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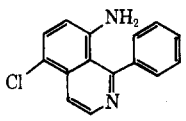

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1,3-Bridged Aromatic Systems. IX. Reactions of Syn and Anti Derivatives of 1-Substituted 12,13-Benzo-16-chloro[10](2,4)pyridinophanes[1]

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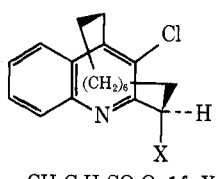
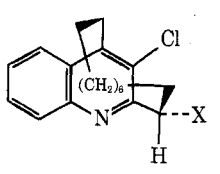
Received July 31, 1973

The reactions of 2,4-bridged meta cyclophanes of type **1** and **2**, containing *syn*- and *anti*-*p*-toluenesulfonyloxy groups (**1a** and **2a**) and *syn*- and *anti*-bromine atoms (**1b** and **2b**) at a benzylic carbon atom in the highly constrained methylene bridge, with a variety of reagents normally employed to effect substitution or elimination reactions are described. The behavior of these compounds is atypical of aliphatic benzyl substituents, which is a consequence of the steric constraint of the fused methylene bridge. The derivatives are highly resistant to bimolecular substitution and elimination reactions and also to ionization reactions. Under forcing conditions ionization reactions can be effected which are highly stereospecific in the syn series with retention of configuration. With silver acetate solvolyses of both **1b** and **2b** are stereospecific (SNi).

The availability of the meta cyclophanes (pyridinophanes) **1a,b** and **2a,b**, of known stereochemistry,[3] has prompted us to investigate in more detail the reactivity of side-chain substituents in these rigid systems. Models show that the back sides of the bridge methine carbon atoms in **1** and **2** are severely shielded to SN2 reactions; furthermore, change in hybridization of these carbon





1a, X = *p*-$CH_3C_6H_4SO_2O$ **1f**, X = $OCOCH_3$
b, X = Br **g**, X = OCH
c, X = H ‖
d, X = OH O
e, X = OC_2H_5 **h**, X = OCH_3

2

atoms from sp^3 to sp^2, which might be expected for SN1 type reactions, would not be favorable since such change in geometry would introduce additional strain into the tightly compacted and rather rigid methylene bridge. Lack of reactivity of such substituents was previously noted by the recovery of **1d** and **2d** unchanged from hot hydrobromic acid.[4]

Reactions of *syn*- and *anti*-1-*p*-Toluenesulfonyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane (1a and 2a). A. With Formic Acid–Water. Reaction of the anti tosylate **2a** in the highly ionizing solvent 90% formic acid–water was slow, but was complete after 48 hr at the reflux temperature. The crude product, which contained only anti alcohol **2d** contaminated with anti formate **2g** (tlc and nmr), was hydrolyzed with potassium hydroxide in methanol to remove formate, and the product thus obtained was analyzed by tlc and by isolation of products. The only product formed (~100% by tlc, 79% by isola-

tion) was anti alcohol **2d**; no syn alcohol **1d** and no more than possible trace quantities of reduced cyclophane **1c** were produced (tlc).

Similar results were obtained by reaction of the syn tosylate **1a** with 90% formic acid under the conditions described for **2a**. Conversion to **1d** (100% tlc, 87% isolated) occurred with complete reaction of configuration; tlc confirmed that no detectable quantities of the anti alcohol **2d** were produced.

Complete retention of configuration in these solvolysis reactions is consistent with two explanations: (A) ionization occurs to give carbonium ions or ion pairs which, owing to structural constraint, retain their stereochemistry during solvolysis, or (B) conversion of **1a** and **2a** to the corresponding alcohols occurs by acid-catalyzed solvolysis of the sulfur-oxygen bond.[5] While no unequivocal decision can be made at this time between these two alternatives, support for B was obtained by studies of the behavior of carbonium ions or ion pairs derived from the related syn and anti bromides **1b** and **2b**, which is discussed subsequently in this report.

B. With KOH–Methanol. The anti tosylate **2a** was quite stable to potassium hydroxide in methanol; after 20 hr at the reflux temperature only low conversion to product was observed. The only product present in the reaction mixture other than recovered **2a** was the anti alcohol **2d** (20%); no syn alcohol **1d** or ethers **1h** or **2h** were detected (tlc).

Similar results were obtained with the syn tosylate **1a**. Analysis of the mixture obtained after **1a** was treated for 24 hr at the reflux temperature with methanolic potassium hydroxide showed the presence of unchanged **1a** (61% recovery, pure) and syn alcohol **1d** (28% yield, pure); no anti alcohol **2d** or ethers were detected (tlc). It was significant to note that the recovered tosylate (63% recovery) from this reaction was pure **2a**, with no evidence for epimerization to **1a** which could occur through a possible carbanion intermediate at the methinyl carbon atom.[6]

Complete retention of configuration of the alcohols obtained from **1a** and **1b** confirmed that no S_N2 substitution occurred; the alcohols **1d** and **2d** were most likely formed by sulfur–oxygen bond cleavage.[7]

C. With Other Nucleophiles. It was apparent from B, above, that both S_N2 and/or E2 reactions of tosylates **1a** and **2a** must have high energies of activation, the former because of hindrance at C-1, and the latter because elimination would introduce two sp^2 carbon atoms into the strained system. This conclusion was further corroborated by the complete lack of reactivity (96% recovery after 30 hr) of both tosylates **1a** and **2a** with the strong nucleophile thiourea in hot 95% ethanol containing enough dioxane to ensure homogeneity. Reactions of undetermined nature could be effected with tosylates **1a** and **2a** with nucleophiles in aprotic solvents under severe conditions; however, even under drastic conditions the tosylates are remarkably unreactive. Thus, anti tosylate **2a** (0.53 mmol) was recovered largely unchanged (91%) after treatment with a solution of sodium cyanide (1.3 mmol) in dimethyl sulfoxide (10 ml) at 100° for 24 hr. Similarly, anti **2a** was recovered unchanged (>50%) after similar treatment at 100° for 48 hr.[8]

Reactions of *syn*- and *anti*-1-Bromo-12,13-benzo-16-chloro[10](2,4)pyridinophane (1b and 2b). A. With Nucleophiles. Reaction of syn bromide **1b**[9] under conditions normally employed to effect S_N2 or E2 reactions with ordinary alkyl halides corroborated the lack of reactivity observed for the tosylates **1a** and **1b**. Thus, **1b** was recovered largely unchanged (84% pure) after treatment with glacial acetic acid containing potassium acetate at the reflux temperature (20 hr). Furthermore, there was little or no reaction of **1b** with lithium chloride in hot (100°) dimethylformamide (16 hr, 86% recovery), or with thiourea in boiling 95% ethanol–dioxane (48 hr, 99% recovery). The reaction with sodium ethoxide in ethanol, which showed formation of a trace of product after 4 hr (tlc), was allowed to continue for 115 hr to give a mixture containing one major and two minor components. The major product, obtained pure in 71% yield, was not a substitution product, but rather the reduced cycophane **1c**.[10] The two minor products (~5 and 6%, respectively) had the same R_f[3] values as syn and anti ethers **1e** and **2e**, respectively; however, they were not further characterized.[11]

It is clear from these results, together with those described for the tosylates **1a** and **2a**, that bimolecular substitution and/or elimination reactions on carbon do not occur readily if at all in these cyclophane systems.

B. With Silver Acetate in Acetic Acid. The syn bromide **1b** reacted slowly with silver acetate in hot glacial acetic acid. The reaction was complete after 48 hr and the syn acetate **1f**, isolated as the alcohol (~100%), was the only product observed; careful analysis (tlc) showed that no anti alcohol was present. Similar results were obtained with the anti bromide **2b**; the only product formed was the anti acetate (isolated 74% yield).

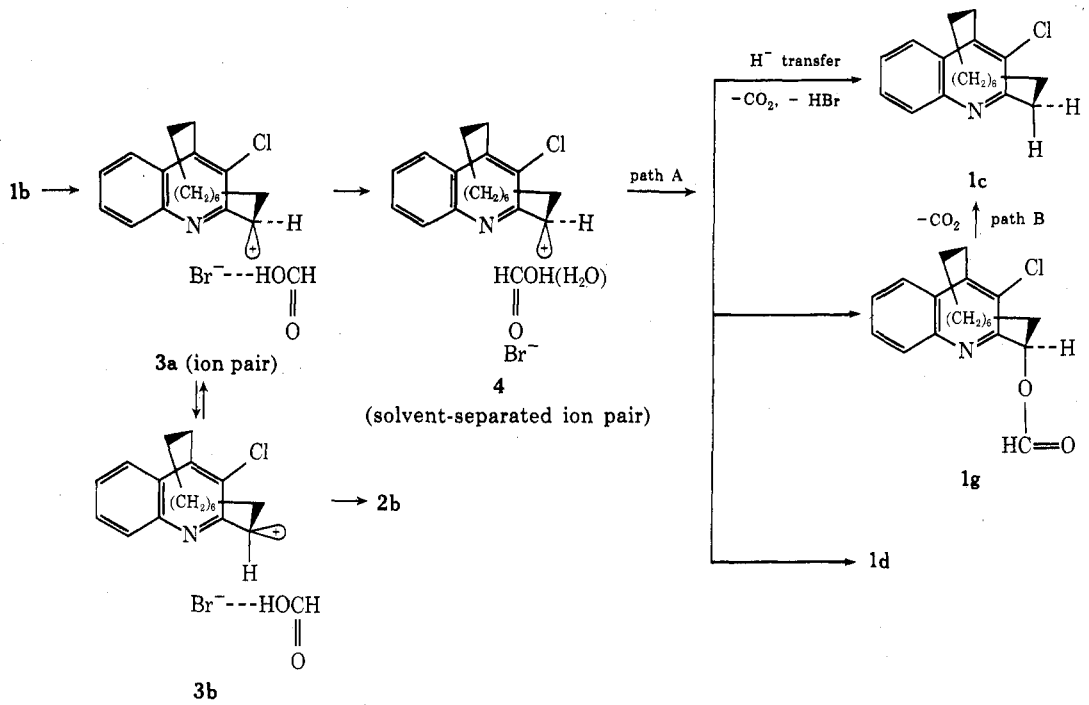
The complete stereospecificity of these reactions is consistent with the conclusion that the reactions are effectively concerted (S_Ni) or that the ion pairs formed in these rigid systems have a high energy barrier to rehybridization.

C. With Formic Acid. The syn bromopyridinophane **1b** was observed to react slowly with hot formic acid (90%). The reaction, which was monitored by tlc, was quenched after 10 days. The resulting mixture contained two minor components (~2 wt % each) and three major components, which were identified as unchanged bromide (23%), reduced cyclophane **1c** (27% based on recovered **1b**), syn alcohol **1d** (60% based on recovered **1b**), and no more than a trace, if any, of anti alcohol. The recovered halide was mostly unchanged **1b**; however, both nmr and tlc indicated that some (~10% of bromide) epimeric bromide **2b** was present. We believe, at this time, that the reaction occurs by a process formally represented as shown in Scheme I. We tentatively suggest that the initial produce formed in this reaction is the tight ion pair **3a**, which can slowly rearrange to the epimeric ion **3b**; either **3a** or **3b** can collapse to regenerate halide (**1b** and **2b**, respectively). The solvolysis studies to be described subsequently with the anti bromide **2b** offer little support for a common planar carbonium ion derived from **1b** and **2b**.

The solvent-separated ion pair **4** (Scheme I) provides a logic for the formation of both **1c** and **1g** (or the alcohol **1d**). Formic acid is a good reducing agent[12] and either hydride transfer to **1c** or solvolysis to **1g** are reasonable paths.

An alternative route for the formation of reduced product **1c** would involve intramolecular hydride transfer from the formate as shown in **1g** (path B) of Scheme I; such reduction would be formally analogous to the Clarke–Eschweiler reaction.[13] If this alternative was the correct one, prolonged treatment of the syn and anti alcohols with hot formic acid, either with or without added hydrogen bromide, should lead to reduction in yield comparable to that observed during the formolysis of the syn bromide **1b**. This was not observed experimentally. Thus, reaction (240 hr) of syn alcohol **1d** with hot (130°) formic acid (90%) containing 1 equiv of hydrogen bromide gave a mixture of unchanged **1d** and syn formate **1g**; no reduction to **1c** or epimerization to **2d** occurred. Similar results were obtained with the anti alcohol **2d**; under the same conditions formate formation (**2g**) was observed but no more

Scheme I



than a possible trace of reduction to **1c** or epimerization to **1d** occurred. Reactions of syn and anti alcohols (240 hr) with hot (130°) formic acid (90%) in the absence of added mineral acid lead to mixtures of alcohols and formates, but to only low yields (~2% and 6% from **1d** and **2d**, respectively) of reduced product **1c**. The low yields of reduction to **1c** in these experiments are in sharp contrast to the relatively high yield of reduction noted during the formolysis of **1b**, an observation more consistent with path A than path B.

The reaction of the anti bromide **2b** with hot (130°) formic acid (90%) was much slower than with the syn bromide **1b** and gave significantly different results; after twice the reaction time used for **1b**, the product obtained from **2b** contained 28% unchanged **2b**, no more than a possible trace of syn bromide **1b**, 11% of anti alcohol **2d**, 36% of the epimeric syn alcohol **1d**, and 19% of reduced material **1c**.

The contrasting results obtained for the formolysis of syn and anti bromides **1b** and **2b** provides rather convincing evidence that a free planar carbonium ion is not involved as a common intermediate for formolysis of **1b** and **2b**. Clearly the ion pair **3b**, derived from **2b**, does not maintain its stereochemical identity, nor does the ion pair **3a**. The anti bromide **2b** is clearly more stable to solvolysis than the syn bromide **1a**. The product distribution, which favors formation of syn products, is consistent with the conclusion that either: (a) the rearrangement of halides **1b** and **2b**, presumably through **3a** ⇄ **3b**, favors formation **1b** (possibly for steric reasons), or (b) the equilibrium **3a** ⇄ **3b** favors **3a** (possibly due to the lone pair on nitrogen).

Attention should also be called to the product distribution obtained when the syn and anti alcohols **1d** and **2d** were treated for prolonged periods with hot (130°) formic acid (90%). Reaction of syn **1d** for 162 hr gave a mixture containing unchanged **1d** (91%), syn formate **1g** (5.5%), and a small amount of reduced pyridinophane **1c** (~2%). By contrast, reaction of anti alcohol **2d** for 240 hr gave a mixture containing unchanged **2d** (52%), anti formate **2g** (30%), **1g** (~6%), and epimeric alcohol **1d** (~10%). Thus, as in the solvolysis of the bromide **1b** and **2b**, the reaction of the anti alcohol with formic acid is slower than that with the syn isomer, and that syn products are favored.

An alternative explanation for the result described above for the solvolysis of bromides **1b** and **2b** in hot formic acid is that substitution is stereospecific and that isomerization **1b** ⇄ **2b** occurred by a thermal reaction involving rotation of the bridge to the other face of the aromatic ring rather than epimerization caused by carbon–bromine bond cleavage. However, available evidence does not support this possibility. If thermal isomerization was effecting product distribution then similar product distributions should be observed during solvolysis of both **1b** and **2b**. More compelling, however, is the observation that the hydrochloride salts of the alcohols **1d** and **2d** were stable and underwent no interconversion when heated in formic acid for extensive periods (10 days). In these cases carbon–oxygen bond cleavage (carbonium ion formation) is inhibited by the positively charged nitrogen atom; no chemically or thermally induced epimerization was observed.

That thermal isomerization of **1b** ⇄ **2b** was not occurring was also suggested by studies of the thermal behavior of **1b** and **2b** in boiling xylene (9 days, N_2 atmosphere). Both samples darkened appreciably which suggested thermal instability; however, the syn bromide was recovered in 82.3% yield; no epimerization to **2b** was observed (by nmr). The anti bromide **2b** was, however, completely destroyed by such treatment and the principal product formed (>50% yield) was reduced cyclophane **1c** (possibly formed by a radical process involving homolytic cleavage of the C–Br bond with subsequent abstraction of hydrogen from solvent). The crude product contained none of the stable epimeric bromide **1b**; consequently, there is no evidence for thermal equilibration of **1b** and **2b**.

Experimental Section

Analysis. By proper choice of conditions it is possible to analyze mixtures of most of the pyridinophanes by tlc on silica gel. Using petroleum ether (bp 60–90°) and ether (1:1) the following R_f values were observed: **1a** (0.34), **1b** (0.65), **1c** (0.57), **1d** (0.48), **1f** (0.40), **1g** (0.37), **2a** (0.37), **2b** (0.63), **2d** (0.16), **2f** (0.40), and **2g** (0.50). Using petroleum ether–ether (3:1) they were as follows: **1a** (0.14), **1b** (0.51), **1c** (0.38), **1d** (0.31), **1f** (0.21), **1g** (0.21), **2a** (0.15), **2b** (0.47), **2d** (0.05), **2f** (0.21), and **2g** (0.28). For those cases where tlc was not conclusive because of close R_f values (for example, syn and anti acetates **1f** and **2f**, anti formate **2g** and syn alcohol **1d**, and syn and anti tosylates **1a** and **2a**), differentiations were made on the basis of the characteristic[3] nmr spectrum of the

methine proton on the bridge; syn acetate **1f** and anti acetate **2f** also showed sharp $CH_3C{=}O$ at δ 2.10 and 2.08, respectively.

Preparative separations were performed using Brinkman Silica Gel PF 254 (2 mm thick plates) with multiple evelopments using petroleum ether (bp 30–60°)–ether mixtures.

Reaction of syn tosylate 1a[3] (206 mg, 0.44 mmol) with formic acid (6 ml, 90%) was carried out for 48 hr at a pot temperature of 130°, after which the mixture was treated with methanol (40 ml) containing potassium hydroxide (6.2 g, 0.11 mol) for 4 hr at the reflux temperature. The mixture was diluted with water (40 ml) and extracted with chloroform. The nmr spectrum of the crude product (143.6 mg) obtained from the dried ($MgSO_4$) chloroform extract was identical with that of syn alcohol. The product was purified by preparative tlc. Pure syn alcohol **1d** (105.7 mg, 84% yield, mp and mmp 159–160°) was obtained; no detectable quantities of other products were noted.

Reaction of anti tosylate 2a (193.2 mg) with formic acid under identical conditions gave 130 mg (100% yield) of **2d** (mp and mmp 204–206°).

Reaction of syn tosylate 1a[3] (180 mg, 0.38 mmol) with potassium hydroxide (174 mg, 3.1 mmol) in boiling methanol (10 ml) was monitored by tlc. Reaction was quite slow and after 4 hr little reaction was noted. After 24 hr the mixture showed two components which were separated by tlc, subsequent to removal of solvent and extraction with chloroform, into recovered **1a** (61% pure) and syn alcohol **1d** (28%, pure); no detectable quantities of **2d** were formed.

Reaction of anti tosylate 2a[3] (193 mg) with potassium hydroxide in methanol was carried out as described for **1a** with similar results. After 20 hr there was obtained recovered **2a** (61% yield pure, subsequent to preparative tlc and recrystallizatiion) and anti **2d** (20% yield); no detectable quantity of syn **1a** was formed.

Reaction of tosylates 1a and 2a (0.43 mmol) with thiourea (0.80 mmol) was carried out in 95% ethanol (3 ml) and dioxane (3 ml) for 30 hr at the reflux temperature. Only unchanged reactants were detected (tlc) and recovered.

Reaction of syn bromide 4b (890 mg, 2.3 mmol) with potassium acetate (1.00 g, 10 mmol) in acetic acid (20 ml) was carried out for 10 hr at 117°. The mixture was diluted with water and extracted with ether, and the ether extract was washed with aqueous sodium bicarbonate (10%) and water. The dried ($MgSO_4$) ether extract was concentrated to give recovered **1b** (84% pure, mp and mmp 147–148°).

Reaction of syn bromide 4b (0.51 g, 1.3 mmol) with sodium ethoxide in ethanol [prepared from sodium (0.413 g, 18 mg-atoms) and ethanol (10 ml)] was maintained at the reflux temperature for 115 hr and then excess alcohol was removed (rotary evaporator). The residue was diluted with ether and the ether was washed with water and dried ($MgSO_4$). The residue (444 mg) obtained from the ether was analyzed by preparative tlc. Five fractions were noted. The principal product (71% yield, mp and mmp 78–81°[3]) was reduced cyclophane **1c**. Two other fractions obtained in low yield (~6% and 4.5% yields, respectively) had the same R_f value as authentic **1e** and **2e**; however, no further attempt to characerize these products was made.

Reaction of syn bromide 1b (276 mg, 1.64 mmol) with silver acetate (1.64 mmol) was carried out under nitrogen in boiling glacial acetic acid (11 ml) for 20 hr. The mixture was filtered and the filtrate was diluted with water, neutralized, and extracted with chloroform. The yellow oil obtained from the filtrate was heated with potassium hydroxide (2.5 g) in methanol (100 ml) for 8 hr at reflux to hydrolyze the ester. The slightly impure syn **1d** (~100% yield) was recrystallized from chloroform–petroleum ether (bp 60–80°) to give pure **1d** (134 mg, 49% yield, mp and mmp 160–163°). Analysis of the mother liquor by tlc showed only one spot corresponding to **1d**; no **2d** could be detected.

Reaction of anti bromide 2b with silver acetate was carried out for 22 hr as described for **1b**. The reaction mixture was then treated with saturated NaCl solution, cooled, and filtered, and the salts were washed with ether. The filtrate was extracted with 5% KOH to remove acetic acid, and the ether solution was then extracted with saturated ammonium chloride and dried ($MgSO_4$). The ether was evaporated (*in vacuo*) to give 73.7 mg of a white solid, which showed only anti acetate **2f** by nmr (a single methyl resonance at δ 2.08; the syn acetate **1f** shows resonance at δ 2.10). Recrystallization of this product from ligroin gave 46.1 mg (74% yield) of syn acetate, mp 143–144°, mmp 145–146°. Examination of the mother liquor by nmr showed a single methyl resonance at δ 2.08.

Reaction of syn bromide 1b (0.525 mmol) with formic acid (5 ml, 90%) was carried out for 10 days at a pot temperature of 130°. The cooled mixture was diluted with water (10 ml) and extracted with chloroform. The organic extract was washed successively with saturated sodium bicarbonate and with water (10 ml). Preparative tlc [silica gel developed three times with petroleum ether (bp 30–60°)–ether (6:1)] showed three major components and two minor components (~2% by weight each). The major components were syn alcohol **1d** (22% based on recovered bromide, mp 152–153°, mmp[3] 153–156°), reduced cyclophane **1c** (20% based on recovered bromide, mp and mmp 80–81°), and recovered bromide (34.6%, mp 140–141°). Examination of the nmr spectrum of recovered bromide confirmed the presence of about 10% epimeric bromide **2b**.

The anti bromide 2b was prepared by the reaction of 12,13-benzo-14-oxo-16-chloro[10](2,4)pyridinophane (1.59 g, 5.00 mmol) with 25 ml of refluxing acetyl bromide (protected by $CaSO_4$ drying tube) for 6 hr. Excess acetyl bromide was then removed by distillation. The residue was dissolved in chloroform (25 ml) and washed with saturated $NaHCO_3$ (15 ml) and water (15 ml). The dried (Na_2SO_4) chloroform solution was concentrated (*in vacuo*), yielding 2.1 g of a viscous yellow oil. Column chromatography on neutral alumina step gradient eluted with petroleum ether–ether gave two major fracions listed in order of increasing R_f: (1) 1.00 g, (55.6%), a mixture of syn and anti acetates **1f** and **2f**; (2) 0.68 g (35.8%), a mixture of bromides. Preparative tlc of these bromides showed four principal bands. The band with highest R_f was syn bromide **1b**, 42.5 mg, mp and mmp 145–146°. The next highest fraction was the anti 1-bromide: 181.5 mg (9.5%); mp 152–153° (from $CHCl_3$–petroleum ether); nmr ($CDCl_3$) δ 8.14–7.50 (m, 4, aromatic H), 5.42 (q, X portion of ABX, $J_{AX} + J_{BX}$ = 17 Hz, 1, CHBr), 3.80–3.04 (m, 3, benzylic CH_2 plus H from bridge), and 2.54 to −0.30 (m, 15, bridge H).

Anal. Calcd for $C_{19}H_{23}NClBr$: C, 59.93; H, 6.08; N, 3.67. Found: 60.11; H, 5.96; N, 3.50.

Evidence for assignment of anti stereochemistry was obtained as previously reported.[3]

The two other fractions (70 and 193 mg, respectively) were not characterized.

Reaction of anti bromide 2b with formic acid (90%) was carried out as described for **1b**. The reaction was monitored by tlc and was much slower than that observed for **1b**. The reaction was continued for 20 days and resolved by preparative tlc [silica gel developed twice with petroleum ether–ether (4:1)]. There was obtained in order of increasing R_f (1) anti alcohol **2d** (11% based on recovered halide, mp and mmp 201–203°); (2) trace (not processed); (3) syn alcohol **1d** (~36% based on recovered halide, mp and mmp 154–165°); (4) a mixture which was resolved by subsequent chromatography [silica gel PF 254 using petroleum ether (bp 30–60°)–ether (9:1)] into reduced **1c** (19% based on recovered halide, mp 79.5–80°, mmp 81–82.5°) and pure anti bromide **2b** (14%, mp 147–149°); and (5) nearly pure anti bromide **2b** (mp 141–145°, combined recovery 27%). The nmr spectrum of this fraction showed[3] no more than a trace of syn bromide **1b**.

Reaction of Syn Alcohol 1d with Formic Acid. The syn alcohol **1d** (300 mg, 0.946 mmol) was heated (pot at 130°) in formic acid (15 ml, 90%) for 162 hr and the mixture was then cooled, poured into water (50 ml), and extracted with chloroform (40 ml total). The chloroform extract was washed with saturated sodium bicarbonate and then with water and was dried (Na_2SO_4) and concentrated to a yellow solid (306 mg, mp 149–153°). This solid was recrystallized [chloroform–petroleum ether (bp 60–90°)] to give 230 mg (76.5% recovery) of pure (tlc, nmr, mp 156–157°) recovered syn alcohol **1d**. The mother liquor was purified by preparative tlc [silica gel developed four times with petroleum ether (bp 30–60°)–ether (4:1)] to give three fractions.

The band of lowest R_f (19.4 mg, 5.5%) was recrystallized with little loss from petroleum ether to give *syn*-1-formyloxy-12,13-benzo-16-chloro[10](2,4)pyridinophane (**1g**): mp 122–122.5°; nmr ($CDCl_3$) δ 8.15 (s, 1, O_2CH), 8.10–7.40 (m, 4, aromatic H), 6.60 (q, X portion of ABX, $J_{AX} + J_{BX}$ = 14 Hz, 1, CHOCHO), 3.60–3.15 (m, 2, benzylic CH_2), 2.6–0.2 (m, ~16 H, bridge CH_2); ir (KBr) $\nu_{C=O}$ 1740 cm^{-1}, ν_{C-H} 2880 cm^{-1}, ν_{C-O} 1170 cm^{-1}.

Anal. Calcd for $C_{20}H_{24}NO_2Cl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.65; H, 6.75; N, 4.03.

The second fraction (42.1 mg) was recovered **1d** (total recovery 91%). The third fraction (5 mg, 2% yield), obtained as an oil, crystallized (mp 74–76°) and was shown to be pyridinophane **1c** by conversion to the picrate (mp and mmp[4b] 172–173°).

Reaction of anti alcohol 2d with formic acid was carried out as described for **1d**. The mother liquor obtained subsequent to removal of some pure recovered **2d** (32%, mp 204–204.5°) by recrystallization from chloroform–petroleum ether (bp 60–90°) was chromatographed on a preparative plate [silica gel PF254 devel-

oped with petroleum ether (bp 30–60°)–ether (2:1)] to give two fractions in addition to additional pure **2d** (total recovery 52%).

The first of these was a mixture (nmr)[3] of syn alcohol **1d** (~10% yield by nmr) and anti formate **2g** (30% yield) which have nearly identical R_f values. The anti formate, which was unknown, was purified by recrystallization of this mixture from chloroform–petroleum ether (bp 60–90°): nmr ($CDCl_3$) δ 8.19 (1, s, O_2CH), 8.19–7.58 (4, m, aromatic H), 6.23 (1, X portion of ABX, $J_{AX} + J_{BX}$ = 16 Hz, q, CHO_2CH), 3.75–0 (broad m, 18, bridge CH_2).

Anal. Calcd for $C_{20}H_{24}NO_2Cl$: C, 69.45; H, 6.99; N, 4.05. Found: C, 69.68; H, 7.01; N, 4.04.

The mother liquor from this recrystallization contained (tlc and nmr) syn alcohol **1d**, anti formate **1d**, and trace amounts of another material assumed to be syn formate **1g**.

The other fraction (5.5 mg, 6% yield) was reduced pyridinophane **1c** (mp and mmp[4b] of picrate 173–174°).

Thermal Stability of Syn and Anti Bromides (1b and 2b). A. A solution of syn **1b** (50.5 mg, 0.133 mmol) in xylene (ACS grade, 0.5 ml) was heated at the reflux temperature under nitrogen for 220 hr. Xylene was removed (*in vacuo*) from the brown, tarry mixture; the residue showed (nmr) unchanged **2a** (δ 6.06) and no epimer **2b** (δ 5.42). The sample was dissolved in chloroform and washed with dilute sodium bicarbonate and the product was recrystallized from petroleum ether to give 41.6 mg (82.3% recovery) of **2a**, mp 141–142°, mmp 143–144° with material melting at 144–145°.

B. A sample of anti **2b** (65.8 mg, 0.173 mmol) was treated in xylene as described above. The nmr spectrum of the crude product showed no **2b** (δ 5.42) or **2a** (δ 6.06) and was quite similar to that of **1c**. The product was decolorized as above and purified by preparative tlc [silica gel, petroleum ether–ether (3:1)] to give 26 mg (50% yield) of **1c** (mp and mmp 78–79°).

Registry No. **1a**, 37781-25-2; **1b**, 25859-37-4; **1d**, 25866-36-8; **1g**, 42880-43-3; **2a**, 37781-31-0; **2b**, 42880-45-5; **2d**, 25907-82-8; **2g**, 42962-81-2.

References and Notes

(1) Support by the National Science Foundation, Grant GP 35429.
(2) Address correspondence to Paul Gross Chemical Laboratory, Duke University, Durham, N. C. 27706.
(3) W. E. Parham, K. B. Sloan, K. R. Reddy, and P. Olson, *J. Org. Chem.*, **38**, 927 (1973).
(4) (a) W. E. Parham, K. B. Sloan, and J. B. Biasotti, *Tetrahedron*, **27**, 5767 (1971); (b) W. E. Parham, R. W. Davenport, and J. B. Biasotti, *J. Org. Chem.*, **35**, 3775 (1970).
(5) Alkylsulfonates normally undergo carbon–oxygen scission under these conditions; the authors are unaware of related acid-catalyzed S–O bond cleavage.
(6) 2- and 4-methylpyridines undergo hydrogen–deuterium interchange on the methyl group, presumably through a carbanion intermediate, under rather mild conditions; *cf.* K. Schofield, "Hetero-Aromatic Nitrogen Compounds," Butterworths, London, 1967, pp 324–327, and references cited therein.
(7) Sulfur–oxygen bond cleavage of alkylsulfonates by base is uncommon, since substitution or elimination at carbon generally occurs. However, arylsulfonates readily undergo S–O bond cleavage by nucleophiles: *cf.* W. D. Closson and P. Wriede, *J. Amer. Chem. Soc.*, **88**, 1581 (1966).
(8) Reactions of **1a** and **1b** with KBr in hot dimethylformamide and in dimethyl sulfoxide were also studied with similar results. The principal products were unchanged starting materials along with complex mixtures which were not examined.
(9) In view of the parallel in reactivity of tosylates **1a** and **2a**, coupled with the fact that the anti bromide **2b** is difficult to obtain in quantity, only selected reactions of both epimers **1b** and **2b** were carried out.
(10) Reduction of alkyl halide by strong base is uncommon but not unknown. Iodoform, for example, is reduced to methylene iodide by base, and the reaction is thought to involve nucleophilic attack at halogen; *cf.* S. Bagnara, *Eng. Mining J.-Press*, **116**, 51 (1923).
(11) Reduction of aryl halides by alkoxide is well known; *cf.* J. F. Bunnet and R. R. Victor, *J. Amer. Chem. Soc.*, **90**, 810 (1968). Formation of low yields of syn and anti ethers under these drastic conditions is not interpreted as evidence for SN2 reactions, since a variety of routes can be postulated for their formation.
(12) Triphenylcarbinol, for example, is efficiently reduced to triphenylmethane; *cf.* H. Kauffmann and P. Pannwitz, *Chem. Ber.*, **45**, 766 (1912).
(13) W. E. Parham, "Synthesis and Reactions in Organic Chemistry," Wiley, New York, N. Y., 1970, pp 258–259.

Nitration and Bromination of Isocytosine-6-acetic Acid. Some Corrections[1]

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Received June 25, 1973

The reported nitration and bromination of isocytosine-6-acetic acid (**1a**) was reinvestigated. Under nitration conditions, oxidation of **1a** occurred to give isocytosine-6-carboxylic acid (**12a**), instead of the reported 5-nitroisocytosine-6-acetic acid (**2a**). Consequently, the reported reduction of **2a** to 5-aminoisocytosine-6-acetic acid (**2b**) may not have occurred. The nitrosation of **1a** produced 6-hydroxyiminomethylisocytosine (**11**), which could also be oxidized to **12a** by nitric acid. By a modification of the reported preparation of **1a**, the direct preparation of ethyl isocytosine-6-acetate (**1b**) was accomplished. Bromination of **1a** at room temperature gave 5-bromoisocytosine-6-acetic acid (**13**) hydrobromide. However, the reported **13** could not be obtained without decarboxylation of **13** to 5-bromo-6-methylisocytosine (**14**). Bromination of **1a** could also be controlled to give di- and tribromo derivatives of **14**.

The preparation of 5-nitroisocytosine-6-acetic acid[2] (**2a**) and the subsequent reduction to 5-aminoisocytosine-6-acetic acid[3] (**2b**) had been reported by Worrall. We desired **2a** as a precursor for 5-amino-6-aminomethylisocytosine (**4**, Scheme I) which we had intended to use as the key intermediate in an improved synthesis of an isomer of ethyl pteroate.[4] Consequently, our isolation of the product from our attempted nitration of **1a** other than the reported **2a** was quite disappointing. We report here our reinvestigation of the nitration of isocytosine-6-acetic acid (**1a**), as well as its bromination as reported by Worrall.[2,3]

The selection of this mode of preparation of **4** was based on similar reactions on pyrimidine substrates of slightly different structures (see Scheme II). Uracil-6-acetic acid (**5**) had been shown to nitrosate and spontaneously decarboxylate to give **7**.[5] Similarly, the 6-methyl group activated by the 5-nitro group of 5-nitrouracil (**8**) could also be

Scheme I