1,4,5,8,9,10-Hexahydro derivative. [r] Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.72; H, 8.48. Mass spectrum, *m/e* 244. [s] Lit.[12] 262 °C. [t] NMR δ 4.76 (unresolved m, 2), 3.88 (q, 4, OCH_2), 2.83-2.46 (12, allylic protons), 1.31 (t, 3, CH_3); mass spectrum, *m/e* 272. Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.43; H, 8.30. [u] Lit.[13] mp 229 °C.

p-toluenesulfonate and zinc in hot trichlorobenzene is of limited preparative value. A stepwise procedure via sodium borohydride reduction of intermediate anthrones (obtained by $NaBH_4$ reduction of anthraquinones, followed by dehydration of the resulting 9,10-dihydro-9,10-anthracenediols), adequate for a number of substituted anthraquinones, proceeded much less satisfactory when applied to the synthesis of 1,4-dimethoxyanthracene.[7]

In connection with work on the synthetic use of *peri*-alkoxyanthracenes as building units for carbocyclic systems we required a reliable and efficient procedure for the reductive aromatization of *peri*-alkoxyanthraquinones. This was readily accomplished by successive sodium borohydride–metal ammonia reductions of alkoxyanthraquinones to the 9,10-dihydroanthracene oxidation state. Dehydrogenation of the latter completed the desired overall anthraquinone → anthracene conversion. This procedure is best suited for 1,5- and 1,8-dialkoxy derivatives, because hydrogenolysis of the alcohol groups in the dihydrodiols is not accompanied by reduction of the aromatic rings under standard metal ammonia reduction conditions, in analogy with similarly constructed anisole derivatives.[8] We have found, not unexpectedly, that over reduction, observed in the other alkoxy derivatives, was readily corrected in the dehydrogenation step of our reaction sequence.

(7) T. R. Criswell and B. H. Klanderman, *J. Org. Chem.*, **39**, 770 (1974).

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Thus, reduction of 1,4-9, 1,5-1, and 1,8-2 dimethoxy- and diethoxyanthraquinones with sodium borohydride, under reaction conditions identical with those employed for other substituted anthraquinones,[7] gave the corresponding 9,10-dihydro-9,10-anthracenediols **10**, **3**, and **4**, respectively, in 90–95% yield[9] (Scheme I). They were generally obtained as a mixture of cis and trans isomers; their composition was not further investigated, because the stereochemistry is irrelevant in the further transformations. These dihydrodiols were used without purification in the next reaction step, because attempted recrystallization frequently led to products that showed carbonyl groups in the infrared spectrum.[10] Addition of lithium or sodium to a solution of dihydrodiols **3a,b** and **4a,b** in a mixture of anhydrous ammonia, tetrahydrofuran, and ethanol gave dihydroanthracenes **5a,b** and **6a,b**, respectively, in 95% yield. As expected, no reduction of the alkoxy-substituted aromatic moieties was observed. Dihydroanthracenes **5** and **6** were smoothly dehydrogenated with an equivalent amount of *p*-chloranil in toluene to give alkoxyanthracenes **7** and **8** in 85% yield.

Reductive elimination of the hydroxyl groups of dihydrodiol **10a,b** was accompanied by reduction of the unsubstituted aromatic ring resulting in the formation of tetrahydroanthracene **11a,b** (95%). Dehydrogenation with the calculated amount of *p*-chloranil gave 1,4-dialkoxyanthracenes **12a,b** (65%). Treatment of dihydrodiol **14a,b**, derived from 2,6-dialkoxyanthraquinone, with alkali metal in liquid ammonia resulted in reduction of both aromatic nuclei with concomitant hydroxyl group elimination to give hexahydroanthracene **15a,b** (70%). Dehydrogenation as above gave 2,6-dialkoxyanthracene **16a,b** (65%).

These results demonstrate that the alkoxyanthraquinone → alkoxyanthracene conversion via the 9,10-dihydroanthracene oxidation stage is an attractive strategy for peri-substituted derivatives. The synthetic sequence may also be employed for the synthesis of other alkoxyanthracenes, although in lower overall yield.

Experimental Section

General. NMR spectra were recorded in $CDCl_3$ with a Varian A-60 spectrometer, using Me_4Si as an internal standard. Mass spectra were recorded on a Perkin-Elmer 137 spectrophotometer. All melting points are uncorrected. Microanalyses were done by Galbraith Laboratories, Knoxville, TN.

General Procedure for Alkoxy-9,10-anthraquinone Reductions. 9,10-Dihydro-9,10-anthracenediols. Sodium borohydride (0.03 mol) was added in small portions to a stirred suspension of the anthraquinone (0.01 mol) in methanol (75 mL) at 0–5 °C. Stirring was continued at this temperature for an additional 2 h. The reaction mixture was poured in water and the resulting precipitate was collected and was washed well with water. The yield of product was 80–95%. The dihydrodiols showed no residual carbonyl absorptions in their infrared spectra and gave satisfactory NMR spectra.

General Procedure for Conversion of 9,10-Dihydro-9,10-anthracenediols to Reduced Anthracenes. Lithium (or sodium) metal (4–8 equiv) was added in small portions to a solution of the 9,10-dihydro-9,10-anthracenediol (0.01 mol) in a mixture of anhydrous ammonia (300 mL), tetrahydrofuran (100 mL), and absolute ethanol (30 mL). The mixture was stirred for an additional 0.5 h. After evaporation of the ammonia, water was added and the resulting mixture was extracted with ether. The ether extracts were washed with water and dried. The ether was removed on a rotary evaporator and the residue was recrystallized from methanol or ethanol. Yields, melting points, and spectroscopic data are collected in Table I.

General Procedure for Aromatization of Reduced Anthracenes. A mixture of the reduced alkoxyanthracene (dihydro, tetrahydro, or hexahydro) (0.01 mol) and *p*-chloranil (slight excess over the theoretical amount) in 100 mL of toluene was refluxed with stirring for 1 h. The mixture was poured in water and was then extracted with ether. The ether extracts were washed successively with aqueous sodium hydrosulfite, potassium hydroxide, and finally water. The residue obtained after evaporation of the solvent was dissolved in benzene and percolated through a short column of Florisil to afford pure alkoxyanthracenes (Table I).

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Registry No. **1a**, 6448-90-4; **1b**, 22924-22-7; **2a**, 6407-55-2; **2b**, 16294-26-1; **3a**, 75829-87-7; **3b**, 75829-88-8; **4a**, 75829-89-9; **4b**, 75829-90-2; **5a**, 75829-91-3; **5b**, 75829-92-4; **6a**, 75829-93-5; **6b**, 75829-94-6; **7a**, 16294-32-9; **7b**, 75829-95-7; **8a**, 16294-34-1; **8b**, 75829-96-8; **9a**, 6119-74-0; **9b**, 75829-97-9; **10a**, 75829-98-0; **10b**, 75829-99-1; **11a**, 75847-32-4; **11b**, 75847-33-5; **12a**, 13076-29-4; **12b**, 75830-00-1; **13a**, 963-96-2; **13b**, 24884-87-5; **14a**, 75830-01-2; **14b**, 75830-02-3; **15a**, 75930-03-4; **15b**, 75830-04-5; **16a**, 36319-03-6; **16b**, 75830-05-6.

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Preparation of Substituted 2-Pyridones by Thermal Rearrangement of Propargylic Pseudoureas. Improvements in the 2-Pyridone Yields by Variations of the Pseudourea NR_2 Substituent

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We recently reported[1,2] that 3,6-dialkyl- (and -diaryl-) 2-pyridones[3] could be conveniently prepared from propargylic alcohols by the thermal rearrangement of propargylic pyrrolidine pseudoureas (Scheme I). When R^6 was an alkyl group, the overall yields of 2-pyridones obtained in this way were excellent. However, when R^6 was hydrogen or an aryl group, the 2-pyridone yields were not satisfactory, since competing nucleophilic addition of the imino nitrogen to the alkyne to give ultimately a substituted oxazole (see Scheme I) was a dominant reaction pathway.[4] Since intramolecular alkyne addition was not observed in related rearrangements[5] of less basic propargylic trichloroacetimidates, we felt that the 2-pyridone synthesis of Scheme I could be improved by employing pseudoureas *less basic* (*and consequently less nucleo-*

(1) (a) Overman, L. E.; Tsuboi, S. *J. Am. Chem. Soc.* **1977**, *99*, 2813. (b) Overman, L. E.; Tsuboi, S.; Roos, J. P.; Taylor, G. F. *Ibid.* **1980**, *102*, 747.

(2) See also: Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218.

(3) 2(1*H*)-Pyridinones.

(4) For other examples of this oxazole-forming reaction and leading references see: Overman, L. E.; Tsuboi, S; Angle, S. *J. Org. Chem.* **1979**, *44*, 2323.

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