Table III. Bond Lengths (Å) in 1,4-Dihydronaphthoic Acid (1) with Estimated Standard Deviations in Parentheses

C(1)-C(2)	1.395 (3)	C(11)-O(1)	1.167 (2)
C(1)-C(9)	1.491 (3)	C(11)-O(2)	1.302 (3)
C(1)-C(11)	1.471 (3)	C(1)-H(1)	0.997 (24)
C(2)-C(3)	1.294 (4)	C(2)-H(2)	0.891 (31)
C(3)-C(4)	1.451 (4)	C(3)-H(3)	0.960 (35)
C(4)-C(10)	1.408 (3)	C(4)-H(4a)	0.952 (33)
C(5)-C(6)	1.288 (4)	C(4)-H(4b)	1.032 (30)
C(5)-C(10)	1.378 (3)	C(5)-H(5)	0.971 (30)
C(6)-C(7)	1.355 (4)	C(6)-H(6)	1.000 (30)
C(7)-C(8)	1.357 (3)	C(7)-H(7)	0.925 (34)
C(8)-C(9)	1.308 (3)	C(8)-H(8)	0.932 (29)
C(9)-C(10)	1.365 (3)	O(2)-H(20)	1.007 (44)

sponding to Marshall's "true boat" and "flattened boat", respectively.[4] We have now established the solid-state geometries of a representative dihydronaphthalene from each of these limiting cases.

Experimental Section

1,4-Dihydronaphthoic acid was prepared as previously described[1] and crystallized from ethanol.

Crystal data: $C_{11}H_{10}O_2$; $M_r = 174$; $a = 5.566$ (1), $b = 6.146$ (1), $c = 29.170$ (4) Å; $\beta = 86.48$ (1)°; $V = 817.1$ Å^3; $D_c = 1.2$, $D_m = 1.2$ (by floatation); monoclinic, space group $P2_1/c$; $Z = 4$; λ(Mo Kα) = 0.710 69 Å.

Initial survey photographs exhibited the systematic absences $0kl$ with $l = 2n + 1$ and $h00$ with $h = 2n + 1$ with no general conditions, indicating the space group $P2_1/c$ with b unique. A selected crystal (0.8 × 0.4 × 0.4 mm) was then mounted on an Enraf-Nonius CAD-4F four-circle diffractometer. An approximate orientation matrix was derived from the coordinates of 21 reflections observed on a rotation photograph; these reflections were automatically centered. The orientation matrix and cell parameters were optimized by a least-squares refinement using the angular coordinates of 25 reflections with $16 < \theta < 18°$.

Automatic data collection by using bisecting geometry yielded 2468 reflections. Four absorption curves were also collected. After application of Lorentz and polarization corrections, the data were merged to give 1371 independent structure amplitudes with $I > 3\sigma(I)$, where I is the final intensity and $\sigma(I)$ is the standard deviation derived from counting statistics.

The structure was solved by direct methods with MULTAN[13] and refined by least-squares[14] methods with the block-diagonal approximation to the full normal matrix. All the hydrogen atoms were evident from a difference Fourier synthesis, and the structure was further refined by full-matrix least-squares methods on a CDC 7600 computer. A three-term Chebyshev series was used as a weighting scheme[15] for the final cycles of refinement, which included the positional parameters and temperature factors (which were anisotropic for the carbon and oxygen atoms).

A comparison of F_{obsd} and F_{calcd} values showed that a correction for the effects of absorption was not necessary despite the rather large size of the crystal used, but one reflection having $F_{obsd} > 2200$ was excluded from the final cycles of refinement. A final R of 0.0484 ($R_w = 0.0676$) was obtained. Bond lengths and angles are presented in Tables II and III.

Registry No. 1, 5111-73-9.

Supplementary Material Available: Tables of atomic coordinates together with observed and calculated factors and thermal parameters for the carbon and oxygen atoms (12 pages). Ordering information is given on any current masthead page.

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Improved Syntheses of (±)-*trans*-9,10-Dihydroxy-9,10-dihydrobenzo[*a*]pyrene and of (±)-*trans*-1,2-Dihydroxy-1,2-dihydrodibenz[*a*,*h*]anthracene

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Non-K-region dihydro diols of polycyclic aromatic hydrocarbons (PAH) generated by the epoxide hydrolase mediated hydration of metabolically formed arene oxides play an important role in the metabolism of PAH.[1-6] They are precursors of dihydro diol epoxides some of which are considered ultimate carcinogenic metabolites of PAH.[7-10]

From the two most thoroughly tested carcinogenic unsubstituted PAH, benzo[*a*]pyrene and dibenz[*a*,*h*]anthracene (DBA), only the non-K-region dihydro diols with the olefinic bond in the bay region,[11] *trans*-7,8-dihydroxy-7,8-dihydrobenzo[*a*]pyrene and *trans*-3,4-dihydroxy-3,4-dihydrodibenz[*a*,*h*]anthracene, have been intensively studied.

The biological role of the non-K-region dihydro diols of these hydrocarbons, **6b** and **13b**, where the olefinic bond is not part of the bay region (in **13b** the position of the double bond is called the M region[12]) is much less well-known, although **6b** and **13b** are formed metabolically in considerable amounts.[13,14] The apparent lack of interest in the dihydro diols **6b** and **13b** stems partly from the fact that their syntheses described in the literature[10,15,16] are more difficult than those of the better studied isomers.[10,16-18]

We therefore devised improved synthetic pathways for **6b** and **13b** that resulted in a six-step synthesis of **6b** (Scheme I) and an eight-step synthesis of **13b** (Scheme II) starting with commercially available compounds.

For the synthesis of **6b**, 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one was transformed to **1**. McCaustland et al.[15] do not recommend the Huang-Minlon procedure[19] for this deoxygenation possibly because of azine formation; they used instead the more laborious Wolff-Kishner method as originally described for the synthesis of **1**.[20]

We found, however, that **1** can be prepared from 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one in very good yield if the Huang-Minlon procedure is slightly modified.

Dehydrogenation of **1** to **2** was achieved with DDQ according to Fu et al.[21] in 65% yield. Due to its tendency to aromatize **2** was never obtained free of benzo[*a*]pyrene. Since this hydrocarbon can be easily removed in the next step, no attempt was made to purify **2**.

The dehydrogenated mixture of hydrocarbons containing **2** was subjected to a Prévost reaction with silver benzoate, yielding **3a** which was contaminated with a small amount of the cis isomer **4a**. McCaustland et al.[15] achieved the separation of the geometrical isomers on the level of the tetrahydro diols **3b** and **4b** by fractional crystallization. This method according to our own experience does not always work well. One recrystallization of the mixed dibenzoates **3a** and **4a** from $CHCl_3$-MeOH, however, furnished easily the *trans*-dibenzoate **3a** in 62% yield without a trace of **4a**. The purity was checked by TLC after methanolysis of **3a** and **4a**. It is interesting to note that the *trans*-dibenzoate **3a** has a higher mobility on silica gel

† This study is part of the M.S. theses of G.S. and H.F.

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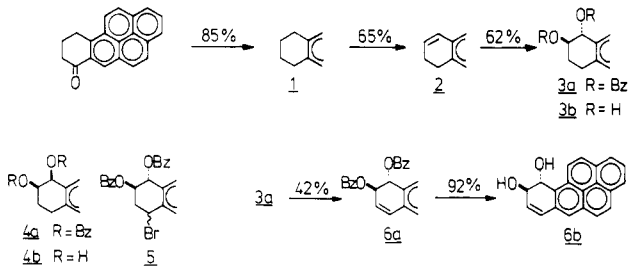
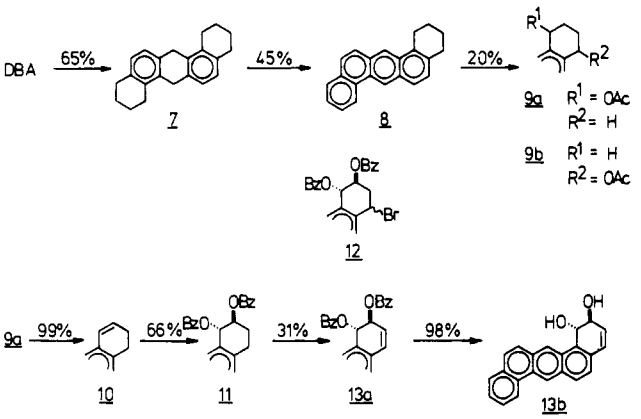
Scheme I



Scheme II



than the cis isomer **4a**, whereas the trans diol **3b** has as usual a smaller R_f value than its cis isomer **4b**.

The remaining steps to **6b** were performed essentially as described in the literature.[15]

For the synthesis of **13b**, dibenz[*a*,*h*]anthracene was hydrogenated in the presence of sodium in boiling *n*-pentanol in 65% yield to 1,2,3,4,7,8,9,10,11,14-decahydrobenz[*a*,*h*]anthracene (**7**). Lijinski[22] obtained under similar conditions a mixture of 7,14-dihydro- and 1,2,3,4,8,9,10,11-octahydrodibenz[*a*,*h*]anthracene.

7 is easily dehydrogenated (even by atmospheric oxidation) in the 7,14-position to 1,2,3,4,8,9,10,11-octahydrodibenz[*a*,*h*]anthracene.

The dehydrogenation of **7** to **8** was performed with 7.2 equiv of DDQ at room temperature, the reaction being monitored by GC. Under these conditions a mixture of 61% **8**, 11% 1,2,3,4,8,9,10,11-octahydrodibenz[*a*,*h*]-anthracene, and 28% DBA was obtained that could be efficiently separated by chromatography on silica gel.

8 could also be synthesized in 72% yield from 1,2-dihydrodibenz[*a*,*h*]anthracen-4(3*H*)-one[16] under the same conditions as described for **1**.

The partial dehydrogenation of **8** to **10** was not possible with DDQ. Under all conditions investigated either no reaction or aromatization to DBA occurred.

Therefore, an alternative route to **10** was devised by using the acetoxylation of **8** with lead(IV) acetate.[20] This reaction furnished a mixture of **9a** (but no detectable amount of **9b**) and 14-acetoxy-1,2,3,4-tetrahydrodibenz-[*a*,*h*]anthracene,[23] the latter being easily separable from **9a** by chromatography due to its facile autoxidation to the more polar 1,2,3,4-tetrahydro-7,14-dibenz[*a*,*h*]anthraquinone.[24] The purity of **9a** was checked by GC and its identity determined by comparing the NMR data with those of **9b** obtained by an independent synthesis.[25]

The highly selective attack of lead(IV) acetate at C-1 of **8** resembles the situation in **1** where under similar conditions mainly 10-acetoxy-7,8,9,10-tetrahydrobenzo-[*a*]pyrene is formed.[20,26] The reason for this selectivity being in both cases the relative ease of carbonium ion formation at the benzylic carbon atom which forms part of a bay region.[27]

Hydrolysis and dehydration of **9a** in boiling acetic acid in the presence of a catalytic amount of concentrated HCl yielded **10**. After Prévost reaction with silver benzoate, **11** was obtained in 66% yield. There was no indication of the formation of the *cis*-dibenzoate.

The remaining steps to **13b** were performed essentially as described in the literature[15] for **6b**.

Experimental Section

9,10-Dihydrobenzo[*a*]pyren-7(8*H*)-one was purchased from Aldrich and dibenz[*a*,*h*]anthracene from Fluka. *N*-Bromosuccinimide (NBS), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were supplied by Merck.

The NMR spectra were measured on a Varian EM 360 spectrometer at 60 MHz with tetramethylsilane as the internal standard in $CDCl_3$ unless stated otherwise. GC chromatograms were obtained with a Packard 427 chromatograph on a 2-m column with 3% OV-17 on Chromosorb WAW-DMCS as the stationary phase.

Melting points are uncorrected. All compounds gave satisfactory microanalyses for C and H (within ±0.3%). Mass and UV spectra were in accordance with the assigned structure.

7,8,9,10-Tetrahydrobenzo[a]pyrene (1). A mixture of 9,10-dihydrobenzo[*a*]pyren-7(8*H*)-one (24.5 g, 91 mmol) and 100% hydrazine hydrate (13.8 g, 270 mmol) in triethylene glycol (150 mL) was stirred at 110 °C for 60 min. After the mixture cooled,

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(23) 14-Acetoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracene: NMR (CD_2Cl_2) δ 1.6–2.1 (m, 4, $H_{2,3}$), 2.50 (s, 3, CH_3), 2.8–3.7 (m, 4, $H_{1,4}$), 7.1–7.9 (m, 7, aromatic), 8.7–8.9 (m, 1, H_8), 8.97 (s, 1, H_7).
(24) 1,2,3,4-Tetrahydro-7,14-dibenz[*a*,*h*]anthraquinone: yellow crystals (MeOH); mp 187 °C; NMR δ 1.6–1.9 (m, 4, $H_{2,3}$), 2.6–2.9 (m, 2, H_4), 3.1–3.4 (m, 2, H_1), 7.3–8.1 (m, 7, aromatic), 9.4–9.6 (m, 1, H_8).
(25) Compound **9b** was prepared by acetylation (Ac_2O, pyridine) of 4-hydroxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracene;[16] **9b** was obtained as white crystals: mp 184 °C; NMR δ 1.8–2.2 (m, 4, $H_{2,3}$), 2.10 (s, 3, CH_3), 3.0–3.4 (m, 2, H_1), 6.0–6.2 (m, 1, H_4), 7.2–8.0 (m, 7, aromatic), 8.33 (s, 1, H_{14}), 8.5–8.9 (m, 1, H_8), 8.97 (s, 1, H_7).
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KOH powder (20.4 g, 360 mmol) was slowly added and the mixture heated to 140 °C for 2 h. The reaction mixture was poured on ice and made acidic with concentrated HCl, and the precipitate was isolated by filtration, dried, and extracted in a Soxhlet apparatus with petroleum ether for 6 h. The extract was evaporated to dryness and recrystallized from benzene–EtOH, yielding **1**: 19.8 g (85%); off-white powder; mp 112 °C (lit.[28] mp 113 °C); NMR δ 1.6–2.0 (m, 4 $H_{8,9}$), 2.8–3.2 (m, 4, $H_{7,10}$), 7.5–8.0 (m, 8, aromatic).

7,8-Dihydrobenzo[*a*]pyrene (2). DDQ (11.4 g, 50 mmol) was added to the solution of **1** (12.8 g, 50 mmol) in benzene (600 mL) resulting in a dark brownish green suspension. Stirring under argon at room temperature for 5 h resulted in a yellowish solution with a gray precipitate. The reaction mixture was percolated through neutral alumina (activity II–III) washing with benzene. The extract was evaporated leaving a yellowish solid (12.6 g) consisting of 66% **2**, 15% **1**, and 19% benzo[*a*]pyrene as determined by GC (column temperature: 280 °C); this product was used directly in the next step. NMR (of **2**): δ 2.0–2.5 (m, 2 H_8), 2.97 (t, 2 H_7), 6.0–6.3 (m, 1, H_9), 7.27 (d, 1, H_{10}), 7.4–8.1 (m, 8, aromatic).

***trans*-9,10-Bis(benzoyloxy)-7,8,9,10-tetrahydrobenzo[*a*]pyrene (3a).** A mixture of the hydrocarbons from the previous reaction (11.8 g, 31 mmol, of **2**) and silver benzoate (15.4 g, 67 mmol) in dry benzene (400 mL) was treated under reflux with a solution of iodine (7.8 g, 31 mmol) in benzene (200 mL). After 4 h the greenish suspension was filtered while hot, the filtrate was brought to dryness, and the unreacted hydrocarbons were removed by chromatography over silica gel eluted with petroleum ether–$CHCl_3$ (4:1). Further elution with CH_2Cl_2 yielded the crude dibenzoate which was recrystallized from $CHCl_3$–MeOH to give **3a**: 9.5 g (62%); white powder; mp 167 °C; NMR δ 2.3–2.6 (m, 2, H_8), 3.2–3.5 (m, 2, H_7), 5.7–5.9 (m, 1 H_9), 7.1–7.4 (m, 7, H_{10} and aromatic), 7.7–8.1 (m, 12, aromatic).

***trans*-9,10-Bis(benzoyloxy)-9,10-dihydrobenzo[*a*]pyrene (6a).** NBS (3.1 g, 17 mmol) and benzoyl peroxide (50 mg) were added to a solution of **3a** (8.6 g, 17 mmol) in CCl_4 (400 mL). The resulting suspensions was brought to reflux under argon. Two more portions of benzoyl peroxide (50 mg) were added after 40 and 60 min, respectively. Half an hour after the last addition the suspension was cooled and filtered, and the filtrate was evaporated to dryness. The resulting yellow solid containing **5** was dissolved in dry THF (100 mL) and stirred after the dropwise addition of DBN (9 mL) at 5 °C under argon for 48 h. The resulting solution was diluted with ethyl acetate (400 mL), extracted successively with ice–water, ice-cold 0.1 N HCl, ice-cold 5% aqueous $NaHCO_3$, and water, dried, and concentrated. Chromatography over neutral alumina (activity II–III) with petroleum ether–CH_2Cl_2 (1:1) yielded **6a**: 3.5 g (42%); off-white powder; mp 150–153 °C; NMR δ 5.7–5.9 (m, 1, H_9), 6.3–6.6 (m, 1, H_8), 7.0–7.4 (m, 8, $H_{7,10}$ and aromatic), 7.7–8.5 (m, 12, aromatic).

***trans*-9,10-Dihyroxy-9,10-dihydrobenzo[*a*]pyrene (6b).** A solution of **6a** (3.0 g, 6 mmol) in a mixture of dry THF (100 mL) and dry MeOH (100 mL) was stirred under argon, treated with NaOMe (0.2 g), and heated to 80 °C for 15 min. The resulting orange solution was neutralized with acetic acid and concentrated. **6b** was precipitated with water, isolated by filtration, and washed with 70% aqueous MeOH to remove methyl benzoate: 1.6 g (92%); off-white powder; mp 203–205 °C (lit.[15] mp 209–210 °C); NMR (acetone-d_6) δ 4.02 (d, 1, OH), 4.24 (d, 1, OH), 4.4–4.6 (m, 1, H_9), 5.6–5.8 (m, 1, H_{10}), 6.3–6.5 (m, 1, H_8), 7.02 (d, 1, H_7), 8.0–8.7 (m, 8, aromatic).

For biochemical investigations **6b** was purified by preparative HPLC with LiChrosorb RP-18 (10 μm; 16 × 250 mm column) as the stationary and 46% (v/v) acetonitrile in water as the mobile phase at a flow rate of 18 mL/min. A maximum amount of 50 mg could be purified in one run under the described conditions.

1,2,3,4,7,8,9,10,11,14-Decahydrodibenz[*a*,*h*]anthracene (7). A suspension of DBA (27.8 g, 100 mmol) in *n*-pentanol (2.5 L) was heated to reflux while sodium (100 g) was added in small pieces within 4 h. The resulting orange solution was cooled under argon, diluted with benzene (2.5 L), and washed neutral with brine. After removal of the solvents under reduced pressure, the resulting yellow oil was recrystallized twice from $CHCl_3$–MeOH and yielded **7**: 18.8 g (65%); white powder; mp 178 °C (lit.[29] mp 179–180 °C); NMR δ 1.6–2.0 (m, 8, $H_{2,3,9,10}$), 2.5–2.9 (m, 8, $H_{1,4,8,11}$), 3.80 (s, 4, $H_{7,14}$), 6.90 (2 d, 4, $H_{5,6,12,13}$).

1,2,3,4-Tetrahydrodibenz[*a*,*h*]anthracene (8). A solution of **7** (18.7 g, 65 mmol) in benzene (2 L) was treated with DDQ (53.1 g, 234 mmol) was stirred at room temperature for 4 days. The resulting light suspension was concentrated and chromatographed over neutral alumina with petroleum ether–$CHCl_3$ (17:3). The eluate was monitored by GC (column temperature was a linear gradient, 260–330 °C/10 min). The hydrogenated derivatives of DBA are eluted in the order of decreasing hydrogen content, DBA being the last compound leaving the column. The fraction containing **8** was brought to dryness, yielding **8**: 8.3 g (45%); yellowish platelets; mp 210 °C (lit.[22] mp 211–212.5 °C); NMR δ 1.7–2.1 (m, 4, $H_{2,3}$), 2.8–3.3 (m, 4, $H_{1,4}$), 7.2–7.9 (m, 7, aromatic), 8.37 (s, 1, H_{14}), 8.7–8.9 (m, 1, H_8), 9.02 (s, 1, H_7).

1-Acetoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracene (9a). Lead(IV) acetate (85%; 17.1 g, 31 mmol) was added under argon to a solution of **8** (8.0 g, 28 mmol) in dry benzene (360 mL) and dry glacial acetic acid (240 mL). The mixture was heated at 80 °C for 5 h, and then ethylene glycol (16 mL) was added. After extraction of the reaction mixture with water, saturated $NaHCO_3$ solution, and water, drying, and concentration, a dark red oil was obtained which was chromatographed over neutral alumina (activity II–III) with petroleum ether–$CHCl_3$ (3:2) to yield **9a**: 1.9 g (20%); colorless crystals; mp 172 °C; NMR δ 1.7–2.3 (m, 4, $H_{2,3}$), 203 (s, 3, CH_3), 2.8–3.1 (m, 2, H_4), 6.6–6.8 (m, 1, H_1), 7.1–8.0 (m, 7, aromatic), 8.23 (s, 1, H_{14}), 8.5–8.8 (m, 1, H_8), 8.97 (s, 1, H_7).

3,4-Dihydrodibenz[*a*,*h*]anthracene (10). Two drops of concentrated HCl were added at 120 °C under argon to a solution of **9a** (1.8 g, 5.3 mmol) in glacial acetic acid (90 mL). After being heated for 1 h, the resulting suspension was poured into water (200 mL), and the precipitate was isolated by filtration and washed neutral to yield **10**: 1.4 g (99%); colorless platelets; mp 204 °C; NMR (CD_2Cl_2) δ 2.2–2.6 (m, 2, H_3), 3.00 (t, 2, H_4), 6.1–6.5 (m, 1, H_2), 7.2–8.0 (m, 8, H_1 and aromatic), 8.57 (s, 1 H_{14}), 8.7–8.9 (m, 1, H_8), 9.03 (s, 1, H_7).

***trans*-1,2-Bis(benzoyloxy)-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracene (11).** Silver benzoate (2.9 g, 12.6 mmol) was added to a solution of **10** (1.3 g, 4.7 mmol) in dry THF (50 mL) under argon. The resulting suspension was treated at 80 °C with a solution of iodine (1.5 g, 6.0 mmol) in dry benzene (50 mL). After 3 h the dark yellow suspension was filtered while hot, and the filtrate was brought to dryness and chromatographed over silica gel with $CHCl_3$–petroleum ether (4:1). The fraction containing **11** was recrystallized from acetone, yielding **11**: 1.6 g (66%); pale yellow solid; mp 156 °C (lit.[16] mp 164–166 °C); NMR δ 2.2–2.6 (m, 2, H_3), 3.0–3.3 (m, 2, H_4), 5.7–5.9 (m, 1, H_2), 7.1–8.2 (m, 18, H_1 and aromatic), 8.47 (s, 1 H_{14}), 8.6–8.9 (m, 1, H_8), 9.13 (s, 1, H_7).

***trans*-1,2-Bis(benzoyloxy)-1,2-dihydrodibenz[*a*,*h*]anthracene (13a).** NBS (562 mg, 3.1 mmol) and 2,2′-azobis(isobutyronitrile) (25 mg) were added to a solution of **11** (1.5 g, 2.9 mmol) in CCl_4 (280 mL). The resulting suspension was brought to reflux under argon and irradiated with a heat lamp (Osram Vitalux, 300 W) for 40 min. After cooling, the reaction mixture was filtered and the filtrate evaporated to dryness. The resulting yellow solid containing **12** was dissolved in dry THF (60 mL), treated with DBN (0.5 mL), and stirred at 5 °C under argon for 3 days. The resulting solution was concentrated, dissolved in CH_2Cl_2 (100 mL), and extracted three times with water. The organic phase was dried, concentrated, and chromatographed over silica gel, eluting with $CHCl_3$–petroleum ether (4:1). The fraction containing **13a** was evaporated to dryness and recrystallized from EtOH–$CHCl_3$, yielding **13a**: 0.47 g (31%); off-white powder; mp 141–143 °C (lit.[10] mp 143–145 °C); NMR (CD_2Cl_2) δ 5.8–6.0 (m, 1, H_2), 6.2–6.6 (m, 1 H_3), 7.03 (d, 1, H_4), 7.2–8.3 (m, 18, H_1 and aromatic), 8.67 (s, 1, H_{14}), 8.7–8.9 (m, 1, H_8), 9.13 (s, 1, H_7).

***trans*-1,2-Dihydroxy-1,2-dihydrodibenz[*a*,*h*]anthracene (13b).** A solution of **13a** (468 mg, 0.9 mmol) in dry THF (10 mL) was treated with a solution of NaOMe (112 mg, 2.1 mmol) in dry MeOH (10 mL) under argon at 0 °C. After being stirred for 4 h, the reaction mixture was worked up as described for the preparation of **6b**, yielding **13b**: 275 mg (98%); off-white powder;

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mp 256–258 °C (lit.[10] mp 257–259 °C); NMR (THF-d_8) δ 4.1–4.4 (m, 1, H_2), 5.4–5.6 (m, 1, H_1), 6.0–6.4 (m, 1, H_3), 6.67 (d, 1, H_4), 7.2–8.1 (m, 7, aromatic), 8.7–8.9 (m, 1, H_8), 8.83 (s, 1, H_{14}), 9.13 (s, 1, H_7).

For biochemical purposes **13b** was purified by HPLC in essentially the same way as described for **6b**.

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Registry No. **1**, 17750-93-5; **2**, 17573-23-8; **3a**, 79970-83-5; **5**, 79970-84-6; **6a**, 79970-85-7; **6b**, 58030-91-4; **7**, 72390-46-6; **8**, 153-39-9; **9a**, 79970-86-8; **9b**, 79970-87-9; **10**, 79970-88-0; **11**, 79970-89-1; **12**, 79970-90-4; **13a**, 79970-91-5; **13b**, 79301-84-1; 9,10-dihydrobenzo[*a*]pyran-7(8*H*)-one, 3331-46-2; silver benzoate, 532-31-0; dibenz[*a*,*h*]anthracene, 53-70-3; 14-acetoxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracene, 79970-92-6; 1,2,3,4-tetrahydro-7,14-dibenz[*a*,*h*]anthraquinone, 79970-93-7; 4-hydroxy-1,2,3,4-tetrahydrodibenz[*a*,*h*]anthracene, 79970-94-8.

Improved 3′-O-Phosphorylation of Guanosine Derivatives by O^6-Oxygen Protection

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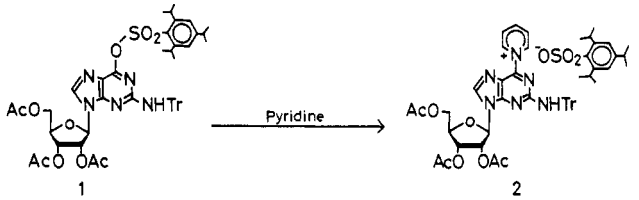
In oligonucleotide synthesis there have still remained some crucial problems during the elongation of oligonucleotide chains.[1] One of them is the side reaction of a condensing agent with the O^6 carbonyl oxygen of the guanosine moiety which occurs to an appreciable extent especially in the ribo series under the usual conditions. Reese[2] reported the reaction of arenesulfonyl azolides with the O^6-carbonyl group of guanosine derivatives to give O^6-azole-substituted guanosine derivatives via O^6-sulfonylated intermediates. On the other hand, we found that O^6-sulfonylated guanosine derivatives such as compound **1** were gradually converted in dry pyridine to pyridinium sulfonate derivatives like compound **2**. From



1 2

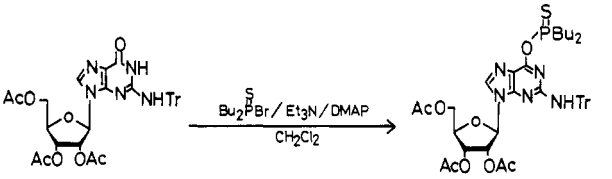
these results, we have felt the necessity of protecting the reactive O^6 position of the guanine moiety with an appropriate protecting group. In a previous paper,[3] we demonstrated the di-*n*-butylthioxophosphoranyl group as a possible blocking group of the O^6-carbonyl function since this group was relatively stable under the conditions where acetyl ester groups could be removed.

Table I. Phosphorylation of 3 with 4 by Use of TPS

ratio of 4/3	ratio of TPS/3	time, h	% yield of 5
1.2	2.2	7	15
2.2	1.1	24	28
4.0	2.0	24	16

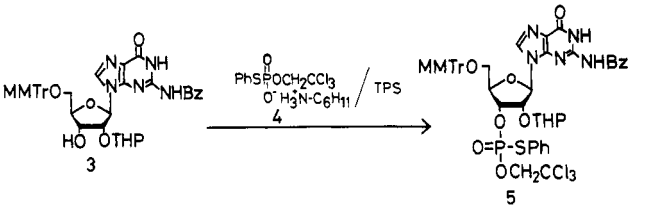
Table II. Phosphorylation of 6 with 4

ratio of 4/6	condensing agent	ratio of TPS or DMS/6	time, h	% yield 5	% yield 10	total % yield of 5 plus 10
1.2	TPS	2.4	72	36	34	70
1.5	TPS	3.0	12	50	33	83
4.0	TPS	2.0	5.5	35	48	83
1.2	DMS	2.4	45	52	39	91
4.0	DMS	2.0	24	55	33	88



In this paper, we report the importance of protecting the O^6-carbonyl group for phosphorylation of guanosine derivatives.

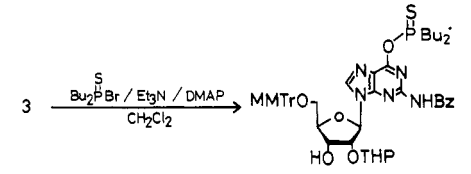
First, we chose N^2-benzoyl-2′-*O*-(tetrahydropyranyl)-5′-*O*-(methoxytrityl)guanosine (**3**) as a substrate for introducing a phosphoryl group onto the 3′-hydroxyl group. As a new phosphorylating agent, cyclohexylammonium 2,2,2-trichloroethyl *S*-phenyl phosphorothioate (**4**), was



3 5

employed. When **3** (0.5 mmol) was treated with **4** (0.6 mmol) in the presence of TPS (1.1 mmol) in dry pyridine (5 mL) for 7 h, the phosphorylated product **5** was isolated in only 15% yield after the usual workup (extraction, evaporation, and chromatography on silica gel). All attempts to improve the yield of **5** under various conditions were unsuccessful (see Table I).

In these reactions considerable amounts of byproducts were formed owing to the side reactions of **4** and TPS with the O^6-carbonyl group of **3** and **5**. Therefore, the di-*n*-butylthioxophosphoranyl group was introduced as a protecting group for the guanine residue to avoid such side reactions. When **3** (1 mmol) was treated with di-*n*-butylthioxophosphoranyl bromide[4] (1.5 mmol) and triethylamine (1.25 mmol) in the presence of 4-(dimethylamino)pyridine (DMAP, 0.04 mmol) in dry CH_2Cl_2 at room temperature for 4 h, the O^6-thioxophosphino derivative **6**



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