(0.072 g, 0.66 mmol). The reaction mixture was refluxed for 68 h and then stirred at room temperature for 24 h. The solvent was removed in vacuo. The ^{31}P NMR ($CDCl_3$) spectrum of the solid residue contained signals for the biisophosphindoline **8**, δ −12.4, the biisophosphindoline monoxide **6**, δ −1.81 and +53.1 (d, $^3J_{PP}$ = 24.4 Hz) and an upfield signal at δ −60.6, which on proton coupling had J_{PH} = 175.8 Hz and was presumed to be that of a secondary phosphine not further examined.

1-[1-(2-Phenyl)isophosphindolinyl]-2-phenylisophosphindoline 2-Oxide (6). To 100 mL of dry benzene was added pyridine (1.797 g, 13.26 mmol) and trichlorosilane (0.599 g, 4.42 mmol) under N_2 at 0 °C. After 20 min dimer **3** (0.400 g, 0.884 mmol) was added to the mixture. The mixture was stirred for 48 h under N_2 and then cooled in an ice–water bath while being hydrolyzed with 30 mL of 30% NaOH. The aqueous layer was separated and extracted with two 20-mL portions of benzene. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The light yellow oil was dissolved in 5 mL of chloroform and a small amount of silica gel was added to the solution. After being stirred for 10 min the solution was filtered and concentrated to give 0.164 g of **6** (44.1%) as an oil not readily crystallizing. ^{31}P and ^{13}C NMR data are given in Table I. Anal. Calcd for $C_{28}H_{24}OP_2$: *m/z* 438.1303. Found: *m/z* 438.1306.

2,2′-Diphenyl-1,1′-biisophosphindoline 2,2′-Dioxide (7). To compound **6** (0.164 g, 0.374 mmol) in 0.3 mL of $CDCl_3$ was added an excess of *tert*-butyl hydroperoxide. The ^{31}P NMR spectrum (δ +53.4) indicated a quantitative conversion of **6** to the dioxide **7** as an oil not readily crystallizing. ^{13}C NMR data are given in Table I. Anal. Calcd for $C_{28}H_{24}O_2P_2$: *m/z* 454.1252. Found: *m/z* 454.1253.

Registry No. **1**, 102979-51-1; **3**, 102979-52-2; **6**, 102979-53-3; **7**, 102979-54-4; **8**, 102979-55-5; phenylsilane, 694-53-1; trichlorosilane, 10025-78-2.

Quinoline-2-aldoxime Methiodide

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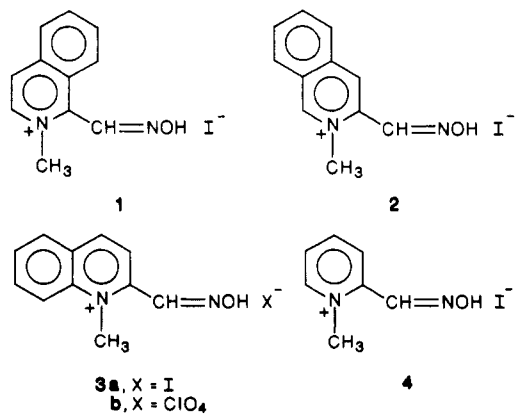
Samples of 3,4-, 4,5- and 5,6-benzannelated analogues **1–3** of 2-pyridinealdoxime methiodide (2-PAM; **4**) were desired to assess regiostructure–activity relationships of hydrophobic areas near the anionic site of the enzyme acetylcholinesterase. Enhanced hydrophobic binding in

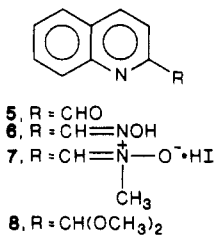


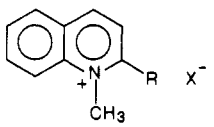
an appropriate analogue may provide for greater efficacy in the displacement of covalently bonded organophosphates from the enzyme. Isoquinoline quaternary salt **2** is unknown; **1** is known, but synthetic methodologies have not been described,[1] and the pharmaceutically desirable quinoline quaternary iodide **3a** has not been reported. The quaternary perchlorate salt **3b** has been described as an intermediate for the synthesis of monomethine cyanine dyes.[2] Several methods for the synthesis of **3a** are compared in this article.

Results and Discussion

Quaternization of quinoline-2-carboxaldehyde (**5**) or its oxime **6** would seem to represent a straightforward approach leading to the synthesis of **3a**. Aldehyde **5** is readily prepared by the oxidation of quinaldine[3] or by the hydrolysis of 2-dibromomethylquinoline.[4] The oxime **6** is available from **5**[5] or by reacting hydroxylamine hydrochloride with 2-dibromomethylquinoline (23% yield). However, quaternization of **5** with iodomethane at 60 °C in a pressure bottle for 50 days provides **9** in only 26% yield.[6] Earlier attempts to quaternize oxime **6** were unsuccessful.[7]

Quaternization reactions are known to be accelerated by polar aprotic solvents of high dielectric constant,[8] and nitromethane has been found to be the solvent of choice for quaternizing pyridine aldoximes that are difficult to alkylate.[1,9] However, we observed that methylation of **6** with CH_3I in nitromethane yields the nitrone hydriodide **7** (33% yield) rather than **3a**.[10,11]





9, R = CHO, X = I
10, R = $CH(OCH_3)_2$, X = I
11, R = $CH(OH)_2$, X = I
12, R = CH=NOH, X = I_3
13, R = CH_3, X = I
14, R = CH_3, X = I_3
15, R = $CH=NC_6H_5$, X = I
16, R = $CH=NC_6H_4N(CH_3)_2$-*p*, X = I

Although approaches leading to **3a** via quaternization of **5** or **6** were clearly unsatisfactory, quaternization of

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(10) Details of methylation of **6** yielding **7** and characterization of the free base of **7** by mass spectra analysis and unequivocal synthesis are given as supplementary material.
(11) (a) For a similar observation, see: Hackley, B. E., Jr.; Poziomek, E. J.; Steinberg, G. M.; Mosher, W. A. *J. Org. Chem.* **1962**, *27*, 4220–4222. Methylation of 6-methylpyridine-2-aldoxime yields a nitrone. (b) Methylation of the oxime nitrogen rather than quinoline nitrogen likely reflects steric hindrance by the peri hydrogen at C-8 and the electron-withdrawing (hydroxyimino)methyl group at C-2. For a comparison of quinoline peri hydrogen steric effects with the steric effects of 2-methyl group in pyridine, see: Deady, L. W.; Stillman, D. C. *Aust. J. Chem.* **1976**, *29*, 1745–1748. A (hydroxyimino) methyl group at the 2-position of pyridine (pK_a ~ 5.17) reduces the pK_a to ~3.42–3.63. See ref 7b and: Hanania, G. I. H.; Irvine, D. H. *J. Chem. Soc.* **1962**, 2745–2749. Cecchi, P. *Ric. Sci.* **1958**, *28*, 2526–2531; *Chem. Abstr.* **1959**, *53*, 14650d.

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acetal 8, prepared from aldehyde 5 in 80% yield, proceeded in a facile manner to give acetal methiodide 10 in 64% yield. Acetal or ketal formation is known to facilitate quaternization of pyridine-2-carboxaldehyde and related heterocyclic systems,[12] possibly owing to partial neutralization of the deleterious electron-withdrawing properties of the C=O functionality and mainly because of the greater rotational freedom for the acetal group providing a concomitant decreased steric crowding in the approach of the electrophile to nitrogen.

Hydrolysis of acetal 10 afforded aldehyde hydrate 11 (NMR, IR), which upon oximation produced 3a in 20% overall yield. The direct conversion of 10 to 3a could be carried out by effecting the hydrolysis of 10 in the presence of hydroxylamine hydrochloride. A maximum yield of 45% of the desired oxime 3a could be achieved by conducting the reaction in 6% aqueous HCl solution at 100 °C for 90 min. In stronger acid medium (18% aqueous HCl), the yield of 3a dropped to 24% due to the formation of a water insoluble oxime triiodide 12 (35% yield). This product was identical in all respect with the triiodide prepared from 3a by treatment with I_2/KI. Formation of 12 from 10 increases with longer reaction times, higher temperatures and greater concentrations and is a consequence of the oxidation of I^- by hydroxylamine hydrochloride in aqueous HCl solution.[13] Similarly, quinaldine methiodide (13) may be converted to the triiodide 14 by reaction with I_2/KI,[14] HI/$NaNO_2$[14] or hydroxlamine hydrochloride in aqueous HCl solution.

Oxime 3a also was prepared by the hydrolysis and oximation of known aldimines 15[14] and 16[15] in 58% and 20% maximum yields, respectively. Again, triiodide 12 is a byproduct whose formation is dependent upon reaction conditions previously described. This method of preparation of 3a has the better overall yield and involves the fewest steps from commercially available and inexpensive quinaldine.

Experimental Section

Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were recorded with a Beckman Model 4230 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Bruker WP-80 or HX-90E spectrometer. Chemical shifts are reported in δ units relative to tetramethylsilane in $CDCl_3$ or to the solvent lock signal at δ 2.49 in Me_2SO-d_6. Mass spectra were recorded at 70 eV on a Kratos MS-30 mass spectrometer. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN.

1-Methyl-2-(dimethoxymethyl)quinolinium Iodide (10). A thin stream of gaseous HCl was bubbled through a refluxing solution of 472 mg (3.0 mmol) of quinoline-2-carboxaldehyde (5) in 10 mL of MeOH for 30 min. The mixture was cooled to room temperature and stirred cautiously into a cold saturated solution of K_2CO_3 in 25 mL of H_2O. The oil that separated was extracted with 3 × 25 mL of $CHCl_3$ and dried (Na_2SO_4). The solvent was removed under reduced pressure to obtain 490 mg (80%) of 2-(dimethoxymethyl)quinoline (8) as an oil: ^{1}H NMR ($CDCl_3$) δ 3.48 (s, 6 H, 2 Me), 5.51 (s, 1 H, acetal CH), 7.4–8.3 (m, 6 H, Ar H).

A solution of 49 mg (2.41 mmol) of the acetal 8 in 2.0 mL of nitrobenzene was treated with 2.0 mL (32.13 mmol) of CH_3I, stirred, and heated under reflux at 80 °C for 24 h. The reaction mixture was cooled to room temeprature, and the solid was filtered, washed with anhydrous Et_2O, and dried. Recrystallization from MeOH–EtOAc afforded 530 mg (64%) of 10 as pale yellow crystals: mp 160–162 °C dec; IR (KBr) 1585, 1030 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 3.51 (s, 6 H, 2 Me), 4.61 (s, 3 H, NCH_3), 6.21 (s, 1 H, acetal CH), 7.9–9.4 (m, 6 H, Ar H). Anal. Calcd for $C_{13}H_{16}INO_2$: C, 45.23; H, 4.67; I, 36.77; N, 4.06. Found: C, 44.98; H, 4.61; I, 37.03; N, 4.01.

Hydrolysis and Oximation of Acetal Methiodide 10. Method I. A solution of 100 mg (0.29 mmol) of acetal methiodide 10 in 1.0 mL of 10% HCl solution was refluxed for 90 min, cooled to room temperature and evaporated to dryness under reduced pressure. Trituration of the residue with anhydrous Et_2O afforded 71 mg (77%) of 2-(dihydroxymethyl)-1-methylquinolinium iodide (11) as a pale brown powdery solid, which softens and slowly decomposes above 175 °C: IR (KBr) 3600–2800, 1625 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 4.61 (s, 3 H, NCH_3), 6.43 (br, 1 H, $CH(OH)_2$), 7.9–9.4 (m, 6 H, Ar H).

Hydroxylamine hydrochloride (18 mg, 0.26 mmol) was dissolved in 0.1 mL of H_2O and neutralized with 14 mg (0.13 mmol) of Na_2CO_3. To the resulting solution was added 20 mg (0.06 mmol) of the crude 11. The mixture was triturated, diluted with 0.1 mL of H_2O and heated on a steam bath for 5 min. The reaction mixture was cooled to room temperature, clarified by filtration, and cooled in a refrigerator to yield 5 mg (25%) of 3a, which was identical with the sample of 3a obtained by Method II.

Method II. To a solution of 104 mg (0.30 mmol) of acetal methiodide 10 in 1.9 mL of H_2O were added 0.38 mL of concentrated aqueous HCl and 63 mg (0.90 mmol) of hydroxylamine hydrochloride. The mixture was heated with stirring under reflux at 100 °C for 90 min. The solid obtained on cooling was filtered, recrystallized from H_2O, and dried under reduced pressure at 60 °C for 6 h to obtain 42 mg (45%) of quinoline-2-aldoxime methiodide (3a) as pale yellow crystals: mp 212–214 °C dec; IR (KBr) 3200–2800, 1590, 1350, 1010 (=NOH) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 4.55 (s, 3 H, NCH_3) 7.9–9.2 (m, 7 H, Ar H, CH=N), 13.55 (br, 1 H, =NOH); MS, m/e (relative intensity) 169 (100), 154 (70), 128 (25). Anal. Calcd for $C_{11}H_{11}IN_2O$: C, 42.06; H, 3.53; I, 40.40; N, 8.92. Found: C, 42.24; H, 3.67; I, 40.15; N, 9.08.

Method III. To a solution of 104 mg (0.30 mmol) of acetal methiodide 10 in 1.14 mL of H_2O were added 1.14 mL of concentrated aqueous HCl solution and 63 mg (0.90 mmol) of hydroxylamine hydrochloride. The mixture was heated in an oil bath at 100 °C with stirring under reflux for 90 min. The reaction mixture was cooled to room temperature, and the brown solid that separated was filtered, dried, and extracted with EtOAc. The extract was dried (Na_2SO_4) and evaporated under reduced pressure and the residue crystallized from absolute EtOH, affording 20 mg (35%) of 12 as shiny dark brown crystals; mp 170–172 °C dec. The product was identical with 12 prepared from 3a. The aqueous filtrate was cooled in a refrigerator, and the resulting solid was combined with the EtOAc insoluble fraction which was crystallized from H_2O to yield 23 mg (24.0%) of 3a.

Hydrolysis and Oximation of Aldimine 15. A suspension of 748 mg (2.0 mmol) of 15 in 2.0 mL of H_2O was treated with 2.0 mL of concentrated aqueous HCl solution and stirred. To the resulting solution was added 417 mg (6.0 mmol) of hydroxylamine hydrochloride. The mixture was stirred at room temperature for 30 min. The solid obtained was filtered, washed with ice-cold H_2O, and dried. Crystallization from H_2O afforded 363 mg (58%) of 3a.

Hydrolysis and Oximation of Aldimine 16. A stirred suspension of 4.17 g (10.0 mmol) of 16 in 25.0 mL of H_2O was treated with 10.0 mL of concentrated aqueous HCl solution followed by 2.09 g (30.0 mmol) of hydroxylamine hydrochloride. The mixture was stirred at room temperature for 24 h and cooled, and the solid obtained was filtered, dried, and extracted with EtOAc (4 × 50 mL). The EtOAc insoluble residue was crysallized from H_2O (charcoal) and dried under reduced pressure to yield 630 mg (20%) of 3a.

Concentration of the EtOAc solution under reduced pressure and recrystallization of the residue from absolute EtOH (charcoal) yielded 57 mg (3%) of the oxime triiodide 12.

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2-[(Hydroxyimino)methyl]-1-methylquinolinium Triiodide (12). A solution of 94 mg (0.30 mmol) of the oxime methiodide **3a** in 7.0 mL of MeOH was vigorously stirred with a solution of 91 mg (0.36 mmol) of I_2 in 6.0 mL of 20% aqueous KI solution at room temperature. After 1 h at room temperature, the solid obtained was filtered, dried, and crystallized from absolute EtOH, yielding 88 mg (52%) of triiodide **12** as brown, shiny crystals: mp 171–173 °C; IR (KBr) 3300 (OH), 1595 (C=N), 1005 (=NOH) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 4.55 (s, 1 H, NCH_3), 7.9–9.2 (m, 7 H, Ar H, CH=N), 13.55 (s, 1 H, =NOH). Anal. Calcd for $C_{11}H_{11}I_3N_2O$: C, 23.26; H, 1.95; I, 67.03; N, 4.93. Found: C, 23.49; H, 1.98; I, 66.73; N, 4.97.

Reaction of 1,2-Dimethylquinolinium Iodide (13) with Hydroxylamine Hydrochloride. To a solution of 86 mg (0.30 mmol) of 1,2-dimethylquinolinium iodide (**13**) in 1.14 mL of H_2O were added 1.14 mL of concentrated aqueous HCl solution and 63 mg (0.90 mmol) of hydroxylamine hydrochloride. The mixture was refluxed for 90 min, cooled to room temperature, and the solid obtained was filtered, washed with H_2O, and dried. Crystallization from MeOH yielded 9 mg (17%) of dark brown crystals, mp 141–143 °C. The compound was identical in all respects with an authentic sample of 1,2-dimethylquinolinium triiodide (**14**) prepared according to the literature method:[14] IR (KBr) 1615, 1525 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 3.08 (s, 3 H, CH_3 at C_2), 4.45 (s, 3 H, CH_3N), 7.9–9.2 (m, 6 H, Ar H).

Acknowledgment. This work was supported by Contract DAMD17-84-C-4118 from the U.S. Army Medical Research and Development Command. We are grateful to the project officer, H. A. Musallam, for helpful suggestions. Mass spectra were obtained at the Ohio State University Chemical Instrumentation Center. Mass spectra were produced by C. R. Weisenberger.

Registry No. 3a, 83484-86-0; **5**, 5470-96-2; **6**, 1131-68-6; **7**, 103068-53-7; **8**, 88612-18-4; **10**, 103068-54-8; **11**, 103068-55-9; **12**, 103068-56-0; **13**, 876-87-9; **14**, 103068-57-1; **15**, 103068-58-2; **16**, 23216-56-0; **17**, 41106-14-3; **18**, 7727-09-5; 2-dibromomethylquinoline, 53867-81-5.

Supplementary Material Available: Full details of synthesis, transformations and spectroscopic characterization of **7** (5 pages). Ordering information is given on any current masthead page.

Modified Taxols. 3. Preparation and Acylation of Baccatin III

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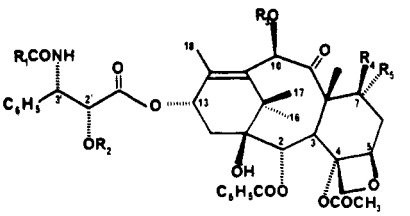
In the previous paper in this series we discussed various oxidation reactions of taxol **1a** and the products resulting therefrom.[1] In this paper we turn our attention to the preparation and reactions of baccatin III (**2**), the diterpenoid nucleus of taxol.

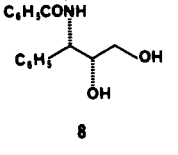
A key component of our studies on structure–activity relationships in the taxol area is the preparation of taxol analogues with modified C-13 ester side chains. One way of preparing these analogues is by the preparation of an appropriate side chain and its attachment to the C-13 position of baccatin III (**2**) (Chart I). Baccatin III, however, is only available in low yield by isolation from the yew *Taxus baccata*,[2] and we thus desired to develop a method to convert the more readily available taxol **1a** into baccatin-III. Any method developed for taxol would be applicable to cephalomannine (**1b**)[3] also and would thus provide a source of pure baccatin III from the difficultly separable mixture of taxol and cephalomannine obtained from *T. brevifolia*.[4]

Chart I



a series $R_1 = C_6H_5$; b series $R_1 = CH_3CH{=}C(CH_3)$

1	$R_2 = R_5 = H$	$R_3 = CH_3CO$	$R_4 = OH$	
3	$R_2 = R_3 = R_5 = H$	$R_4 = OH$		
6	$R_2 = R_4 = H$	$R_3 = CH_3CO$	$R_5 = OH$	
9	$R_2 = R_3 = CH_3CO$	$R_4 = OH$	$R_5 = H$	
14	$R_2 = R_3 = R_4 = H$	$R_5 = OH$		



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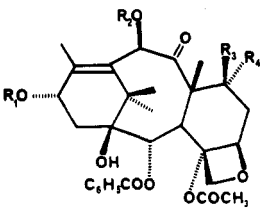

2	$R_1 = R_4 = H$	$R_2 = CH_3CO$	$R_3 = OH$	
4	$R_1 = R_2 = R_4 = H$	$R_3 = OH$		
5	$R_1 = R_2 = R_3 = H$	$R_4 = OH$		
7	$R_1 = R_3 = H$	$R_2 = CH_3CO$	$R_4 = OH$	
10	$R_1 = R_2 = CH_3CO$	$R_3 = OH$	$R_4 = H$	
11	$R_1 = R_4 = H$	$R_2 = CH_3CO$	$R_3 = CH_3COO$	
12	$R_1 = R_4 = H$	$R_2 = CH_3CO$	$R_3 = CCl_3CH_2OCOO$	
13	$R_1 = R_2 = CH_3CO$	$R_3 = CCl_3CH_2OCOO$	$R_4 = H$	
15	$R_1 = R_2 = CH_3CO$	$R_3 = CH_3COO$	$R_4 = H$	

Preparation of baccatin III from taxol has not previously been reported, but cephalomannine was converted to baccatin III by methanolysis in the presence of sodium bicarbonate.[3] This reaction only gave a 19% yield of baccatin III, however, with the remaining products being identified as 10-deacetylcephalomannine (**3b**), 10-deacetylbaccatin III (**4**), and 10-deacetylbaccatin V (**5**).

A noteworthy feature of the methanolysis reaction described above is that all of the products except baccatin III have undergone methanolysis of the C-10 acetate function. In earlier work we had shown that the C-10 acetate function is sterically very hindered, since acetylation of a crude mixture derived from *T. brevifolia* yielded a diacetate of 10-deacetyltaxol.[5] We thus surmised that the use of a bulky base would suppress deacetylation at C-10 and yield a higher proportion of baccatin III. It was

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