after 3 h the sample was colorless. At the same time, there was no observable increase in the absorption due to unphotolyzed starting material.

Low-Temperature Irradiation of 2b at 254 and 350 nm. A. A Vycor tube was charged with 11.0 mg of **2b** and 32 ml of 3-methylpentane. After degassing, it was simultaneously irradiated at 77 K for 6 h using eight 254-nm and seven 350-nm lamps. Upon warmup to room temperature, the solution was colorless. NMR analysis of the concerned photolysis mixture showed a mixture of **2b** (63%) and **3b** (37%).

B. 2b (12.0 mg) was dissolved in 32 ml of 3-methylpentane in a Vycor tube, degassed, and sealed. The tube was irradiated for 3 h (eight 254-nm lamps) at 77 K and allowed to warm to room temperature. It was then irradiated at 30 °C for an additional 4.5 h (eight 350-nm lamps). At this point, the solution was colorless and free of polymer. NMR analysis of the mixture indicated 62% **2b** and 38% **3b**. In a control experiment 13.1 mg of **2b** in 32 ml of degassed 3-methylpentane was irradiated for 6.5 h (15 350-nm lamps). Removal of the solvent yielded 10.1 mg of the starting material (77%) and none of the exo isomer **3b**.

Trapping of 5b by Hydrogenation. A Vycor tube was charged with 15 mg of **2b** and 30 ml of 3-methylpentane. The tube was vigorously degassed with nitrogen, sealed, and irradiated at 254 nm (77 K) for 7 h. The solution was allowed to warm to −10 °C and rapidly transferred under nitrogen to a hydrogenation vessel containing 50 mg of prereduced PtO_2. The hydrogen pressure was maintained by a balloon for 15 h while stirring at 25 °C. The catalyst was filtered and GLC analysis (6 ft × ¼ in. glass, 10% SE-30 on 60/80 Gas Chromosorb Q, T-150 °C) showed the presence of starting material and dihydroderivative **10** in the ratio of 1:2. GLC collection on the above column (160 °C) yielded 9 mg of the bicyclic derivative **10** which was spectrally and chromatographically identical with a sample prepared by an independent route.

3,4-Benzobicyclo[4.2.1]nonane (10). 3,4-Benzotetracyclo-[4.3.0.$0^{2,8}$.$0^{5,7}$]nonane (**4**) (53 mg) was dissolved in pentane and hydrogenated (1 atm) for 1.5 h over Pd/C. Filtration and removal of the solvent yielded **10** in quantitative yield: mp 43.5–45 °C; ^{1}H NMR τ (CCl_4) 3.15 (br s, 4 H), 7.23 (d, J = 4.5 Hz), 7.57 (m, 2 H), 8.03 (m, 1 H), 8.38 (d, J = 12 Hz, 1 H), 8.39–9.0 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 142.4, 133, 127, 47, 46, 37, and 30; IR (neat) 3050, 3010, 2920, 2900, 1490, 1465, 1445, 1440, and 735 cm^{-1}; mass spectroscopic molecular weight 172. Anal. ($C_{13}H_{16}$): C, H.

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Communications to the Editor

A Polyamide Support for Oligonucleotide Synthesis

Sir:

Despite substantial success in the peptide field,[1] solid phase methods have achieved little in oligodeoxyribonucleotide synthesis.[2] Yields in internucleotide bond-forming reactions have often been so low that after three or four cycles the desired oligonucleotide is no longer even the major product. In part we attribute this relative failure to the widespread use of polystyrene and other nonpolar supports in these polar reactions. Recently we described a new, more polar polymeric support which gave improved results in both peptide synthesis[3,4] and protein sequencing[5] applications. We now show, by efficient stepwise synthesis[6] of d(pT_6-C) and d(pC-A-G-T-G-A-T) sequences required as primers for use in mRNA structure determination, that the new resin is also effective in the oligonucleotide field.

The preparation of the cross-linked polydimethylacrylamide resin has been reported previously.[3,4] It swells to about ten times its dry bed volume in pyridine, *N,N*-dimethylformamide, and other polar solvents. The amino-groups of β-alanine residues (0.4 mequiv g^{-1}), present as *tert*-butoxycarbonyl derivatives, serve as anchoring points. To obtain a suitable reversible linkage of the first nucleotide to the support, the β-hydroxythio ether, $HO(CH_2)_2S{\cdot}C_6H_4{\cdot}(CH_2)_2COOC_6Cl_5$ (I) was synthesized by standard methods[7] and attached to the support by one cycle of the activated ester peptide synthesis program.[3] This involves acidic removal of *tert*-butoxycarbonyl groups, neutralization, and reaction with a five-fold excess of I. Completion of the reaction was assayed qualitatively by the ninhydrin test.[8] The substituted support is now in effect a polymeric protecting group for the 5′-phosphate of a growing oligonucleotide chain, similar to those already used successfully in solution.[9-11] Cleavage of oligonucleotides from the support is effected by *N*-chlorosuccinimide oxidation of the sulfide to the sulfone followed by β-elimination under mildly alkaline conditions.

In a preliminary experiment the dinucleotide d(pT-T) was synthesized. A diester approach analogous to that developed by Khorana was used.[12] Pyridinium 3′-*O*-acetylthymidine-

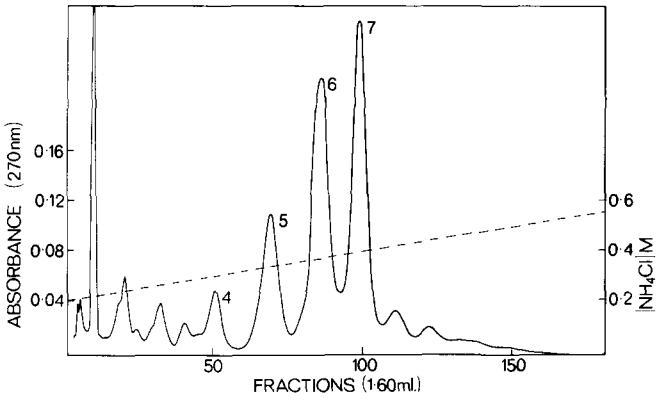

Figure 1. Chromatography of the mixture of synthetic oligonucleotides obtained in the preparation of the heptanucleotide, d(pT_6-C), performed on a column of Dowex I ×2 (−400 mesh; 0.3 × 100 cm) preequilibrated in 0.2 M ammonium chloride (pH 7.5)/40% ethanol solution. A gradient of ammonium chloride (- - -) was used and the column was run at 16 ml h^{-1} at 150–250 psi. Peak 7 contained the desired heptanucleotide, d(pT_6-C).

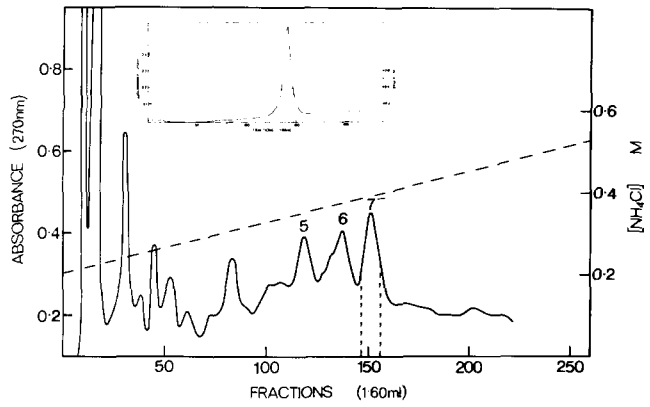

Figure 2. Chromatography of the mixture of synthetic oligonucleotides obtained in the preparation of the heptanucleotide d(pC-A-G-T-G-A-T), on a column of Dowex I x2 (0.3 × 150 cm). Conditions as in Figure 1. Peak 7 contained the desired heptanucleotide which was rechromatographed on the same column (inset).

5′-phosphate (II) (0.8 mmol) was preactivated by treatment for 2 hr with triisopropylbenzenesulfonyl chloride (TPS) (1.2 mmol) in anhydrous pyridine[13] and added to 0.2 g of functionalized polymer in the same solvent.[14] After 4 h at room temperature the reaction was terminated by conventional aqueous pyridine treatment.[12] The thymine content[15] of the polymer was 220 ± 30 μmol g^{-1}. The polymer was treated for 4 h with phenyl isocyanate (0.09 ml) in anhydrous pyridine to block any unreacted hydroxyl groups[16] and this reaction stopped by addition of methanol (1 ml). Cleavage of 3′-*O*-acetyl groups was accomplished by treatment (2 × 5 min) with 0.2 N sodium methoxide in methanol/pyridine (1:1).[17,18] Further reaction of the polymer-supported mononucleotide with II under identical conditions afforded the dinucleotide derivative which was cleaved from the support by treatment with 0.2 N *N*-chlorosuccinimide in 0.2 M phosphate buffer (pH 7.5)/dioxane (1:1) (2 × 15 min) followed by 0,2 N sodium hydroxide in dioxane/water (1:1) (2 × 5 min). After neutralization the liberated nucleotidic material (650 A_{265} units) was analyzed by chromatography on RPC5[19] and Dowex I[20] columns and by subsequent comparison of the UV absorbance of the peaks. A total of 93% of the nucleotide absorbance was accounted for by the dinucleotide d(pT-T) corresponding to 87% molar conversion from polymer bound dpT. The overall yield including cleavage from the resin was 33 μmol (75%).

Similarly the polymer-supported derivative of the heptanucleotide d(pT_6-anC-OAc) was prepared by sequential addition of appropriately protected mononucleotides. In each of six successive cycles 0.3 g of functionalized support was reacted in turn with (a) preactivated II (1 mmol in a total volume of about 5 ml; 4–6 h), (b) phenyl isocyanate (0.15 ml in 5 ml of pyridine; 4 h), and (c) excess 0.2 N sodium methoxide in methanol/pyridine (1:1) (10 ml; 2 × 5 min). After each nucleotide addition samples of polymer (1–5 mg) were analyzed by cleavage from the support and fractionation of the cleaved oligonucleotides on RPC5 or Dowex I. Based on polymer-linked dpT, estimated overall molar conversions to desired length oligomers after two-six cycles were 87, 79, 68, 56, and 43%, respectively.

In the final step the support was treated with preactivated pyridinium 3′-*O*-acetyl-N^4-anisoyl-2′-deoxycytidine-5′-phosphate (III) (1 mmol). The nucleotidic products (500 A_{270} units) were cleaved from the support and the desired heptanucleotide separated as the major product by conventional DEAE cellulose chromatography,[12] deprotection with concentrated ammonia (50 °C for 3 h or 25 °C for 48 h) and rechromatography on DEAE cellulose in the presence of 7 M urea.[21] Alternatively and more conveniently, the whole mixture was first deprotected with ammonia and products fractionated directly on Dowex I[20] (Figure 1).[22] The major peak (peak 7) corresponded to the heptanucleotide d(pT_6-C) (24% molar conversion from polymer bound dpT), which was desalted using Biogel P2[20] and characterized by standard sequence analysis techniques.[23]

Analysis of the minor products from the synthesis indicated that peak 6 contained dpT_6 and d(pT_5-C). The latter could have arisen from incomplete reaction of phenyl isocyanate with unreacted hydroxyl groups in step (b) of the synthetic cycle, possibly due to retention of water in the polymer matrix after aqueous pyridine treatment. Thus in the subsequent synthesis of d(pC-A-G-T-G-A-T) a much larger excess of phenyl isocyanate was used (10 ml of a 10% solution in pyridine, 2 × 30 min and 1 × 4 h).[24] Otherwise the procedures used were essentially unchanged. Protected mononucleotides[25] were added sequentially, each synthetic cycle (including analysis) being completed within 2 days. The synthetic oligonucleotide mixture (580 A_{270} units) was cleaved from the support, deprotected with concentrated ammonia, and fractionated on Dowex I (Figure 2). The heptanucleotide, d(pC-A-G-T-G-A-T), was the major product (20% approximate molar conversion from polymer bound dpC) which was characterized by full sequence analysis as before.[23]

These experiments using a polyamide support demonstrate that a rapid and routine solid phase synthesis of medium length oligodeoxyribonucleotides is now a practical proposition. Work is in progress to extend the range of synthetic oligonucleotides accessible by this approach by further optimization of reaction conditions and by application of improved fractionation techniques.

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(24) Residual 3′-hydroxyl groups appeared now to be blocked efficiently since, for example, no d(panC-ibG) was detected during analysis at the d(panC-bzA-ibG) stage.
(25) II, III, pyridinium 3′-*O*-acetyl-N^6-benzoyl-2′-deoxyadenosine-5′-phosphate, and pyridinium 3′-*O*-acetyl-N^2-isobutyryl-2′-deoxyguanosine-5′-phosphate were the four protected mononucleotides used.

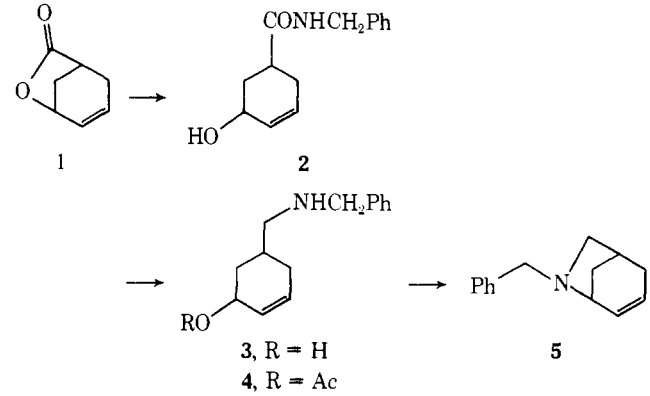
M. J. Gait, R. C. Sheppard*
Medical Research Council Laboratory for Molecular Biology
Cambridge CB2, 2QH, England
Received August 9, 1976

Palladium Catalyzed Cyclizations to Alkaloid Skeletons. Facile Synthesis of Desethylibogamine

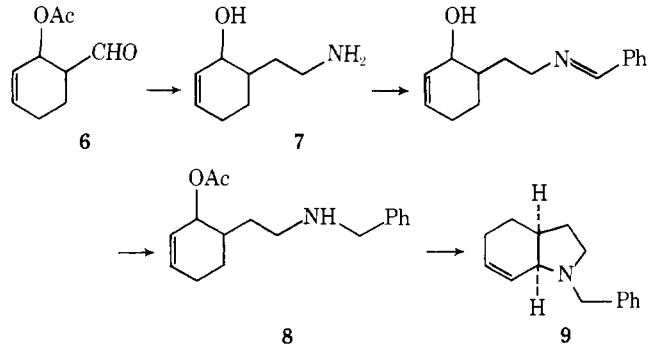
Sir:

Difficulties in alkaloid syntheses stem in large part from the high reactivity of the nitrogen. The chemospecificity demonstrated by palladium catalyzed reactions suggested their applicability to this important class of natural products without the need to protect the nitrogen, e.g., as an amide. We have now determined that, in the palladium catalyzed allylations of amines,[1] the allylic position is substituted with predominant *retention of configuration*[2] and such a reaction can be accomplished in an intramolecular sense (i.e., cyclization). This finding allows one to make use of the endo selectivity in the Diels–Alder reaction to generate facile approaches to the ring skeletons of many alkaloids. We have synthesized the basic ring system of three different classes of alkaloids, representatives of which are actinobolamine,[3] ibogamine,[4] and mesembrine.[5] We have further illustrated the utility of this approach by a short regiocontrolled total synthesis of desethylibogamine.[6]

Scheme I. Synthesis of 6-Azabicyclo[3.2.1]oct-3-ene System



Scheme II. Synthesis of 2,3,3a,4,5,7a-Hexahydro-1*H*-indole System



A second key step in the latter sequence employs a palladium catalyzed intramolecular alkylation of an olefin.

Scheme I outlines the synthesis of 6-benzyl-6-azabicylo[3.2.1]oct-2-ene. The lactone **1**,[7] readily available from the Diels–Alder adduct of butadiene and acrylic acid, was opened with benzylamine (neat, 120–125 °C, 89%) to give amide **2**, mp 123–124 °C, and the resulting amide subsequently reduced with lithium aluminum hydride (THF, reflux, 98%) to give amino alcohol **3**. Acetylation at oxygen to give **4**[8] required complete protonation of the amine and careful workup to avoid O to N acetyl migration (1.1 equiv of $HClO_4$, Ac_2O, CH_2Cl_2, O → 25 °C). Treatment of the allylic acetate **4** with a catalytic quantity of tetrakistriphenylphosphinepalladium[9] in the presence of additional triphenylphosphine and triethylamine at 55 °C for 8.5 h gave the desired product **5**[8,10] in 67% distilled yield (bp 78–85 °C at 0.1 mm).

A mesembrine skeleton is available from the Diels–Alder adduct **6** of acrolein and 1-acetoxy-1,3-butadiene as outlined in Scheme II. Reduction ($NaBH_4$, methanol, 0 °C, 100%), tosylation (TsCl, pyridine, 0 °C, 72%), cyanide displacement (NaCN, Me_2SO, 70 °C, 90%, bp 100–105 °C at 0.1 mm), and reduction (LAH, ether, room temperature, 94%) gave the desired amino alcohol **7**. Imine formation (PhCHO, PhH, Dean–Stark trap, 64%), reduction ($NaBH_4$, methanol, room temperature, 100%), and acetylation (70% yield) as previously described gave the crucial allylic acetate **8**.[8] Cyclization to **9**[8] was achieved at 70 °C in acetonitrile in the presence of a catalytic amount of the Pd^0 complex and triethylamine (>50% yield). The stereohomogeneity of **9** was established chromatographically and spectroscopically.[11] The cis stereochemistry was confirmed by the J = 7 Hz coupling constant for the protons on C(3a) and C(7a) and the low field absorption (δ 2.88, td, J = 8.7, 2.4 Hz) for one proton on C(2).[12]

The same adduct **6** serves as a precursor to the isoquinuclidine[13] skeleton as illustrated in Scheme III. In particular, reductive amination by forming the Schiff's base ($PhCH_3$, $MgSO_4$, −25 to 0 °C) followed by sodium borohydride workup (add CH_3OH, −15 to 0 °C) gave the desired amino acetates