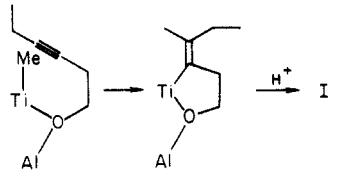
methylated olefinic alcohol (I) with 3-hexyn-1-ol. For reasons summarized previously[5] we favor a reaction scheme involving methylation of a titanium center followed by an intramolecular syn carbotitanation of the yne group which on protonolysis yields I.



The ^1H NMR shift data for our product agree with those reported by others,[2,3] and in particular the peak at 1.69 ppm in the absence of one near 1.60 ppm is reliable evidence for the *Z* configuration.[9,10] The occurrence of the olefinic CH_3 group at 22.96 ppm in the ^{13}C NMR spectrum rather than in the 12–15-ppm region confirms the *Z* configuration arising from a syn addition,[11] which is observed in all group IVa–organoalane alkyne carbometalations.[5,6,8,12]

The NMR spectra do not, to this point, distinguish between the two syn addition possibilities, I and (*Z*)-3-methyl-3-hexen-1-ol. This ambiguity is resolved by reference to the ^{13}C NMR shift data for 4-methyl-3-penten-1-ol.[13] For this compound the disubstituted olefinic carbon resonance ($(CH_3)_2C=$) occurs at 134.64 ppm while that of the remaining olefinic carbon occurs at 120.21 ppm. From ^{13}C chemical shift additivity relationships one calculates that the chemical shift parameters (relative to ethylene) of the CH_2CH_2OH group in a trisubstituted olefin are $\alpha = 7.48$ and $\alpha' = -1.10$.[14] For I, olefinic carbon shifts (C_3 and C_4) are calculated to be 119.0 and 141.1 ppm,[15a] which are in excellent agreement with the shifts observed for our product. For the internally substituted product possibility, (*Z*)-3-methyl-3-hexen-1-ol, shifts of 130.5 and 129.6 ppm are calculated,[15b] clearly excluding this isomer from further consideration.

This work and that of others reported recently continues to suggest that early transition metal promoted carbometalation reactions may be synthetically useful and that further study is warranted.

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Registry No. I, 21019-60-3; 3-hexyn-1-ol, 1002-28-4; trimethylaluminum, 41561-11-9; titanium tetrachloride, 7550-45-0.

(9) D. J. Faulkner, *Synthesis*, 175 (1971).
(10) B. M. Trost, *Acc. Chem. Res.*, **3**, 120 (1970).
(11) (a) E. Breitmaier and W. Voelter, "^{13}C NMR Spectroscopy", 2nd ed., Verlag Chemie, Weinheim and New York, 1978; (b) E. Breitmaier, G. Haas, and W. Voelter, "Atlas of Carbon-13 NMR Data", Heyden, London, 1979.
(12) B. B. Snider, M. Karras, and R. S. E. Conn, *J. Am. Chem. Soc.*, **100**, 4624 (1978).
(13) This compound, which has no stereochemistry, has been synthesized by us via a carbometalation procedure and is unambiguously characterized by proton NMR to be free from the internal addition product, 3-methyl-3-penten-1-ol: ^{13}C NMR δ 62.30 (C_1), 31.60 (C_2), 120.21 (C_3)8 136.64 (C_4), 25.78 (CH_3 trans to H), 17.81 (CH_3 cis to H). Additional details are to be published.
(14) Referring to ref 9 one calculates the α and α' CH_2CH_2OH shift parameters relative to ethylene as follows: $\alpha = 120.2 - 123 - 2(-5.14) = 7.48$; $\alpha' = 134.6 - 123 - 2(6.35) = -1.10$.
(15) (a) C_3 shift = 123 + 7.48 + 2(−5.14) + (−1.22) = 119.0; C_4 shift = 123 + (−1.10) + 2(6.35) + 6.47 = 141.1; (b) C_3 shift = 123 + 7.48 + 6.35 − 5.14 − 1.22 = 130.5; C_4 shift = 123 + (−1.10) − 5.14 + 6.35 + 6.47 = 129.6.

Synthesis of Guanidino-*N*-alkylarginines by the Use of Polymeric Pseudoureas

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Guanidino-*N*-alkyl (N^G-alkyl) derivatives of arginine which retain the charge and have different hydrophobicity are required, in order to study the importance of the guanidino groups of arginine in peptides. The only known N^G-alkylarginine derivatives which are present in several proteins are N^G-methylarginine and N^G,N'^G-dimethylarginine.[1] These methylarginines were synthesized in low yield from the corresponding methyl pseudoureas and the copper complex of ornithine. The synthesis was complicated and required more than a week for the reaction and subsequent chromatographic purification.[2,3]

Recently we have shown that the reaction between polysaccharides and cyanogen bromide yields cyanoesters ($ROC{\equiv}N$),[4] which upon reaction with amines give polymeric pseudoureas ($POC(=NH)NR_1R_2$), where R^1 and R^2 are either H or alkyl groups.[5] These polymeric pseudoureas or N-substituted isoureas can be used for the synthesis of any unsymmetrical or symmetrical guanidine, as described in Scheme I.

In this report the use of the polymeric pseudoureas for the synthesis of the as yet unknown N^G-alkylarginines and N^G-alkylhomoarginines is described (Table I). The reaction is fast and the yields are high compared to other methods.

The insoluble polysaccharides agarose, Sephadex, and cellulose were activated with cyanogen bromide under conditions which were found to give the highest activation yield.[4] Excess copper complex of ornithine and lysine was added to the activated polymers in order to obtain the maximum coupling yield. The use of the copper complex enabled the binding of the amino acids through the ω-amino groups without covalent protection of the α-amino group. The copper complex also enabled the direct isolation of free arginine derivatives. The excess complex was not lost, since after the reaction it was filtered and used again after determination of the amount of complex left. The use of the copper complex also enabled the fast determination of the amount of amino acid coupled to the polymer by titration of the amount of copper bound. The amount of ornithine coupled was also determined by amino acid analysis after total hydrolysis. Of the many polysaccharides checked, the best were Sepharose and cellulose. We chose to continue with cellulose as carrier because of its low price, better stability, and ease of handling. Under optimal conditions the activated cellulose bound about 100 μmol/g of ornithine or lysine. Incubation of the ornithine- or lysine-containing polymers with different amines for 24 h at 50 °C gave the required arginines in high yield (Table I). No racemization was detected in the arginines synthesized. The optical rotations of the arginine and N^G-methylarginine prepared were identical with those of the commercially available products. The polysaccharide, after removal of the arginine, can be used again for the complete

(1) W. K. Pail and S. Kim, *Science*, **174**, 114–119 (1971).
(2) Y. Kakimoto and S. Akazawa, *J. Biol. Chem.*, **245**, 5751–5758 (1970).
(3) J. R. McDermott, *Biochem. J.*, **154**, 179–184 (1976).
(4) J. Kohn and M. Wilchek, *Biochem. Biophys. Res. Commun.*, **84**, 7–14 (1978).
(5) M. Wilchek, T. Oka, and Y. J. Topper, *Proc. Natl. Acad. Sci. U.S.A.*, **72**, 1055–1058 (1975).

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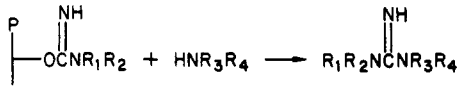
Table I. Synthesis and Properties of N^G-Alkylarginines

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).
(3) J. W. Cook and P. L. Pausen, *J. Chem. Soc.*, 2726 (1949).
(4) M.-J. Brienne and J. Jacques, *Bull. Chim. Soc. Fr.*, 190 (1973).
(5) W. Kelly and J. S. Shannon, *Austr. J. Chem.* **13**, 103 (1960).
(6) D. W. Cameron and P. E. Schütz, *J. Chem. Soc. C*, 2121 (1967).

0022-3263/81/1946-0809$01.00/0