(D_2O, 60 MHz)[26] δ 1.26 (d, 3, CH_3CH, J = 7.0 Hz), 1.84–2.48 (m, 2, $ArCHCH_2$), 2.70 (s, 3, NCH_3), 2.77–3.22 (m, 3, ArCH and CH_2N), 3.74 (s, 2, CH_2CO_2H), 3.88 (s, 3, OCH_3), 6.89 (1, 1, aromatic H, J_{ortho} = 8.5 and J_{meta} = 2.5 Hz), 7.01 (d, 1, aromatic H, J_{meta} = 2.5 Hz), 7.26 (d, 1, aromatic H, J_{ortho} = 8.5 Hz).

Anal. Calcd for $C_{14}H_{22}ClNO_3$: C, 58.4; H, 7.7; N, 4.9. Found: C, 58.6; H, 7.7; N, 4.6.

Registry No.—**1**, 37436-85-4; **1** HCl, 37436-86-5; **2**, 37436-87-6; **3**, 37436-88-7; **4**, 37440-18-9; **4** HBr, 37440-19-0; **5**, 37440-20-3; **6**, 37436-89-8; **7**, 37436-90-1; **8**, 37436-91-2; **9**, 37436-79-6; **10**, 37436-80-9; **11**, 37436-81-0; **11** HBr, 37436-82-1; **12**, 37436-83-2; **12** HBr, 37567-13-8; **13** HCl, 37436-84-3; *m*-methoxyacetophenone, 586-37-8; *N*-methylbenzylamine, 103-67-3.

(26) 3-(Trimethylsilyl)propanesulfonic acid sodium salt was the internal standard.

Acknowledgments.—The nmr measurements and some interpretations are due to Dr. Herman Yeh and most of the mass spectra were performed by Mr. William Landis, both of this laboratory. Dr. H. M. Fales of the National Heart and Lung Institute, NIH, made available the LKB-9000 instrument for combined gas chromatography–mass fragmentography.

Reaction of Aromatic Amine Oxides with Acid Halides, Sulfonyl Halides, and Phosphorus Oxychloride. Stereochemical Configuration of Substituents in the 1 Position of 12,13-Benzo-16-chloro[10](2,4)pyridinophanes[1]

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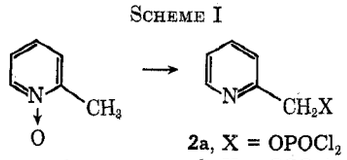
The reaction of 12,13-benzo-16-chloro[10](2,4)pyridinophane *N*-oxide (**3**) with benzoyl chloride, *p*-toluenesulfonyl chloride, phosphorus oxychloride, phosphorus thiotrichloride, and one hydrazidic bromide are described. Reactions of **3** with organic anhydrides or acid chlorides give mixtures of syn and anti esters; reaction with *p*-toluenesulfonyl chloride gives exclusively the syn tosylate **4d**. Reaction of **3** with phosphorus oxychloride is the first example in which a stable phosphate ester is formed; evidence is presented that alkyl chlorides, usually formed when alkylpyridine *N*-oxides react with *p*-toluenesulfonyl chloride or phosphorus oxychloride, are secondary products derived from intermediate esters. A new procedure has been developed to determine whether derivatives of type **4** or **5** have the syn or anti configuration at C-1 which is based on the chemical shifts observed for the methinyl proton when **4** or **5** is converted into the corresponding *N*-oxide.

Reactions of heterocyclic amine oxides with reagents such as acid anhydrides, sulfonyl halides, and acid chlorides have been intensively investigated and reviewed.[3–5] While there is a great deal known about these synthetically useful reactions, a number of points remain obscure. Among these, and of particular interest to us, is the question as to whether chlorides such as **2c**[6,7] (Scheme I), generally formed from appropriately

SCHEME I



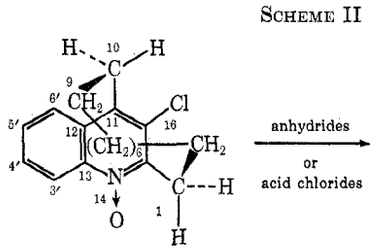
1

2a, X = $OPOCl_2$
b, X = OSO_2Ar
c, X = Cl

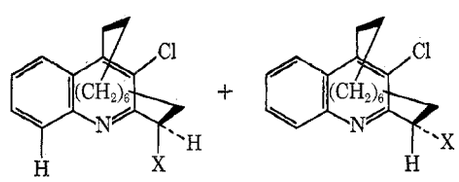
substituted *N*-oxides such as **1** by reaction with *p*-toluenesulfonyl chloride or phosphorus oxychloride, are primary products or whether they are derived in secondary reactions involving intermediate phosphate (**2a**) or sulfonate (**2b**) esters with the hydrogen chloride liberated.

The availability of metacyclophanes of type **3** (Scheme II) is of particular interest in this regard, since

SCHEME II



3



4a, X = $OCOCH_3$
b, X = OH
c, X = $OCOC_6H_5$
d, X = $OSO_2C_6H_4CH_3$
e, X = $OPOCl_2$
f, X = $OPO(OC_2H_5)_2$
g, X = Cl
h, X = Br
j, X = OCH_2CH_3
k, X = H

5a, X = $OCOCH_3$
b, X = OH
c, X = $OCOC_6H_5$
d, X = $OSO_2C_6H_4CH_3$
j, X = OCH_2CH_3

(1) This work was supported by the National Science Foundation, Grant No. GP-11918.

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(3) E. Ochiai, "Aromatic Amine Oxides," transl. by D. V. Mizoguchi, Elsvier, Amsterdam, 1967.

(4) V. J. Traynelis in "Mechanisms of Molecular Migrations," Vol. 2, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1969, pp 1–42.

(5) A. R. Katritsky and J. M. Lagowsky, "Chemistry of Heterocyclic N-Oxides," Academic Press, New York, N. Y., 1971, pp 349–367.

(6) T. Kato, *Yakugaku Zasshi*, **75**, 1239 (1955); ref 3, p 264.

(7) E. Matsumura, *Nippon Kagaku Zasshi*, **74**, 363 (1953); ref 3, p 278.

data accumulated[8-10] suggest that functional groups on the methylene bridge (specifically at the benzylic methylene group at position 1) in such compounds are resistant to both SN1 and SN2 type reactions.

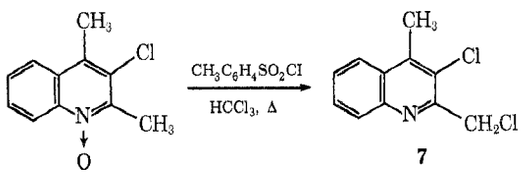
The reaction of **3** with acetic anhydride has been reported[8] and the structures of the derived syn and anti alcohols (**4b** and **5b**, respectively) have been established. We have now investigated the reactions of **3** with benzoyl chloride,[11] *p*-toluenesulfonyl chloride, and phosphorus oxychloride, and the results constitute the major subject of this report.

The reaction of **3** with benzoyl chloride in hot chlorobenzene proceeded in a manner analogous to that reported for **3** with acetic anhydride[8] and gave both the syn benzoate **4c** (21% pure) and the anti benzoate **5c** (62% crude, 46% pure). There was no evidence for the formation of the chloro derivative **4g**. Stereochemical assignments were made by analysis of the nmr spectral data (see subsequent discussion) and by hydrolysis of **4c** to **4b** (76% yield) and **5c** to **5b** (91% yield) by action of potassium hydroxide in methanol.

The reaction of **3** with *p*-toluenesulfonyl chloride in hot chloroform gave almost exclusively a single product (73% yield, pure) which was shown to be syn tosylate **4d** by its independent synthesis from **4b** (by treatment with *n*-butyllithium and *p*-toluenesulfonyl chloride). The anti isomer **5d** was similarly prepared from anti alcohol **5b**; nmr studies (see subsequent discussion) provided additional support for the assigned structures **4d** and **5d**.

It is of significance to note that the reaction of the model compound **6** with *p*-toluenesulfonyl chloride and chloroform, under identical conditions used for **3**, gave only the chloride **7** (74% yield, Scheme III).

SCHEME III



6 7

The reaction of **3** with excess phosphorus oxychloride at 100° gave a mixture, presumably containing **4e**, which was processed by the addition of ethanol; two products were isolated, the syn phosphate **4f** (30% yield) and the deoxygenated derivative of **3** (**4k**, 13% yield). The yield of **4f** was improved somewhat (40%) when the reaction was carried out in hot chloroform; a small amount (1–2%) of *syn*-1-chloro-12,13-benzo-16-chloro[10](2,4)pyridinophane (**4g**) was also isolated from this reaction. The stereochemical assignment of **4f** was tentatively made on the basis of its hydrolysis with potassium hydroxide in methanol to syn alcohol **4b** (64% yield). The stereochemical assignment of **4g** was made by nmr studies (see subsequent discussion).

(8) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *J. Org. Chem.*, **35**, 3775 (1970).

(9) W. E. Parham, K. B. Sloan, and J. B. Biasotti, *Tetrahedron*, **27**, 5767 (1971).

(10) Additional evidence on this point will be presented in a subsequent communication.

(11) I. J. Pachter, *J. Amer. Chem. Soc.*, **75**, 3026 (1953); J. Vozza, *J. Org. Chem.*, **27**, 3856 (1962).

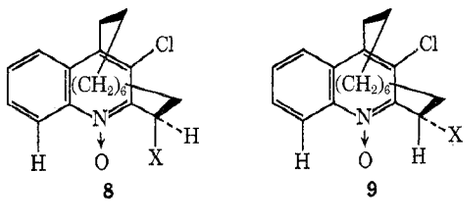
Similar results were obtained with 12,13-(5′-chlorobenzo)-14-oxo-16-chloro[10](2,4)pyridinophane,[12] the 5′-chloro analog of **3**; the phosphate, obtained in 30% yield, was assumed by analogy to **4f** to have the 1-syn configuration corresponding to the 5′-chloro analog of **4f**. The formation of **4f** and the 5′-chloro analog of **4f** are the first instances, to our knowledge, where stable phosphate esters have been obtained by reaction of an *N*-oxide with phosphoric acid derivatives.

While we are not at present able to define the reasons for the difference in stereochemistry observed for the products of reaction of **3** with acetic anhydride and benzoyl chloride (mixture of syn and anti isomers) as opposed to that obtained by reaction of **3** with *p*-toluenesulfonyl chloride where only the syn isomer (**4d**) was formed, the results are of mechanistic interest and constitute the subject of further studies in our laboratory. The observations described here suggest that chlorides of type **2c**, usually formed when *N*-oxides of type **1** are treated with sulfonyl halides or phosphorus oxychloride, are indeed secondary products derived from the intermediate esters of type **2a** and **2b**.

A number of reactions of **3** with other acid halides (as shown in Scheme II) were run. Reaction of **3** with phosphorus thiochloride ($PSCl_3$) gave only the reduced product, 12,13-benzo-16-chloro[10](2,4)pyridinophane (**4k**, isolated in 53% yield as the hydrochloride). Similarly, reaction of **3** with *N*-(2-bromo-4-nitrophenyl)benzhydrazidic bromide[13] gave only **4k** (48% isolated yield).

It was recognized that further studies of reactions on derivatives of 1-substituted pyridinophanes of type **4** and **5** would require a convenient and accurate method of determining the stereochemistry of the substituent at the 1 position (syn or anti).

It was anticipated that the chemical shift of a methinyl proton at C-1 in the nmr spectrum of an appropriately substituted pyridinophane *N*-oxide, in which the methinyl proton is rigidly held in or near the plane of the *N*-oxide group, should be quite informative concerning the anisotropic effect of the *N*-oxide group. The *N*-oxides **8** and **9**, respectively, of the pyridinophane derivatives of type **4** and **5** were of particular interest in this regard.



8 9

In **8** (syn orientation of the substituent) the methinyl proton is held away from the *N*-oxide group, and no anisotropic effect due to the *N*-oxide group on the methinyl hydrogen is expected. In **9** (anti orientation of the substituent) the methinyl proton is held in or near the plane of the *N*-oxide group, and one would expect the methinyl proton to experience the anisotropic effect of the *N*-oxide group. Therefore, no appreciable shift would be expected in the nmr absorption of the methinyl proton in **4** in going to the *N*-oxide **8**. On the other hand, in the corresponding *N*-

(12) W. E. Parham and K. B. Sloan, *Tetrahedron Lett.*, 1947 (1971).

(13) J. M. Burgess and M. S. Gibson, *Tetrahedron*, **18**, 1001 (1962).

oxide **9** of the anti isomer **5**, the methinyl proton should be deshielded by the *N*-oxide bond, and a large downfield shift in the nmr signal for the methinyl proton should be observed in going from the free base **5** to its *N*-oxide **9**.

The *N*-oxides of the 1-substituted derivatives of the 12,13-benzo-16-chloro[10](2,3)pyridinophane were prepared by oxidation of the corresponding derivative **4** or **5** with *m*-chloroperbenzoic acid or with hydrogen peroxide in glacial acetic acid, and the products were characterized by nmr, mp and elementary analysis. The nmr spectrum of the *N*-oxides in both syn and anti series showed a characteristic downfield shift of the peri proton at C-3′ (**3**) by as much as 1.5 ppm.

As expected, there was only a slight shift (0.01–0.09 ppm) in the methinyl proton in going from *syn*-pyridinophanes to the *N*-oxides (**4** → **8**). On the other hand, the corresponding protons in the anti series are deshielded by the *N*-oxide, and there is a shift of 1.42–1.73 ppm in going from the *anti*-pyridinophane derivative to the corresponding *N*-oxide (compare **5** and **9**).

The structures of syn and anti alcohols **4b** and **5b** (from ir data),[8] syn and anti ethers **4j** and **5j** (synthesis from the corresponding alcohols),[9] syn and anti tosylates **4d** and **5d** (synthesis from the corresponding alcohols), and syn and anti benzoates **4c** and **5c** (hydrolysis to corresponding alcohols) are known. The nmr signal data therefore provide confirmation of their structures and permit the assignment of the chloride **4g** and the previously reported bromide **4h**[8] as syn on the basis of no appreciable shift of the methinyl proton in the *N*-oxide when compared to the free base.

This procedure of comparing the nmr spectra of the free base to that of the corresponding *N*-oxide constitutes a convenient method of assigning the stereochemistry of syn and anti derivatives in the 12,13-benzo-16-chloro[10](2,4)pyridinophane system.

Experimental Section

The Reaction of 12-13-Benzo-14-oxo-16-chloro[10](2,3)pyridinophane (3) with Benzoyl Chloride.—A solution of **3** (1.5 g, 4.8 mmol) and benzoyl chloride (0.80 g, 5.7 mmol) in chlorobenzene (30 ml) was heated at the reflux temperature for 24 hr. Tlc (silica gel, petroleum ether[14]–diethyl ether, 50:50) showed only two spots, R_f 0.55, 0.45, and the absence of *syn*-1-chloro-12,13-benzo-16-chloro[10](2,4)pyridinophane (**4g**). The reaction mixture was diluted with chloroform (50 ml) and was extracted with 100 ml of 20% sodium hydroxide. The chloroform solution was dried ($MgSO_4$) and was chromatographed on alumina (375 g) using petroleum ether[14]–diethyl ether (50:50) as solvent to afford the following products in order of elution.

1. ***syn*-1-Benzoyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane (4c)**: 425 mg, mp 131–134° from ethyl acetate–petroleum ether,[14] 21% yield. Tlc (as above) and nmr showed the absence of **5c** (anti isomer). Pure **4c** melted at 147–148° (from ethyl acetate): ir (Nujol) 1720 (C=O) and 1275 cm^{-1} (C–O); nmr[15] ($CDCl_3$) δ 8.4–7.3 (m, 9 aromatic H), 6.90–6.60 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 14$ Hz), 1, CHOC=O], and 3.8–3.2 (m, 2, benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ϵ) 326 (3.52), 312 (3.54), 236 (4.67), 216 (4.52), and 200 (4.39).

Anal. Calcd for $C_{26}H_{28}ClNO_2$: C, 74.01; H, 6.68; N, 3.32. Found: C, 74.26; H, 6.77; N, 3.28.

2. ***anti*-1-Benzoyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane (5c)**: 905 mg; 46% yield; mp 116–118° from ethyl acetate–petroleum ether;[14] ir (Nujol) 1730 (sh) and 1720 (C=O) and 1270 cm^{-1} (C–O); nmr[15] ($CDCl_3$) δ 8.4–7.25 (m, 9, aromatic H), 6.48–6.21 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 16$ Hz), 1, CHOC=O], and 3.8–3.2 (m, 2 benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ϵ) 325 (3.46), 311 (3.51), 236 (4.77), 216 (4.48), and 200 (4.40).

Anal. Calcd for $C_{26}H_{28}ClNO_2$: C, 74.01; H, 6.68; N, 3.32. Found: C, 73.76; H, 6.66; N, 3.12.

Traces (less than 1%) of *syn*-1-chloro-12,13-benzo-16-chloro-[10](2,4)pyridinophane (**4g**) were detected when the reaction was run in excess benzoyl chloride as solvent.

The Hydrolysis of *syn*-1-Benzoyloxy-12,13-benzo-16-chloro[10]-(2,4)pyridinophane (4c).—The benzoate **4c** (126 mg, 0.3 mmol) was treated with KOH (0.5 g) in methanol (50 ml) at 90° for 20 hr and was then cooled and diluted to 100 ml with water. The solution was filtered and the residue was air-dried to give 95 mg (mp 157–159°, 100% yield) of syn alcohol (**4b**) which showed only one spot on tlc analysis (silica gel, petroleum ether[14]–diethyl ether, 50:50). The product was recrystallized from chloroform–petroleum ether[14] to give 72 mg (mp 160–161.5°, mmp 158.5–160.5°, 76% yield) of syn alcohol **4b**.

The Hydrolysis of *anti*-1-Benzoyloxy-12,13-benzo-16-chloro-[10](2,4)pyridinophane (5c).—The benzoate **5c** (0.3 g, 0.7 mmol) was dissolved in hot methanol (30 ml) and allowed to react with 5 ml of 20% potassium hydroxide at reflux for 24 hr. The methanol was evaporated and the residue was dissolved in chloroform (40 ml). The chloroform was washed with water (100 ml) and evaporated to afford 0.2 g (mp 197–202°) of a white solid which showed only one spot on tlc analysis. Recrystallization of the solid gave 0.15 g (mp 204.5–206.5°, from petroleum ether[14]–diethyl ether, mmp 205–207°, 66% yield) of anti alcohol **5b**.

Reaction of 12,13-Benzo-14-oxo-16-chloro[10](2,4)pyridinophane (3) with *p*-Toluenesulfonyl Chloride.—A solution of **3** (1.352 g, 4.3 mmol) and *p*-toluenesulfonyl chloride (1.349 g, 7.1 mmol) in chlorobenzene (10 ml) was heated at 100° for 44 hr. The cooled reaction mixture was diluted with chloroform (50 ml) and extracted with 100 ml of 20% sodium hydroxide. Analysis of the organic extract by tlc (silica gel, petroleum ether[14]–diethyl ether, 50:50) showed one major spot (R_f 0.50) and a minor spot (R_f 0.75). The solution was chromatographed on alumina (200 g) using petroleum ether[14]–diethyl ether as eluent to give 2.05 g of a light oil (R_f 0.50). The oil was crystallized from chloroform–petroleum ether[14] to give 1.481 g (mp 105–107°, 73% yield) of *syn*-1-*p*-toluenesulfonyloxy-12,13-benzo-16-chloro-[10](2,4)pyridinophane (**4d**): nmr[15] ($CDCl_3$) δ 7.33 [q (AB, $J_{AB} = 8$ Hz, $\Delta\nu_{AB} = 41$ Hz), 4, tosyl aromatic H], 8.1–7.3 (m, 4, aromatic H), 6.53–6.26 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 16$ Hz), 1, $CHOSO_2$], 3.6–3.3 (m, 2, benzylic CH_2), and 2.16 (s, 3, CH_3); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ϵ) 326 (3.42), 312 (3.50), 233 (4.65), 229 (4.63), and 215 (4.53).

Anal. Calcd for $C_{26}H_{30}ClNO_3S$: C, 66.15; H, 6.41; N, 2.97; S, 6.79. Found: C, 66.15; H, 6.56; N, 2.90; S, 6.93.

When chloroform (20 ml) was used as the solvent for reaction of **3** (1.6, g, 5.1 mmol) with *p*-toluenesulfonyl chloride (1.1 g, 5.8 mmol) at a pot temperature of 80° (48 hr), the yield of **4d** was 55–58%; unchanged **3** was recovered as the hydrochloride (mp 172–180°) from petroleum ether[14]–chloroform.

Anal. Calcd for $C_{19}H_{25}Cl_2NO$: C, 64.41; H, 7.11; N, 3.96; Cl, 20.01. Found: C, 64.26; H, 7.7; N, 3.88; Cl, 20.12.

Reaction of 3-Chloro-2,4-dimethylquinoline *N*-Oxide (6) with *p*-Toluenesulfonyl Chloride.—The reaction of **6** (500 mg, 2.4 mmol) with *p*-toluenesulfonyl chloride was carried out in chloroform solvent as described for **3**. The reaction mixture was cooled, extracted with 50 ml of 20% potassium hydroxide, and concentrated to give 0.7 g of greenish solid. The solid was chromatographed on alumina (40 g) using petroleum ether[14]–diethyl ether (50:50) as eluent to give 402 mg (mp 97–99°, 75% yield) of 3-chloro-2-chloromethyl-4-methylquinoline (**7**) as a white solid. The solid was recrystallized from petroleum ether[14] to give a pure sample of **7**: 341 mg; mp 101–103°; 63% yield; ir (Nujol) 1580 and 1500 cm^{-1} (w) (aromatic); nmr[15] ($CDCl_3$) δ 8.26–7.40 (m, 4, aromatic H), 5.00 (s, 2, CH_2Cl), and 2.76 (s, 3, CH_3); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ϵ) 325 (3.40), 311 (3.48), 282 (3.65), 235 (4.76), and 215 (4.15).

Anal. Calcd for $C_{11}H_9Cl_2N$: C, 58.43; H, 4.01; N, 6.20. Found: C, 58.47; H, 4.01; N, 6.17.

Reaction of 12,13-Benzo-14-oxo-16-chloro[10](2,4)pyridinophane (3) with Phosphorus Oxychloride.—A mixture of **3** (1.1 g, 3.48 mmol) and phosphorus oxychloride (1.0 g, 6.5 mmol)

(14) Petroleum ether of bp 60–70°.

(15) In addition to the benzylic protons, which are given in the Experimental Section, a broad complex absorption weighted ~16 protons at δ 2.6–0.0 (±0.2) is characteristic for the 12,13-benzo-16-chloro[10](2,4)pyridinophane system and their *N*-oxides (*cf.* ref 8).

was heated at 100° for 0.5 hr [reflux condenser equipped with drying tube ($CaCl_2$)]. The mixture was cooled; nmr analysis showed an absorption at δ 6.53–6.13 (CHOP=O) which when integrated corresponded to 50% conversion into the substitution product. The mixture was heated for an additional 17 hr at 100°, then absolute ethanol (1.5 ml) and *N*,*N*-dimethylaniline (2.4 g) was added to the hot solution. The mixture was stirred at 30° for 1 hr and then diluted with benzene (50 ml). The benzene solution was extracted with aqueous hydrochloric acid (0.6 *N*, 20 ml) and concentrated. Analysis of the concentrate on tlc (silica gel, petroleum ether[14]–diethyl ether, 50:50) showed products with R_f 0.0, 0.32, and 0.87. The concentrate was chromatographed on silica gel (100 g) using petroleum ether[14]–diethyl ether (50:50) as eluent to give the following.

(a) The fraction with R_f 0.87 was a yellow oil (0.35 g) which crystallized from ethyl acetate to give 142 mg (mp 77–80°, mmp 78–81°, 13.5% yield) of 12,13-benzo-16-chloro[10](2,4)-pyridinophane (**4k**).

(b) The fraction with R_f 0.32 was isolated as a dark yellow oil (1.00 g) which crystallized from petroleum ether[14] to give 474 mg (mp 83–85°, 30% yield) of *syn*-diethyl 12,13-benzo-16-chloro[10](2,4)pyridinophane-1-phosphate (**4f**): mp 84.5–86.5° from petroleum ether;[14] ir (Nujol) 1575 and 1505 (w) (aromatic), 1275 (s) (P=O), and 1040, 1030, 980, and 970 cm^{-1} (s) (COP=O); nmr[15] ($CDCl_3$) δ 8.30–7.53 (m, 4, aromatic H), 6.53–6.11 (m, 1, CHOP=O), 4.40–3.80 (m, 4, $POCH_2CH_3$), and 3.63–3.53 (m, 2, benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ϵ) 235 (4.71) and 213 (4.49); mass spectrum (70 eV) *m/e* (rel intensity) 453 (100 M^+), 455 (37), 300 and 299 (23), 264 (96), 233 (M^*, M_1 = 300, M_2 = 264) and 198 (M^*, M_1 = 453, M_2 = 300).

Anal. Calcd for $C_{23}H_{33}ClNO_4P$: C, 60.95; H, 7.52; N, 2.91; Cl, 8.39. Found: C, 61.17; H, 7.52; N, 3.00, Cl, 8.08.

(c) *syn*-1-Chloro-12,13-benzo-16-chloro[10](2,4)pyridinophane (**4g**) [mp 144–145° (from petroleum ether[16])] was isolated (1.2–2.4% yields, two runs) from the chromatogram: nmr[15] ($CDCl_3$) δ 8.33–7.53 (m, 4, aromatic H), 6.13–5.85 (apparent t, 1, J = 8 Hz, CHCl) and 3.66–3.33 (m, 2, benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ϵ) 215 (4.42), 238 (4.62), 314 (3.52), and 328 (3.43).

Anal. Calcd for $C_{19}H_{23}Cl_2N$: C, 67.86; H, 6.89; N, 4.17; Cl, 21.08. Found: C, 68.09; H, 6.99; N, 4.03; Cl, 21.10.

Hydrolysis of *syn*-Diethyl 12,13-Benzo-16-chloro[10](2,4)pyridinophane-1-phosphate (4f).—The phosphate (**4f**) (800 mg, 1.77 mmol) was dissolved in 100 ml of methanol and treated with 6 ml of 20% potassium hydroxide (21.0 mmol) at reflux for 3 hr. The methanol was evaporated and the residue was suspended in 500 ml of water and extracted with chloroform (2 × 200 ml). The combined chloroform extracts were washed with water (200 ml), dried ($MgSO_4$), and evaporated to give 0.65 g of a wax. Nmr analysis of the wax showed only syn alcohol **4b** (CHO absorption at δ 5.60–5.30); no anti alcohol **5b** (δ 5.33–4.80) was present. Tlc (alumina, petroleum ether[14]–diethyl ether, 75:25, as eluent) showed one spot with R_f 0.65 corresponding to syn alcohol **4b** (anti alcohol under these conditions had R_f 0.13). The residue was crystallized from chloroform–petroleum ether[14] to give 360 mg (mp 159–161°, mmp 159–161°, 64% yield) of the syn alcohol **4b**.

Reaction of 12,13-(5′-Chlorobenzo)-14-oxo-16-chloro[10](2,4)-pyridinophane with Phosphorus Oxychloride.—A sample of the pyridinophane *N*-oxide[12] (800 mg, 2.27 mmol) in chloroform (50 ml) was treated with phosphorus oxychloride (0.7 g, 4.5 mmol) at the reflux for 12 hr. Absolute ethanol (1 ml) was added and after 1 hr of additional reflux the mixture was chromatographed on alumina (200 g) using petroleum ether[14]–diethyl ether (50:50) as eluent to give diethyl 12,13-(5′-chlorobenzo)-16-chloro[10]-(2,4)pyridinophane-1-phosphate as a white solid: 405 mg; 30% yield; mp 114–116° from petroleum ether[14]; ir (Nujol) 1240 (s) (P=O), 1495, 1570, and 1610 (w) (aromatic), and 1030 and 970 cm^{-1} (broad s) (COPO=O); nmr[15] ($CDCl_3$) δ 6.46–6.10 (m, 1, CHOP=O), 8.01 [d (X portion of ABX, J_{BX} = 2 Hz), 1, 6′-H), 7.86 [q (AB portion of ABX, J_{AB} = 12 Hz, $\Delta\nu_{AB}$ = 28 Hz), 2, 3′- and 4′-H], 4.36–3.76 (m, 4, $POCH_2CH_3$) and 3.60–3.26 (m, 2, benzylic CH_2); $\lambda_{max}^{95\%\ EtOH}$ mμ (log ϵ) 332 (3.55), 317 (3.50), 238 (4.72), and 220 (4.46).

Anal. Calcd for $C_{23}H_{32}Cl_2NO_4P$: C, 56.56; H, 6.61; N, 2.87; Cl, 14.52. Found: C, 56.76; H, 6.74; N, 2.80; Cl, 14.37.

Reaction of 12,13-Benzo-14-oxo-16-chloro[10](2,4)pyridinophane (3) with Phosphorus Thiochloride.—A solution of *N*-oxide **3** (1.0 g, 3.16 mmol) in chloroform (20 ml) was treated with phosphorus thiochloride (800 mg, 4.7 mmol) as described above. To the mixture was added absolute ethanol (0.2 ml, 3.5 mmol) and the reaction mixture was heated at reflux for 36 hr. A calcium chloride drying tube was employed to protect the reaction from atmospheric moisture. More absolute ethanol (5 ml) was added to the solution, and it was refluxed for 8 hr. The solution was chromatographed on silica gel (100 g) using petroleum ether[14]–diethyl ether (50:50) as eluent to give 1.0 g of a light yellow oil which was dissolved in dry ether and treated with dry ether saturated with hydrogen chloride. The light yellow solid that precipitated (557 mg, mp 178–186°, 52.5% yield) was recrystallized from chloroform–diethyl ether to give 420 mg (mp 191–199°, 38% yield) of 12,13-benzo-16-chloro[10](2,4)-pyridinophane hydrochloride: ir (Nujol) 2300 and 1960 (broad, s) ($^+$NH), 1640, 1580 and 1490 (m) (aromatic), and 1520 cm^{-1} (broad, w) (aromatic); nmr[15] ($CDCl_3$) δ 9.25–9.06 (m, 1, 3′-H), 8.45–7.86 (m, 3, 4′-, 5′-, and 6′-H), and 4.36–3.20 (m, 4, benzylic CH_2).

Anal. Calcd for $C_{19}H_{25}NCl_2$: C, 67.45; H, 7.45; N, 4.14. Found: C, 67.32; H, 7.46; N, 3.92.

Reaction of 12,13-Benzo-14-oxo-16-chloro[10](2,4)pyridinophane (3) with *N*-(2-Bromo-4-nitrophenyl)benzyhydrazidic Bromide.[13]—A solution of **3** (1.0 g, 3.16 mmol) and the benzhydrazidic bromide[13] (1.3 g, 3.26 mmol) was heated at a pot temperature of 90° for 18 hr, protected from atmospheric moisture by a calcium chloride drying tube. The solution was chromatographed on alumina (180 g) using petroleum ether[14]–diethyl ether (50:50) as eluent. In addition to some recovered *N*-oxide **3** there was obtained 450 mg (mp 76–78.5°, mmp 76–80°, 48% yield) of 12,13-benzo-16-chloro[10](2,4)pyridinophane (**4k**).

***syn*-1-*p*-Toluenesulfonyloxy-12,13-benzo-16-chloro[10](2,4)-pyridinophane (4d).**—*n*-Butyllithium (0.81 ml, 2.1 *M* solution in hexane, 1.7 mmol) was added to a solution of syn alcohol **4b** (500 mg, 1.56 mmol) in tetrahydrofuran (10 ml, distilled from lithium aluminium hydride) maintained under nitrogen atmosphere. *p*-Toluenesulfonyl chloride (315 mg, 1.65 mmol) was then rapidly added. After 1 hr the reaction mixture had developed a white suspension. The suspension was filtered and the solvent was removed (*in vacuo*) to yield a pasty light yellow oil (1.1 g). The oil was dissolved in chloroform. The chloroform layer was washed with water, dried ($MgSO_4$), and concentrated (*in vacuo*) to give an oil, which was crystallized from chloroform–petroleum ether[14] to give crystals of pure **4d** (305.5 mg, 41.5% yield, mp 117.5–118°, mmp 116–119° with sample prepared by the reaction of the *N*-oxide **3** with *p*-toluenesulfonyl chloride).

***anti*-1-*p*-Toluenesulfonyloxy-12,13-benzo-16-chloro[10](2,4)-pyridinophane (5d)** was prepared from anti alcohol **5b** (1.164 g, 3.67 mmol) essentially as described above for **4d**. The crude oil was crystallized from chloroform–petroleum ether[14] to give anti tosylate **5d** (mp 121–123°, 1.22 g, 70.5% yield): ir (KBr) 1370 (s), 1180 cm^{-1} (COS); nmr[15] ($CDCl_3$) δ 8.1–6.8 (m, 8, aromatic H) and 5.83–5.60 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz), 1, $CHOSO_2$].

Anal. Calcd for $C_{26}H_{30}ClNO_3S$: C, 66.15; H, 6.41; N, 2.97. Found: C, 66.04; H, 6.43; N, 2.86.

Preparation of the *N*-Oxides of the Syn- and Anti Derivatives (8 and 9).—The *N*-oxides of 1-substituted derivatives of the 12,13-benzo-16-chloro[10](2,4)pyridinophanes were prepared by oxidation of the corresponding bases (**4** or **5**) with *m*-chloroperbenzoic acid in chloroform at room temperature (method 1) or by treatment with hydrogen peroxide in glacial acetic acid at 90° (method 2). The products were characterized by nmr, mp, and elementary analysis.

***syn*-1-Hydroxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (8b).**—A chloroform (10 ml) solution of syn alcohol **4b** (390 mg, 1.23 mmol) was treated with 85% *m*-chloroperbenzoic acid (290 mg, 1.68 mmol). The mixture was warmed slightly to ensure solution and was kept at room temperature for 12 hr. Analysis of the mixture by tlc showed the presence of trace quantities of unreacted starting material. Therefore, 100 mg (0.58 mmol) of *m*-chloroperbenzoic acid was added, and the reaction was continued for four more hr. The reaction mixture was washed with a solution of potassium carbonate, followed by water. The chloroform layer was concentrated (*in vacuo*) to give a residue which on crystallization from diethyl ether gave pale yellow crystals (250 mg, 61% yield, mp 174–175°) of the *N*-oxide (**8b**): nmr[15] ($CDCl_3$) δ 9.03–8.70 (m, 1 peri 3′-H), 8.33–7.56 (m, 3, 4′-, 5′-, and 6′-H), 7.46–7.00 (m, 1, OH, dis-

(16) Petroleum ether of bp 30–60°.

appears on adding D_2O), 5.76–5.40 (m, 1, CHOH) and 3.90–3.16 (m, 2, benzylic H).

Anal. Calcd for $C_{19}H_{24}ClNO_2$: C, 68.05; H, 7.19; N, 4.19. Found: C, 67.96; H, 7.32; N, 4.19.

***anti*-1-Hydroxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (9b).**—Oxidation of **5b** (530 mg) was carried out essentially as described for **4b**. The *N*-oxide **9b** (400 mg from chloroform–petroleum ether,[14] 72% yield) showed mp 220–230° dec; nmr[15] ($CDCl_3$) δ 8.68 (d, 1, peri 3′-H), 7.88–7.48 (m, 3, aromatic H), 6.64–6.34 [doublet of doublets (X portion of ABX system, $J_{AX} + J_{BX} = 16$ Hz), 1, CHOH], 3.35 (m, 1, CHOH), and 3.10–2.48 (m, 2, benzylic H).

Anal. Calcd for $C_{19}H_{24}ClNO_2$: C, 68.05; H, 7.19; N, 4.19. Found: C, 67.91; H, 7.33; N, 3.87.

***syn*-1-*p*-Toluenesulfonyloxy-12,13-benzo-14-oxo-16-chloro[10]-(2,4)pyridinophane (8d)** was prepared from **4d** as described for **8b**: mp 145° from petroleum ether[14]–chloroform; 68% yield; nmr[15] ($CDCl_3$) δ 8.83–8.40 (m, 1, peri 3′-H), 6.57–6.30 (m, 1, $CHOSO_2$), 8.3–6.8 (m, 7, aromatic H), and 4.00–2.76 (m, 3, benzylic CH_2 and 1 H from bridge methylene).

Anal. Calcd for $C_{26}H_{30}ClNO_3S$: C, 64.01; H, 5.54; N, 2.88. Found: C, 63.90; H, 5.73; N, 2.83.

***anti*-1-*p*-Toluenesulfonyloxy-12,13-benzo-14-oxo-16-chloro[10]-(2,4)pyridinophane (9d)** was prepared from **5d** (59 mg) as described for **8b**. The crude product was dissolved in ether and washed with aqueous potassium hydroxide; the solid obtained from the dry ether was recrystallized from chloroform–petroleum ether[14] to give pure **9d**: hygroscopic; mp 166–167°; 41% yield; nmr[15] ($CDCl_3$) δ 8.9–8.6 (1, m, peri 3′-H), 8.40–6.94 [m, 8, 7 aromatic H and a clear quartet centered at 7.28–7.08 (doublet of doublets) (X portion of ABX, $J_{AX} + J_{BX} = 16$ Hz, 1, $CHOSO_2$)], 3.80–2.68 (m, 3, benzylic CH_2 and 1 H from bridge methylene), 2.10 (s, 3, CH_3).

Anal. Calcd for $C_{26}H_{30}ClNO_3S$: C, 64.01; H, 5.54; N, 2.88. Found: C, 63.80; H, 5.89; N, 2.71.

***anti*-1-Ethoxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (9j)** was prepared from **5j** (380 mg) as described for **8b**: mp 160° from diethyl ether; nmr[15] ($CDCl_3$) δ 9.10–8.66 (m, 1, peri 3′-H), 8.23–7.43 (m, 3, aromatic H), 6.46–6.13 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 15$ Hz), 1, $CHOC_2H_5$] and 4.0–3.2 (m, 4, benzylic H and OCH_2).

Anal. Calcd for $C_{21}H_{21}ClNO_2$: C, 69.72; H, 7.75; N, 3.87. Found: C, 69.9; H, 7.86; N, 3.76.

***syn*-1-Ethoxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (8j)** was prepared from **4j** (100 mg) as described for **8b**. The *N*-oxide was purified by preparative tlc (silica gel, petroleum ether[14]–10% diethyl ether as eluent) to give 59 mg (59% yield) of **8j** as an oil: nmr[15] ($CDCl_3$) δ 9.10–8.65 (m, ~1, peri 3′-H), 8.35–7.35 (m, ~3, aromatic H), 5.65–5.35 [doublet of doublets (X portion of ABX $J_{AX} + J_{BX} \cong 15$ Hz), 1, $CHOC_2H_5$], 4.0–3.2 (m, 4, benzylic CH_2 and OCH_2CH_3). The oil was hydroscopic and satisfactory C and H analyses were not obtained.

***syn*-1-Benzoyloxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (8c)** was prepared from **4c** (227 mg) essentially as described for **8b**. The *N*-oxide **4c** was obtained as an oil which resisted crystallization: nmr[15] ($CDCl_3$) δ 8.96–8.68 (m, 1, peri 3′-H), 8.33–7.23 (m, 8, aromatic H), 7.00–6.60 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 16$ Hz), 1, CHO], 3.80–2.80 (m, 3, benzylic CH_2 and 1 H from bridge methylene).

The hydrochloride of **8c** was prepared in diethyl ether saturated with dry hydrogen chloride: mp 146–150° from chloroform–diethyl ether, 56% yield pure from **4c**; nmr[15] ($CDCl_3$) δ 11.73 (broad s, 1, ^+NH), 9.10–8.86 (m, 1, peri 3′-H), 8.38–7.33 (X, 3, aromatic), 7.00–6.66 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 16$ Hz), 1, CHO], and 4.00–2.90 (m, 3, benzylic CH_2 and 1 H from bridge methylene).

Anal. Calcd for $C_{26}H_{29}Cl_2O_3N$: C, 65.82; H, 6.17; N, 2.95 Found: C, 65.58; H, 6.08; N, 2.96.

***anti*-1-Benzoyloxy-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (9c).**—A solution of anti benzoate **5c** (198 mg, 0.47 mmol), glacial acetic acid (10 ml), and 30% hydrogen peroxide (0.5 ml) was heated at 85° for 24 hr. More hydrogen peroxide (0.5 ml) was added, and the reaction mixture was maintained at 85° for additional 24 hr. The reaction mixture was cooled and diluted with chloroform (50 ml), and water (500 ml) was added. The chloroform layer was removed and the water layer was extracted with chloroform. The solution was chromatographed on silica gel (40 g) using diethyl ether as eluent to give an oily wax. The oily wax was crystallized from chloroform–petroleum ether[15] to give the *anti*-benzoyloxy *N*-oxide **9c** (37 mg, 18% yield, mp 175–178°). The product was recrystallized from chloroform–petroleum ether[14] to give a pure sample: 25 mg; mp 176–178°; nmr[15] ($CDCl_3$) δ 9.06–8.86 (m, 1, peri 3′-H) and 8.30–7.43 (m, 9, aromatic H and CHO).

Anal. Calcd for $C_{16}H_{23}ClNO_3$: C, 71.30; H, 6.45; N, 3.20. Found: C, 71.05; H, 6.58; N, 3.09.

***syn*-1-Chloro-12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (8g)** was prepared from **4g** (90 mg) essentially as described for **8b** and showed mp 189.5–191° from chloroform–petroleum ether;[14] 58% yield; nmr[15] ($CDCl_3$) δ 8.63–8.33 (m, 1, peri 3′-H), 8.16–7.46 (m, 3, aromatic H), 6.16–5.88 [doublet of doublets (X portion of ABX, $J_{AX} + J_{BX} = 15$ Hz), 1, CHCl], and 3.70–3.00 (m, 3, benzylic CH_2 and 1 H from bridge methylene).

Anal. Calcd for $C_{19}H_{23}Cl_2NO$: C, 64.77; H, 6.57; N, 3.98; Cl, 20.12. Found: C, 64.81; H, 6.57; N, 3.84; Cl, 20.14.

Registry No.—**3**, 25907-81-7; **3** HCl, 37781-22-9; **4b**, 25866-36-8; **4c**, 37781-24-1; **4d**, 37781-25-2; **4f**, 37781-26-3; **4g**, 37781-27-4; **4k**, 22200-39-1; **5b**, 25907-82-8; **5c**, 37781-30-9; **5d**, 37781-31-0; **6**, 37781-32-1; **7**, 37781-33-2; **8b**, 37781-34-3; **8c**, 37781-35-4; **8c** HCl, 37781-36-5; **8d**, 37781-37-6; **8g**, 37781-38-7; **8j**, 37781-39-8; **9b**, 37781-40-1; **9c**, 37781-41-2; **9d**, 37781-42-3; **9j**, 37781-43-4; 12,13-(5′-chlorobenzo)-14-oxo-16-chloro[10](2,4)pyridinophane, 37781-44-5; diethyl 12,13-(5′-chlorobenzo)-16-chloro[10](2,4)pyridinophane-1-phosphate, 37781-45-6; 12,13-benzo-16-chloro[10](2,4)pyridinophane hydrochloride, 25866-34-6.