composition to be **37**, 9%, **44**, 47%, and another alcohol, 44%. The infrared spectrum of the mixture showed a certain resemblance to that of 1-bicyclo[2.2.2]octenol (**45**)[61] and the resonance at δ 2.42 in the nmr spectrum was clearly that of a bridgehead proton of another alcohol similar in structure to **44**. On these considerations, the other major product was assigned structure **45**. Other products isolated in variable yield from **36** were *p*-tolyl disulfide and *p*-tolyl *p*-toluenethiolsulfonate, characterized as before.[30]

Registry No.—**5**, 15023-39-9; **5**, S-benzylisothiuronium salt, 15023-57-1; **5**, phenacyl ester, 15026-12-7; **5a**, 15023-40-2; **7**, 698-39-5; **7**, S-benzylisothiuronium salt, 15023-42-4; ethyl ester of **7**, 15023-43-5; methyl norbornene-2-carboxylate, 701-15-5; **8**, 15023-45-7; **9**, 15023-46-8; **10**, 15023-47-9; **12**, 15023-48-0; **13**, 15023-49-1; **14**, 15023-50-4; **15**, 15023-51-5; **18**, 15023-52-6; **19**, 15023-53-7; **20**, 25023-54-8; **21**, 15023-55-9; **22**, 15023-56-0; **23**, 15019-68-8; **24**, 15019-69-9; **25**, 15019-70-2; **27**, 15019-71-3; **29**, 15019-72-4; **30**, 15019-73-5; **33**, 15019-74-6; **34**, 15019-75-7; **34**, 2,4-dinitrophenylhydrazone, 15019-76-8; **35**, 15019-77-9; **35**, 2,4-dinitrophenylhydrazone, 15019-78-0; **36**, 15019-79-1; **37**, 6814-81-9; **38**, 15019-81-5; **40**, 15019-82-6; **40**, S-benzylisothiuronium salt, 15156-48-6; **41**, 15019-83-7; **41**, S-benzylthiuronium salt, 15156-49-7; **41**, methyl ester, 15019-84-8; **44**, 15019-85-9; N-(*exo*-2-bromo-1-norbornyl)benzamide, 15019-86-0; ethyl norbornene-1-carboxylate, 15019-87-1; 2-norbornenyl chloride, 694-93-9.

(61) A. B. Sayigh, Dissertation, Columbia University, 1954.

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Synthesis of Deoxyguanylyldeoxyguanosine on an Insoluble Polymer Support[1,2]

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Procedures are described for attaching N-dimethoxytrityldeoxyguanosine to an insoluble polymer support and for converting the resulting derivative into N-dimethoxytrityldeoxyguanylyl(N-dimethoxytrityl)deoxyguanosine and deoxyguanylyldeoxyguanosine.

In the synthesis of oligonucleotides on polymer supports 5′-O-trityldeoxycytidine and thymidine have been utilized as anchor nucleosides. Trityldeoxycytidine was joined to the support through the amino group of the cytosine ring;[4] thymidine was joined at the 3′-O[5] and 5′-O[6] of the deoxyribose ring. The nucleotide chain has been lengthened both by the phosphodiester route[5,6] developed by Khorana for reactions in solution and by the phosphotriester route.[4] In extending the scope of the syntheses on insoluble polymer supports we have investigated the possibility of utilizing deoxyguanosine as an anchor nucleoside and of building the chain by addition of deoxyguanosine units by the phosphotriester approach. The present paper reports the synthesis of deoxyguanylyldeoxyguanosine by this method. Deoxyguanylyldeoxyguanosine was previously prepared by Schaller and Khorana with a homogeneous reaction system.[7]

The support was an insoluble polymer made from styrene (89 mole %), *p*-divinylbenzene (0.1%), and *p*-vinylbenzoic acid (11%). It was converted to the acid chloride (Ⓟ—COCl),[8] I, by reaction with thionyl chloride in benzene[9] and then treated with excess N-di-*p*-methoxytrityldeoxyguanosine[10] in pyridine for a period of 48 hr. Residual acid chloride groups were esterified by reaction with methanol (Chart I) and the polymer II was collected, washed, dried, and weighed. As judged by the increase in weight (I → II), polymer II contained 0.46 mmole of N-dimethoxytrityldeoxyguanosine per gram, which corresponds to esterification of 61% of the carboxyl groups in the initial support with N-dimethoxytrityldeoxyguanosine.

Polymer II was phosphorylated with β-cyanoethyl phosphate with dicyclohexylcarbodiimide as the activating agent. The extent of phosphorylation was estimated by hydrolyzing a portion of the product with alkali and eluting the nucleotidic material; after removal of the dimethoxytrityl groups by acid hydrolysis, the deoxyguanosine and deoxyguanosine phosphate were separated by paper chromatography and assayed spectrophotometrically. These experiments showed that 58% of the dimethoxytrityldeoxyguanosine on the support was phosphorylated within 9 days. It is noteworthy that the solvent (solvent C) used in the paper chromatography serves to separate deoxyguanosine 3′-phosphate from deoxyguanosine-5′

(1) Part IX in series on Nucleotide Chemistry. For part VIII see R. L. Letsinger and K. K. Ogilvie, *J. Am. Chem. Soc.*, **89**, 4801 (1967).

(2) This research was supported by the Division of General Medical Sciences, National Institutes of Health, GM-10265.

(3) Department of Hydrocarbon Chemistry, Kyoto University, Kyoto, Japan.

(4) R. L. Letsinger and V. Mahadevan, *J. Am. Chem. Soc.*, **87**, 3526 (1965); **88**, 5319 (1966).

(5) R. L. Letsinger, D. M. Jerina, and M. H. Caruthers, *Biochemistry*, **6**, 1397 (1967).

(6) H. Hayatsu and H. G. Khorana, *J. Am. Chem. Soc.*, **88**, 3182 (1966); F. Cramer, R. Helbig, H. Hettler, K. H. Scheit, and H. Seliger, *Angew. Chem.*, **78**, 640 (1966); L. R. Melby and D. R. Strobach, *J. Am. Chem. Soc.*, **89**, 450 (1967).

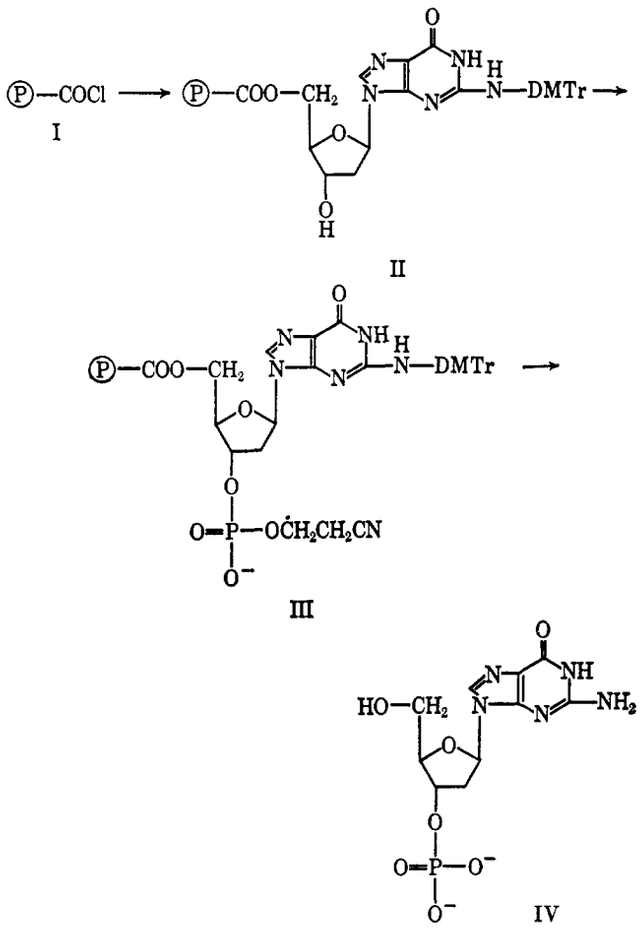
(7) H. Schaller and H. G. Khorana, *ibid.*, **85**, 3828 (1963).

(8) Ⓟ refers to the portion of the insoluble polymer other than the active functional groups.

(9) R. L. Letsinger, M. J. Kornet, V. Mahadevan, and D. M. Jerina, *ibid.*, **86**, 5163 (1964).

(10) The dimethoxytrityl group is used to protect the guanine ring in the subsequent phosphorylation steps. It was introduced for this purpose by H. Schaller, G. Weimann, B. Lerch, and H. G. Khorana, *ibid.*, **85**, 3821 (1963).

CHART I[a]

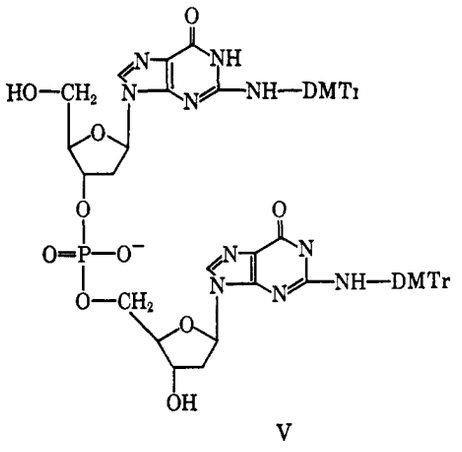


[a] For convenience the dimethoxytrityl group is represented on the amino group, though the exact position it occupies in the guanine ring has not been established with certainty (see ref 10).

phosphate. Since the only nucleotide observed on the paper chromatogram was deoxyguanosine 3′-phosphate, we conclude that the dimethoxytrityldeoxyguanosine was joined to the support through the 5′-oxygen.

Activation of polymer III with mesitylenesulfonyl chloride and condensation with N-di-*p*-methoxytrityldeoxyguanosine gave polymer IV. On alkaline treatment, the ester links holding the nucleotide products to the support were cleaved and the cyanoethyl groups were eliminated. The product, N-di-*p*-methoxytrityldeoxyguanylyl-N-(di-*p*-methoxytrityl)-deoxyguanosine (V) (the absorbance was 38% of the total absorbance of the material eluted from the polymer), was isolated as the pyridinium salt and characterized by the ultraviolet spectrum, an elemental analysis, and hydrolysis to deoxyguanylyldeoxyguanosine. The latter, in turn, was identified by its chromatographic and electrophoretic properties and by the hydrolysis catalyzed by snake venom phosphodiesterase, an enzyme selective for oligonucleotides which possess a free 3′-hydroxyl group and the 3′→5′ phosphodiester linkage.[11] Under conditions where thymidylyl(3′→5′)thymidine is completely degraded by the venom enzyme, 98% of the deoxyguanylyldeoxyguanosine thus prepared was hydrolyzed to deoxy-

(11) W. E. Razzell and H. G. Khorana, *J. Biol. Chem.*, **234**, 2105 (1959).



guanosine and deoxyguanosine 5′-phosphate (dpG/dG = 0.93).

These experiments demonstrate that the stepwise synthesis of oligonucleotides on a polymer support can be initiated with a deoxyguanosine unit and that a deoxyguanosine unit can be added to the chain successfully in the two-step sequence that yields a phosphotriester. The procedure provides a convenient route to deoxyguanylyldeoxyguanosine, 98% of which is the 3′→5′ linked isomer.

For the synthesis of high molecular weight material several aspects of the procedure need improvement. (1) The yields at each stage should be increased. (2) A better blocking group for the amino function should be used. In the course of the phosphorylation reaction some of the dimethoxytrityl groups were lost. The resulting exposed amino groups may have yielded phosphorylated derivatives which contributed to the material undegraded by the venom enzyme. (3) A blocking group for the 3′-oxygen of the nucleoside used in the condensation step with the phosphorylated polymer may be desirable. Work on these problems is in progress. Recent experiments indeed show that the yields in the initial phosphorylation step can be greatly enhanced and the time of reaction reduced by using mesitylenesulfonyl chloride in place of dicyclohexylcarbodiimide as the condensing agent. Thus, the reaction of polymer–dimethoxytrityldeoxyguanosine with cyanoethyl phosphate in the presence of mesitylenesulfonyl chloride was found to be complete within 50 hr.

Experimental Section

N-Di-*p*-methoxytrityldeoxyguanosine, mp 166–168°, was prepared by the procedure of Schaller, *et al.*[10] Barium cyanoethyl phosphate (California Biochemical Corp.) was converted to the pyridinium salt[12] and rendered anhydrous by repeated additions of dry pyridine and concentration of the solution. Mesitylenesulfonyl chloride, mp 57°, was prepared by the method of Wang and Cohen.[13]

Reactions were carried out in pyridine at room temperature in a glass-stoppered flask equipped with a magnetic stirrer. At the end of a reaction the insoluble polymer was separated from the solution of reagents and by-products by filtration or decantation.

Paper chromatography was performed by the descending technique with Whatman 3M paper. The solvents were: A, isopropyl alcohol–concentrated ammonia–water (7:1:2); B, *n*-butyl alcohol–acetic acid–water (5:2:3); and C, ethyl

(12) P. T. Gilham and G. M. Tener, *Chem. Ind.* (London), 542 (1959); G. M. Tener, *J. Am. Chem. Soc.*, **83**, 159 (1961).

(13) C. H. Wang and S. G. Cohen, *ibid.*, **79**, 1924 (1957).

alcohol–1 *M* ammonium acetate at pH 7.2 (7:3). Paper electrophoresis was carried out using a Savant flat plate apparatus operated at 1500–1900 v with a phosphate buffer at pH 8.0 (the buffer contained 9.03 g of disodium hydrogen phosphate and 0.453 g of potassium hydrogen phosphate per liter). Nucleotides and nucleosides were observed under ultraviolet light, and di-*p*-methoxytrityl-containing compounds were observed by the orange color which developed when the paper was sprayed with 10% aqueous perchloric acid and subsequently warmed at 60° for 30 min.

Ⓟ—**COCl.**—Freshly distilled styrene (6.0 g, 57.5 mmoles), *p*-divinylbenzene (8.3 mg, 0.064 mmole), and *p*-vinylbenzoic acid[14] (1.02 g, 6.90 mmoles) were placed with a few seeds of popcorn polymer and 0.5 mg of benzoyl peroxide in an erlenmeyer flask which had been well purged with nitrogen. After the mixture had stood for 3 days at 50–60° the polymer was collected, washed several times with benzene and ether, ground in a ceramic mortar, washed again with ether, and dried. It was then heated with 10 g of thionyl chloride in 100 ml of benzene overnight, washed three times with benzene, and stored in a vacuum desiccator over phosphorus pentoxide. The infrared spectrum showed two strong bands in the carbonyl region at 1740 and 1770 cm^{-1}.

Addition of N-Di-*p*-methoxytrityldeoxyguanosine to Polymer Support.—N-Di-*p*-methoxytrityldeoxyguanosine (3.42 g, 6.6 mmoles) was stirred with 5.0 g (3.5 mequiv) of polymer acid chloride (I) for 48 hr in 40 ml of pyridine; then 20 ml of methanol was added and the mixture stirred for an additional 12 hr. The polymer was collected by filtration, extracted with methanol in a Soxhlet extractor until N-di-*p*-methoxytrityldeoxyguanosine was no longer extracted, and dried over phosphorus pentoxide. It exhibited a maximum in the infrared at 1695 cm^{-1}. From the observed weight increase (1.40 g) of the polymer and the weight changes calculated for esterification of the acid chloride groups with methanol and with N-di-*p*-methoxytrityldeoxyguanosine, the fraction of acid chloride groups esterified with N-di-*p*-dimethoxytrityldeoxyguanosine is estimated to be 61%. The observed weight increase agreed satisfactorily with the amount of unreacted N-dimethyltrityldeoxyguanosine that was recovered from the reaction by concentrating the filtrate and methanol extractions and precipitating the nucleoside derivative with ether (the recovered material was identified by melting point and the infrared spectrum).

Two similar experiments carried out with 6.0 g of Ⓟ—COCl in 50 ml of pyridine with (a) 4.56 g of N-di-*p*-dimethoxytrityldeoxyguanosine for 12 hr and (b) 4.00 g of N-di-*p*-dimethoxytrityldeoxyguanosine for 24 hr showed weight increases of the polymer of 0.41 and 0.86 g, respectively, indicating that the reaction of the acid chloride is rather slow.

Phosphorylation of Polymer–Deoxyguanosine Derivative II.—β-Cyanoethyl phosphate (12.5 mmoles) in 40 ml of dry pyridine was stirred with 8.24 g (40 mmoles) of dicyclohexylcarbodiimide for 10 hr; then 6.0 g of polymer–deoxyguanosine derivative II (0.46 mmole of nucleoside per gram) was added and stirred with the mixture for a total of 9 days. Water (20 ml) was added and, after an additional 24 hr of stirring, the mixture was filtered. The solids were washed with pyridine–water (1:1), with methanol, with ethanol, and then with ethanol–cyclohexane (1:1) until no solute was found on concentration of the wash. The residual polymer III was washed with ether and dried in a desiccator over phosphorus pentoxide.

During the reaction small aliquots of the polymer were removed at intervals and analyzed for the extent of phosphorylation. This was done by treating the aliquot with a mixture of 2 *M* aqueous sodium hydroxide–ethanol–dioxane (1:2:2 by volume) for 5 hr, filtering, neutralizing the filtrate with pyridinium Dowex 50 resin, and concentrating the solution. The resulting solution was treated with 80% aqueous acetic acid for 5 hr at room temperature to cleave the dimethoxytrityl groups, evaporated *in vacuo*, made alkaline with ammonium hydroxide, filtered to remove the insoluble organic matter, and chromatographed on Whatman 3M paper with solvent A. Spots corresponding to deoxyguanosine (R_f 0.37–0.46) and deoxyguanosine 3′-phosphate (R_f 0.03–0.11) were eluted with water and the absorbances at 260 mμ were determined (in addition to these two spots, faint spots at R_f 0.7 and 0.8 were generally observed in the chromatograms). These solutions were then concentrated and electrophoresced at pH 8.0. The electrophoretic mobility and ultraviolet spectrum of the material with R_f 0.03–0.11 were the same as found for a model compound, deoxyguanosine 5′-phosphate. Data for these experiments are summarized in Table I. From the ratio of the

TABLE I
PHOSPHORYLATION OF POLYMER–DIMETHOXYTRITYLDEOXYGUANOSINE

Reacn time, days	Absorbance dGp	Absorbance dG	dGp[a]/(dGp + dG)
4	2.61	4.20	0.39
7	2.49	2.07	0.52
8	2.34	1.80	0.57
9	3.00	2.56	0.58

[a] Ratio of absorbance for dGp to sum of absorbances for dGp and dG; dGp and dG refer to deoxyguanosine 3′-phosphate and deoxyguanosine, respectively.

absorbances for deoxyguanosine and deoxyguanosine 3′-phosphate it may be estimated that approximately 58% of the deoxyguanosine units on the support polymer had been phosphorylated. In the course of the phosphorylation reaction the polymer turned from white to orange (3 days) to brown (9 days). This discoloration apparently results from reaction of some of the dimethoxytrityl groups.

N-Di-*p*-methoxytrityldeoxyguanylyl(N-di-*p*-methoxytrityl)deoxyguanosine.—A mixture of 4.0 g of polymer III and 2.19 g (10 mmoles) of mesitylenesulfonyl chloride in 40 ml of pyridine was stirred for 24 hr; then the solid was allowed to settle and the supernatant liquid was removed. The solid was washed three times with dry pyridine to remove the major portion of mesitylenesulfonyl chloride and stirred for 3 days with 2.12 g (4 mmoles) of N-di-*p*-methoxytrityldeoxyguanosine in 30 ml of pyridine. Methanol (30 ml) was added and after 3 hr of stirring the mixture was filtered and the solid washed with methanol and ether. One-half (2.0 g) of the polymer was stirred with a mixture of 10 ml of 2 *M* aqueous sodium hydroxide, 20 ml of ethanol, and 20 ml of dioxane for 12 hr in order to cleave the nucleotidic material from the support. The polymer was collected by filtration and washed several times with ethanol. The alkaline solution, together with ethanol washes of the polymer, was neutralized with Dowex 50 (pyridinium form) and, after removal of the Dowex resin, was concentrated to a volume of 1 ml and diluted to 2.5 ml with ethanol.

One-ninth of this solution was applied to a Sephadex LH 20 column (12 mm × 120 cm) and eluted with ethanol at a rate of 0.5 ml/min. The results are given in Table II. The third and

TABLE II
FRACTIONATION ON SEPHADEX LH 20

Fraction	Volume, ml	Optical density units (260 mμ)
1	84	
2	119	1100
3	27	1530
4	41	150
5	224	815
6	125	10
7	478	703
8	104	57

fourth fractions contained the N-di-*p*-methoxytrityldeoxyguanylyl(N-di-*p*-methoxytrityl)deoxyguanosine. Fraction 3 was concentrated to 2 ml and precipitated with ether and the N-di-*p*-methoxytrityldeoxyguanylyl(N-di-*p*-methoxytrityl)deoxyguanosine thus obtained was dried under vacuum over phosphorus pentoxide at the temperature of boiling acetone: R_f in solvent A, 0.91; λ_{max} in ethanol, 278 mμ (ε 36,100), 261 (38,200), 235 (51,900); λ_{min} ethanol, 273 mμ (ε 35,100), 250 (34,400), 226 (48,800). The weight, ~42 mg, corresponds to conversion of ~35% of the deoxyguanosine on the support to

(14) J. R. Leebrick and H. E. Ramsden, *J. Org. Chem.*, **23**, 935 (1958).

the pyridinium salt of V. On the basis of the total optical density units of product (1680), the conversion amounts to 42%.

Anal.[15] Calcd for $C_{62}H_{61}O_{14}N_{10}P \cdot C_5H_5N$: C, 62.90; H, 5.20; N, 12.12. Found: C, 62.93; H, 5.56; N, 11.66.

A portion of this compound was treated with 2 ml of 80% aqueous acetic acid for 3 hr. The acetic acid was evaporated, 20 ml of dilute ammonium hydroxide was added, and the mixture was centrifuged and the supernatant concentrated to 0.5 ml. This solution was applied to a Sephadex G25 column (1.5 cm × 120 cm) and eluted with 0.02 *M* aqueous ammonium bicarbonate. The second peak (102–130 ml), which appeared after a very small first peak (in the 87–98-ml portion), was collected and lyophilized. The dGpdG thus obtained was homogeneous in solvent A (R_f 0.07). A portion was incubated at 37° for 12 hr with 0.1 ml of venom phosphodiesterase preparation[16] in 2.5 ml of 0.33 *M* Tris buffer at pH 9.1. On chromatography in solvent C three spots were obtained: R_f 0.06, 0.36, and 0.68, corresponding to dGpdG, deoxyguanosine 5′-phosphate, and deoxyguanosine. The optical density units found on eluting these spots were 0.3, 8.2, and 8.8, respectively. These results show that 98% (neglecting hypochromic effects) of the dinucleoside phosphate was hydrolyzed; dpG/dG = 0.94.

Two-thirds of the solution (product from elution of the polymer support) was worked up without isolation of the dimethoxytrityl derivative. In this case the solution was evaporated to dryness and the residue was treated with 5 ml of 80% acetic acid to cleave off the dimethoxytrityl group. The acetic acid was then evaporated, 30 ml of dilute ammonium hydroxide was added, and the solution was centrifuged to remove insoluble organic matter. The pH was adjusted to 10 and the solution applied to a DEAE-cellulose column (5 cm × 25 cm, bicarbonate form). On gradient elution (0.5–0.7 ml/min) with 2 l. of 0.02 *M* ammonium bicarbonate in the mixing vessel and an equal volume of 0.5 *M* ammonium bicarbonate in the reservoir, dGpdG was obtained in a band from 680 to 2530 ml. Lyophilization yielded 133 mg of product as a white powder. As in the previous case, a portion was further purified by elution from Sephadex G25 and then treated with snake venom phosphodiesterase. In this case the enzymatic hydrolysis yielded 6.9 optical density units of deoxyguanosine, 6.5 optical density units of deoxyguanosine 5′-phosphate, and 0.2 optical density unit of undegraded material; *i.e.*, 98% (neglecting hypochromic effects) of the dGpdG was hydrolyzed; dpG/dG = 0.94.

The physical properties of the deoxyguanylyldeoxyguanosine are: R_f in solvent A, 0.06–0.09; mobility on electrophoresis at pH 8 relative to deoxyguanosine 5′-phosphate, 0.39–0.41; λ_{max} in 0.01 *M* hydrochloric acid, water, and 0.01 *M* ammonium hydroxide, respectively, 255, 254, and 256 mμ; λ_{min} in 0.01 *M* hydrochloric acid, water, and 0.01 *M* ammonium hydroxide respectively, 228, 226, and 232 mμ; ε 260/280 in water 1.59.

Phosphorylation with β-Cyanoethyl Phosphate and Mesitylenesulfonyl Chloride.—Since the phosphorylation reaction utilizing dicyclohexylcarbodiimide was very slow and incomplete even after 9 days, experiments were conducted with mesitylenesulfonyl chloride as the activating agent to see if more extensive phosphorylation could be achieved. The results show that the mesitylenesulfonyl chloride is indeed a much more effective reagent; essentially complete phosphorylation was achieved within 50 hr.

In this case polymer prepared from 6.0 g (57.5 mmoles) of styrene, 5.2 mg (0.04 mmole) of *p*-divinylbenzene, and 0.94 g (6.35 mmoles) of *p*-vinylbenzoic acid was converted to the acid chloride form. The acid chloride polymer (1.0 g) was esterified successively with 1.28 g (2.46 mmoles) of N-di-*p*-methoxytrityldeoxyguanosine in 25 ml of pyridine over a 48-hr period and with excess methanol as in the previously described case. From the gain in weight of the polymer (0.120 g) the percentage of carbonyl groups of the support that were joined to the nucleoside is estimated to be 30%. A 1.0-g sample of this polymer derivative was stirred with 0.44 g (2 mmoles) of mesitylenesulfonyl chloride and 1 mmole of β-cyanoethyl phosphate in 30 ml of pyridine for 50 hr at room temperature. At the end of this period the polymer had a yellow color. Small samples of the polymer were removed at intervals during the reaction and subjected to hydrolysis and analysis as in the reactions with dicyclohexylcarbodiimide. Phosphorylation of the dimethoxytrityldeoxyguanosine moiety was incomplete after 12 hr but was essentially complete after 50 hr (see Table III). In addition to the major spots corresponding to deoxyguanosine (R_f 0.63–0.64 in solvent C) and deoxyguanosine 3′-phosphate (R_f 0.47–0.49 in solvent C), a faint spot was observed in each case at R_f 0.82.

TABLE III

PHOSPHORYLATION WITH β-CYANOETHYL PHOSPHATE AND MESITYLENESULFONYL CHLORIDE

Reacn time, hr	Absorbance dGp	Absorbance dG	dGp[a]/(dGp + dG)
12	1.3	2.0	0.39
24	2.6	2.0	0.51
50	4.2	0	1.0

[a] Ratio of absorbance for dGp to sum of absorbancies for dGp and dG.

Registry No.—V, 15185,-78-1; deoxyguanylyldeoxyguanosine, 15180-30-0.

(15) Analysis by Micro-Tech Laboratories, Skokie, Ill.

(16) Calbiochem Corp., Los Angeles, Calif.