C.—A similar reaction was carried out with the lactone III (423 mg.). After 24 hr. the precipitate (40 mg.) was collected; it had almost the same infrared spectrum as the precipitates from A and B; as with the material from A there was a slight absorption at 2300 cm.$^{-1}$ indicating the presence of a trace of B–H. Samples of the precipitate were titrated[23] for hydride and the hydride content was estimated as 0.06 and 0.09%.

Acknowledgment.—We thank Dr. J. T. Edward (for samples and spectra of some of the compounds), Dr. D. N. Kevill (for helpful discussions about the kinetics), and Mr. E. Lukenbach (who helped prepare some of the starting materials). The work was supported by U. S. Public Health Service Grants CY-5087 and CA-05796 from the National Cancer Institute and by Petroleum Research Fund Grant 559-A. Grateful acknowledgment is made to the donors of these funds.

Phosphonic Acid Analogs of Nucleoside Phosphates. III. The Synthesis of Adenosine-5′-methylenediphosphonate, a Phosphonic Acid Analog of Adenosine-5′-diphosphate[1,2]

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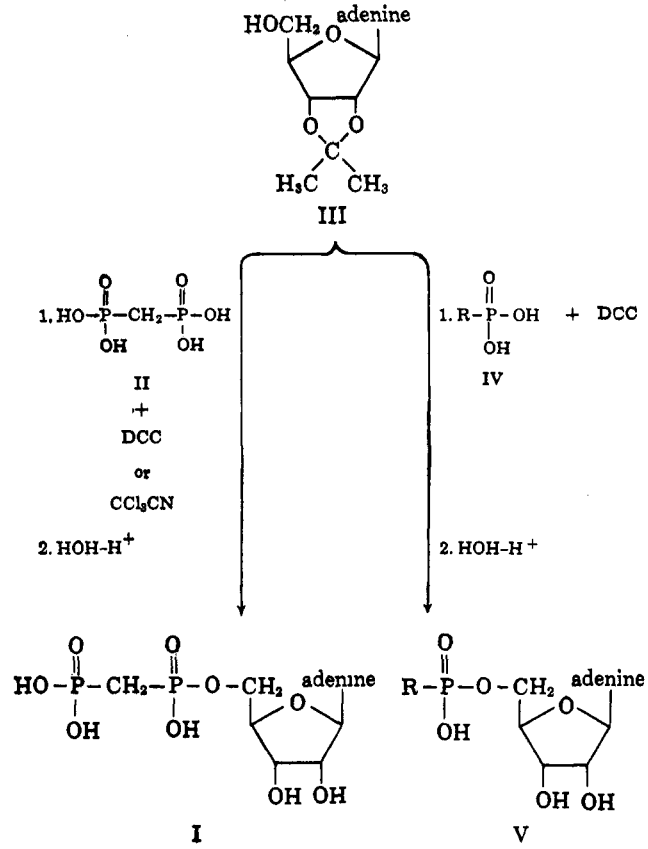
The synthesis of adenosine-5′-methylenediphosphonate (I) has been accomplished *via* the reaction of 2′,3′-isopropylideneadenosine with methylenediphosphonic acid as mediated by trichloroacetonitrile and by dicyclohexylcarbodiimide. Adensoine-5′-methylphosphonate (V, R = CH_3) and -5′-ethylphosphonate (V, R = CH_2CH_3) were prepared in an analogous fashion with use of dicyclohexylcarbodiimide.

The development of methods for the synthesis of nucleoside esters of phosphonic acids has been undertaken in these laboratories as part of a program on the preparation and biological properties of phosphonic acid analogs of nucleoside phosphates.[3]

The work relating to the synthesis of adenosine-5′-methylenediphosphonate (I) is presented in the present paper. This compound, an analog of ADP in which the pyrophosphate oxygen has been replaced with a methylene group, is an adenosine ester of methylenediphosphonic acid (II). Accordingly, methods used for the synthesis of phosphate esters of nucleosides were investigated for its preparation. These include the esterification of methylenediphosphonic acid with 2′,3′-isopropylideneadenosine (III) as mediated by dicyclohexylcarbodiimide (DCC) and by trichloroacetonitrile followed by removal of the protecting isopropylidene grouping by acid hydrolysis.[4]

The dicyclohexylcarbodiimide esterification of two alkylmonophosphonic acids, methyl- and ethylphosphonic acid (IV, R = CH_3 and R = CH_2CH_3), was studied as a preliminary to the work with the more complicated methylenediphosphonic acid.[5] Both of these acids smoothly underwent esterification in anhydrous pyridine to give, after removal of the isopropylidene group, adenosine-5′-methylphosphonate (V, R = CH_3) and adenosine-5′-ethylphosphonate (V, R = CH_2CH_3) as crystalline solids in yields of 86 and 54%, respectively.[6] These esters were characterized by elemental analysis and by equivalent weight estimation from ultraviolet absorbancy measurements.



Analogously the synthesis of adenosine-5′-methylenediphosphonate (I) was accomplished by the re-

(1) This work was supported by grants from the National Science Foundation (G-2191) and from the National Institutes of Health (CY2856).

(2) The following abbreviations are used: ATP, adenosine-5′-triphosphate; ADP, adenosine-5′-diphosphate; AMP, adenosine-5′-phosphate; and DCC, dicyclohexylcarbodiimide.

(3) Paper I: T. C. Myers, K. Nakamura, and J. W. Flesher, *J. Am. Chem. Soc.*, **85**, 3292 (1963); paper II: T. C. Myers and L. N. Simon, *J. Org. Chem.*, **30**, 443 (1965).

(4) For procedures analogous to those used in the dicyclohexylcarbodiimide esterifications, see (a) D. B. Straus and E. Goldwasser, *Biochim. Biophys. Acta*, **47**, 186 (1961); (b) M. Smith and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 1141 (1958); (c) H. G. Khorana, "Some Recent Developments in the Chemistry of Phosphate Esters of Biological Interest," John Wiley and Sons, Inc., New York, N. Y., 1961, Chapters 2, 5, and 6; to those used in the trichloroacetonitrile esterification, see (d) F. Cramer, K. H. Scheit, and H. J. Baldauf, *Chem. Ber.*, **95**, 1657 (1962); (e) F. Cramer and H. J. Weimann, and G. Weimann, *ibid.*, **94**, 996 (1961).

(5) Dicyclohexylcarbodiimide-mediated esterification of high molecular weight alkylmonophosphonic acids has been recently reported by J. A. Maynard and J. M. Swan [*Australian J. Chem.*, **16**, 609 (1963)].

(6) The preparation of adenosine-5′-ethylphosphonate as an amorphous solid has been previously reported *via* reaction of isopropylideneadenosine with benzyl ethylphosphonochloridate followed by removal of the protecting groups: N. Anand and A. R. Todd, *J. Chem. Soc.*, 1867 (1951).

action of methylenediphosphonic acid with isopropylideneadenosine in the presence of DCC (molar ratio of 4:1:16) and excess tri-*n*-butylamine in anhydrous pyridine solution. The reaction was carried out at 60° for 14 hr. After the removal of N,N′-dicyclohexylurea and pyridine, followed by hydrolysis with 15% acetic acid to remove the isopropylidene group, the reaction mixture was fractionated on a Dowex-2 (formate) ion-exchange column. This produced two major ultraviolet-absorbing fractions.[7] The second fraction contained the desired adenosine-5′-methylenediphosphonate (I) in essentially pure form as indicated by paper chromatography. Upon concentration, the product was obtained as an amorphous white solid which produced colorless needles (61% yield) upon crystallization from water.

The conditions for this reaction are substantially different from those usually employed in DCC-mediated esterifications of monoesters of phosphoric acid which are normally done with the pyridine salt at room temperature. In fact the trialkylamine salt would be expected to be unreactive. Tri-*n*-butylamine was used in the present work because of the insolubility of methylenediphosphonic acid in pyridine. Preliminary experiments indicated the desirability of the higher reaction temperature.[7]

Adenosine-5′-methylenediphosphonate was also prepared with the use of trichloroacetonitrile as the condensing agent. Methylenediphosphonic acid, tri-*n*-hexylamine, and isopropylideneadenosine, in the molar ratio of 1.5:0.88:1.0, were allowed to react in dimethylformamide solution for 3 hr. at 80° in the presence of a large excess of trichloroacetonitrile. The tri-*n*-hexylamine was added in order to dissolve the otherwise insoluble methylenediphosphonic acid. Increasing the relative amount of this amine did not produce an increase in yield of product. After removal of the isopropylidene grouping using 5 *N* sulfuric acid, the product was purified by adsorption onto Norit-A charcoal followed by elution with aqueous ethanolic ammonium hydroxide (after exhaustive washing of the Norit with water) and fractionation on a Dowex-1 column (formate form) using 6 *N* formic acid as the eluting solvent. As with the DCC esterification this method also produced two major ultraviolet-absorbing fractions.[7] Adenosine-5′-methylenediphosphonate (I) was isolated from the second fraction as the crystalline free acid in 18% yield.

The assignment of the structure of adenosine-5′-methylenediphosphonate to the products of both reactions was supported by elemental analysis (including analysis of the cyclohexylammonium salt) and by determinations of the spectral equivalent weight and of the neutralization equivalent. Electrometric titration produced a titration curve essentially identical with that obtained under similar conditions for ADP except, as anticipated, in the region of the final acid dissociation, *i.e.*, the region of secondary "phosphoryl" dissociation for ADP and of secondary "phosphonyl" dissociation for the analog. Here the curve for ADP showed a pK_A' of 7.0 and the curve for the analog a pK_A' of 8.0. Moreover the titration curve for the analog showed a ratio of strong acid groupings ($pK_A' < 5$) to weak acid groupings ($pK_A' > 6$) to adenine (as determined from ultraviolet-absorbancy measurements on completion of the titration) of 2:1:1 in accordance with the structure of adenosine-5′-methylenediphosphonate. Paper chromatograms of the product gave positive reactions with periodate–benzidine spray, showing the presence of *vic*-hydroxyl groupings.

The preparative reactions described above are of interest in relation to the recent work by Khorana and others on the mechanism of the esterification of phosphates with use of reagents such as carbodiimides and trichloroacetonitrile.[8] Thus the work of Khorana indicates that the active phosphorylating agents are cyclic trimetaphosphates. The exact nature of the active "phosphonylating agents" in these reactions together with the factors which affect the reactions are under investigation and will be the subject of a future publication.[7]

The rationale for the design of adenosine-5′-methylenediphosphonate was that it might act as an inhibitor with respect to ADP in processes in which there is cleavage of P–O–P linkage and as a substitute for ADP in other types of processes, for example, those in which ADP is phosphorylated to produce ATP.[3] Studies in both types of systems are in progress.

Experimental

Materials.—Methylphosphonic acid was obtained by hydrolysis in concentrated hydrochloric acid–acetic acid (15:1) of its dimethyl ester which was prepared by the reaction of methyl iodide with excess trimethyl phosphite.[9] Diethyl ethylphosphonate was prepared and hydrolyzed in an analogous manner to give ethylphosphonic acid.[9] Methylenediphosphonic acid was prepared as previously described.[3] Dicyclohexylcarbodiimide, trichloroacetonitrile, and 2′,3′-isopropylideneadenosine were purchased from Aldrich Chemical Co., Inc., and were used without further purification.

Methods.—Paper chromatography was performed using two solvent systems: (A)[10] 5% disodium hydrogen phosphate–isoamyl alcohol; ascending technique used, and (B)[11] isobutyric acid–1 *N* ammonia–0.1 *M* disodium ethylenediaminetetraacetate, 100:60:1.6 (v./v.), descending technique used.[3] Products bearing *vic*-hydroxy groupings were detected on the chromatograms by use of a periodate–benzidine spray.[12] The molar concentrations of the adenine-containing compounds as well as their "spectral equivalent weights" were determined as described in paper I.[3] Electrometric titrations were conducted as described in paper I. The titrametric results are reported in the preparative experiments in terms of pK_A' values of the adenine ammonium grouping and the ratios of adenine (determined spectrophotometrically) to strong acid ($pK_A' < 5$) to weak acid ($pK_A' > 6$). The phosphorus obtainable as orthophosphate after Kjeldahl digestion with concentrated sulfuric acid and hydrogen peroxide was estimated colormetrically by a modification of the method of Fiske and SubbaRow as previously described.[3] Analyses for C, H, and N were conducted by the Microtech Laboratories, Skokie, Ill.

Preparation of Adenosine-5′-methylenediphosphonate (I). A. Trichloroacetonitrile Method.—Methylenediphosphonic acid

(7) The first fraction (both from the dicyclohexylcarbodiimide reaction and from the trichloroacetonitrile reaction) gave, upon concentration, a white ultraviolet-absorbing solid which appeared to consist of P^1,P^2-diadenosine-5′-methylenediphosphonate in essentially pure form. The formation of this product and other factors relating to the mechanism of these esterifications will be the subject of a future publication.

(8) G. Weimann and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 4329 (1962); see also ref. 4c, Chapter 6.

(9) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Chapter 7.

(10) W. E. Cohn and C. E. Carter, *J. Am. Chem. Soc.*, **72**, 4273 (1950).

(11) H. A. Krebs and R. Hems, *Biochem. Biophys. Acta*, **12**, 172 (1953).

(12) M. Viscontini, D. Hoch, and P. Karrer, *Helv. Chim. Acta*, **38**, 642 (1955).

(10.6 g., 60 mmoles) and 2′,3′-isopropylideneadenosine (12.48 g., 40 mmoles) were dissolved in dimethylformamide (130 ml.) containing tri-*n*-hexylamine (9.32 g., 35 mmoles). Trichloroacetonitrile (80 ml., 800 mmoles) was added and the mixture was stirred until a clear solution was obtained. The solution was heated (80–90°) with stirring for 3 hr. during which time a small amount of solid precipitated and the solution developed a yellow color. The reaction mixture was cooled to room temperature, the insoluble material was filtered off with suction, and the yellow filtrate was concentrated on a flash evaporator to a volume of 130 ml. The solid which precipitated on evaporation was filtered off and the filtrate was treated with sulfuric acid (5 *N*, 360 ml.) in a separatory funnel. The resulting mixture separated into two phases upon standing overnight (12 hr.) at room temperature. The bottom phase was a heavy brown oil while the top phase (aqueous) was essentially colorless. The oil layer was separated and extracted with water (three times, a total of 100 ml.), the water washings were added to the aqueous (top) layer, and the total solution was diluted to 1 l. This solution contained 280,000 O.D. units (at 260 mμ) corresponding to 18 mequiv. of adenine-containing compounds.

The solution was treated with acid-washed charcoal (Norit-A) (100 g.) in four parts. During this treatment the optical density of the solution dropped to 2.5. The Norit was thoroughly washed with water (*ca.* 15 l.) until no precipitation was observed upon treatment of the washings with aqueous silver nitrate solution. Elution from the charcoal was accomplished using 10% concentrated ammonium hydroxide (by volume) in 50% ethanol in 1-l. batches. A total of 10 l. of the eluent solution was used. The combined eluates were evaporated on a rotary evaporator at 30° to 500 ml. and then filtered to remove traces of charcoal. This gave a slightly yellow solution (total O.D. units 186,000).

The solution was further concentrated to 20 ml., made basic (pH 8–9) with 10 *N* sodium hydroxide, and then passed through a column of Dowex-1 ion-exchange resin (formate form, 2% cross linked, 5 × 60 cm.) at a rate of *ca.* 1 ml./min. After the column was washed with water (3000 ml., total O.D. units 54,000), fractionation was carried out at a rate of 4 ml./min. using 6 *N* formic acid as the eluting medium. Ten-milliliter fractions were collected. The optical density of each fraction was determined at 260 mμ. Two major ultraviolet-absorbing peaks were obtained: peak I,[7] fractions 71–91, total optical density units 10,000; peak II, fractions 108–204, total optical density units 98,000.

The solution containing peak II was evaporated on a rotary evaporator at 30° (20 mm.) to a white solid. The solid was dissolved in water and the solution was again evaporated in order to remove traces of formic acid. This procedure was repeated three times. The solid was again dissolved in water and lyophilized to a white powder which was recrystallized from water as clusters of colorless needles: 3.1 g., 18%; m.p. 203–205° dec.

Anal. Calcd. for $C_{11}H_{17}N_5O_9P_2$: C, 31.06; H, 4.04; N, 16.46; P, 14.57; mol. wt., 425.3; adenine–strong acid–weak acid, 1:2:1. Found: C, 30.93; H, 4.15; N, 16.66; P, 14.77; equiv. wt. (by ultraviolet-absorption measurements), 410.6; mol. wt. (from titration data), 422.5 (pK = 4.00, 8.15); adenine–strong acid–weak acid, 1:2:1.[13]

Paper chromatography of the product gave single clean spots: solvent system A, R_f 0.77, R_{ADP} 0.96; solvent system B, R_f 0.52, R_{ADP} 1.15. The product gave a positive reaction when the chromatograms were sprayed with periodate–benzidine spray.

B. Dicyclohexylcarbodiimide Method.—A mixture of methylenediphosphonic acid (2.80 g., 16 mmoles), freshly distilled anhydrous pyridine (200 ml.), and tri-*n*-butylamine (28 ml.) was heated at 60° with stirring until a clear solution was obtained. After cooling to room temperature, isopropylideneadenosine (1.24 g., 4 mmoles) and dicyclohexylcarbodiimide (13 g., 64 mmoles) were added. The resulting solution was heated at 60° for 14 hr. with stirring with the careful exclusion of moisture. The reaction mixture (white precipitate plus supernatant liquid) was evaporated on the flash evaporator at 35° to a gummy solid. This material was treated with 50 ml. of water and the insoluble white solid was filtered off and washed with four 20-ml. portions of water. The filtrate and washings were combined and extracted with five 100-ml. portions of ether. The aqueous solution was concentrated to dryness on a flash evaporator at 30°. This process was repeated three times. Finally the residual sirup was dissolved in 30 ml. of water and the solution was lyophilized to produce a yellow solid. The solid was dissolved in 100 ml. of 10% acetic acid and the solution was heated for 1 hr. on the steam bath and then concentrated to dryness by use of the flash evaporator at 30°. The residue was dissolved in 30 ml. of water and the solution was concentrated to dryness. This procedure was repeated a total of four times.

The residue was dissolved in 30 ml. of water and the solution was adjusted to pH 8–9 with 1 *N* NH_4OH and applied to a Dowex-2 (formate form, X-8) ion-exchange column (4.5 × 13 cm). The column was washed with 1 l. of water and then with 1 l. of 0.1 *N* formic acid. Elution was carried out by a linear gradient technique with 1 l. of 0.1 *N* formic acid in the mixing chamber and 2 l. of 0.5 *N* formic acid in the reservoir, at a flow rate of about 1.5 ml./min., with 15-ml. fractions being collected. Fractionation was followed by ultraviolet-absorbancy measurements at 260 mμ. A single major ultraviolet-absorbing fraction was obtained (in addition to a very small fraction near the start of the elution which was discarded). This fraction (I)[7] occurred at tubes 113–165 and contained 11,500 O.D. units. After the eluting system described above was exhausted, elution was continued with 1 l. of 0.5 *N* formic acid in the mixing chamber and 3 l. of 1.2 N formic acid in the reservoir. This produced a single fraction (II), tubes 160–232 (numbered from start of new elution), which contained 39,000 O.D. units.

Fraction II, on paper chromatography, produced single spots in solvent systems A and B with R_f values essentially identical with those given by adenosine-5′-methylenediphosphonate prepared by the trichloroacetonitrile method. The fraction was concentrated on the flash evaporator to a white solid which was dissolved in a minimum of water; the solution was lyophilized. This last procedure was repeated to give 1.26 g. of a clean white solid. Adenosine-5′-methylenediphosphonate was recrystallized from water (4 ml.) as clusters of colorless needles: 1.05 g., 61%; m.p. 203–204° dec.; m.m.p. 203–204° dec. with a sample prepared by the trichloroacetonitrile method. The product produced single spots on paper chromatography with solvent systems A and B with R_f values essentially identical with those given by a sample prepared by the trichloroacetonitrile method: solvent system A, R_f 0.77, R_{ADP} 0.96; solvent system B, R_f 0.53, R_{ADP} 1.15.

Anal. Calcd. for $C_{11}H_{17}N_5O_9P_2$: mol. wt., 425.3. Found: mol. wt. (from titration data), 428 (pK_A = 3.90, 8.15); equiv. wt. (by ultraviolet-absorption measurements), 429.

The tricyclohexylammonium salt was prepared by the addition of cyclohexylamine (to pH 8) to an aqueous solution of the acid, followed by lyophilization to a white powder and crystallization from 95% ethanol (m.p. 156–157°).

Anal. Calcd. for $C_{29}H_{59}N_5O_9P_2$: C, 47.01; H, 7.91; N, 15.13; P, 8.36. Found: C, 47.18, H, 8.10; N, 15.07; P, 8.66.

Preparation of Adenosine-5′-methylphosphonate (V, R = CH_3).—Methylphosphonic acid (5 g., 0.052 moles) and isopropylideneadenosine (8 g., 0.26 moles) were dissolved in dry pyridine (50 ml.) and the solution was evaporated to dryness on a rotary evaporator at 30° (1 mm.). This procedure was repeated three times to assure a dry reaction mixture. The residue was dissolved in dry pyridine (100 ml.), dicyclohexylcarbodiimide (21.2 g., 0.104 mole) was added, and the solution was allowed to stand overnight at 35°. The mixture was diluted with water (100 ml.) and the solid was filtered off and washed thoroughly with water. The combined filtrate and washings were extracted three times with ether and the aqueous solution was evaporated to dryness on a flash evaporator at 30° (20 mm.). Water was added and the solution was again evaporated to dryness. This procedure was repeated until no odor of pyridine could be detected.

The solid was dissolved in acetic acid (150 ml., 10%); the solution was heated at 100° for 1.5 hr. and then evaporated to dryness on the rotary evaporator at 30° (20 mm.). The solid residue was redissolved in water and the solution was again evaporated to dryness. The residual white solid was dissolved in water (30 ml.), the insoluble material was filtered off, ethanol (75 ml.) was added to the clear filtrate, and the solution was allowed to stand overnight at room temperature. The crystalline precipitate was filtered and washed with ethanol: 8.3 g., 86%; m.p. 180–181° dec. The product showed a single spot

(13) Titration under similar conditions of a solution of ADP prepared by treating a solution of monosodium ADP (Pabst Laboratories) with Dowex 50 (H) ion-exchange resin gave adenine–strong acid–weak acid, 1:2:1 (pK = 4.20, 7.10).

on paper chromatography: solvent system A, R_f 0.77; solvent system B, R_f 0.52.

Anal. Calcd. for $C_{10}H_{16}O_6N_5P \cdot 0.5H_2O$: C, 37.30; H, 4.83; N, 19.74; P, 8.48; mol. wt., 344. Found: C, 37.30; H, 4.72; N, 19.87; P, 8.46; equiv. wt. (by ultraviolet-absorption measurements), 346.6.

Preparation of Adenosine-5′-ethylphosphonate (V, R = CH_2CH_3).—A solution of ethylphosphonic acid (4.6 g., 0.041 mole), isopropylideneadenosine (6.5 g., 0.031 mole), and dicyclohexylcarbodiimide (17.3 g., 0.084 mole) in 100 ml. of dry pyridine was allowed to stand overnight at 35° and the product was isolated as described for the preparation of adenosine-5′-methylphosphonate. After recrystallization from aqueous ethanol the crystalline product (4.7 g., 54%, m.p. 193–194°) showed a single spot upon paper chromatography: solvent system A, R_f 0.70; solvent system B, R_f 0.80.

Anal. Calcd. for $C_{11}H_{16}O_6N_5P \cdot 0.5H_2O$: C, 39.13; H, 5.20; N, 19.02; P, 8.41, mol. wt., 368.3. Found: C, 39.30; H, 5.46; N. 18.91; P, 8.32; equiv. wt. (by ultraviolet-absorption measurements), 361.4.

The Chemistry of Thioether-Substituted Hydroquinones and Quinones. III. An Unexpected Rearrangement of a Heterocyclic Group

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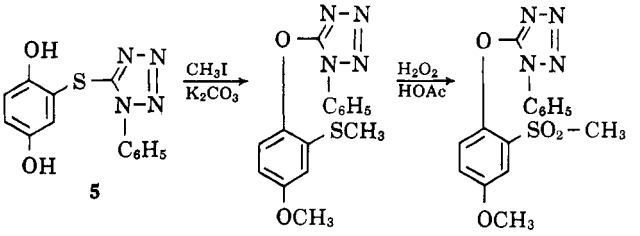
The structures of the methylation products of 1-phenyl-5-tetrazolyl thioether-substituted hydroquinones have been determined by n.m.r. studies. The structure was verified in one case by degradation and synthesis. A rearrangement of the tetrazole group from sulfur to oxygen was found to occur during the methylation.

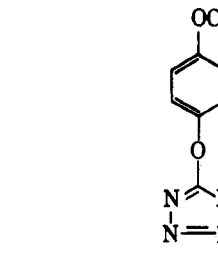
Discussion

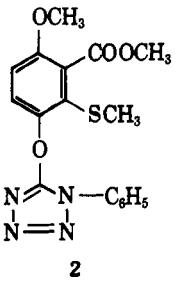
In the preceding paper[1] in this series concerned with the substituent effects in the 1,4-addition of 1-phenyl-5-mercaptotetrazole to monosubstituted quinones, it was necessary to methylate several of the resultant disubstituted hydroquinones so that the coupling constants of the hydroquinone ring protons could be determined. At first it was assumed that the expected dimethyl ethers had been obtained, but inspection of the n.m.r. spectra revealed that only one methoxyl group in the range τ 6.18–6.22 was present. However, another methyl group appeared in the range τ 7.55–7.82, suggesting the presence of an S–CH_3 group.

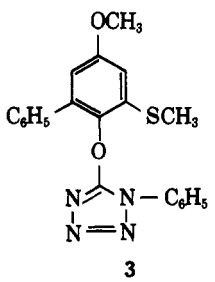
The four dimethyl derivatives, **1**, **2**, **3**, and **4**, reported previously,[1] all exhibited this S–CH_3 absorption. Inspection of the structure indicates that an unexpected rearrangement of the 1-phenyl-5-tetrazolyl group must have occurred. To elucidate this phenomenon, a simpler monothioether-substituted hydroquinone, 1′-phenyl-5′-tetrazolylthiohydroquinone[2] (**5**), was employed as a model for use in degradation studies. Methylation gave a dimethyl derivative whose n.m.r. spectrum exhibited one methoxyl at τ 6.18 and a three-proton peak at τ 7.60 indicative of an S–CH_3 group. Oxidation of this dimethyl derivative with peroxide in acetic acid produced the sulfone **7** which showed peaks in its n.m.r. spectrum at τ 6.17 and 6.76 assigned to methoxyl and methylsulfonyl, respectively. This sulfone was cleaved by strong alkali to give the tetrazole[3]

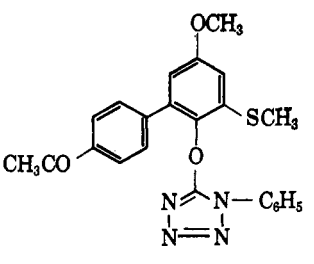


8 and the phenol **9**. The structure of **9** was confirmed by comparison with a sample synthesized by the sequence **11** → **12** → **13** → **14** → **9**. As further confirmation, the phenol **9** was allowed to react with 5-bromo-1-phenyltetrazole[4] (**10**) to produce the sulfone **7**, derived by oxidation from the original methylation product whose formula must be that represented by structure **6**. Since the methylation product **6** exhibited the S–CH_3 absorption and the sulfone **7** exhibited the









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(3) (a) G. Heller and A. Siller, *J. prakt. Chem.*, [2] **123**, 257 (1929); (b) M. Freund and H. Hempel, *Ber.*, **28**, 74 (1895).

(4) R. Stolle and Fr. Henke-Stark, *J. prakt. chem.*, [2] **124**, 261 (1930).