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(23) We wish to acknowledge the help of the late Mr. A. Wajngurt and Mr. M. Loo with large-scale preparations of the dimethyl ester.
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Indolizidines, α-Arylthiohemiaminals, and α-Arylsulfonylhemiaminals from a Quinolizidine Enamine and an Arenesulfonyl Chloride[1]

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The treatment of the quinolizidine enamine 6-dehydrodeoxynupharidine (**1**) with *p*-toluenesulfonyl chloride in benzene solution produces the following compounds: *p*-tolyl disulfone (**2**); *p*-tolyl disulfide (**3**); 7β-(*p*-tolylthio)-deoxynupharidin-6-ol (**4**); 7α-(*p*-tolylthio)-7-epideoxynupharidin-6-ol (**5**); 7β-(*p*-toluenesulfonyl)deoxynupharidin-6-ol (**6**); 7α-(*p*-toluenesulfonyl)-7-epideoxynupharidin-6-ol (**7**); and two epimeric indolizidinecarboxaldehydes, **8** and **9**, which arise by skeletal rearrangement. All of the products are isolated except for one of the epimeric indolizidines, **8**. Gross structures assigned are consistent with spectral evidence and elemental analyses. The C-7 configuration in the α-thiohemiaminals **4** and **5** is determined by circular dichroism and the configuration at the same center in the α-sulfonylhemiaminals **6** and **7** is established by chemical correlation with **4** and **5**. The C-3 configuration and the stereochemistry of the ring fusion in the isolated indolizidinecarboxaldehyde, 5α-(3-furyl)-3β,10β-dimethylindolizidine-3α-carboxaldehyde (**9**), is ascertained through infrared studies of the primary alcohol, **14**, obtained from **9** by reduction. Primary alcohol **14** gives Bohlmann infrared bands, indicating the trans-fused indolizidine ring system, and infrared bands revealing the intramolecular hydrogen bonding of the primary alcohol to the nitrogen. The rationale for product formation is based on *p*-toluenesulfonyl chloride acting as an ambident electrophile.

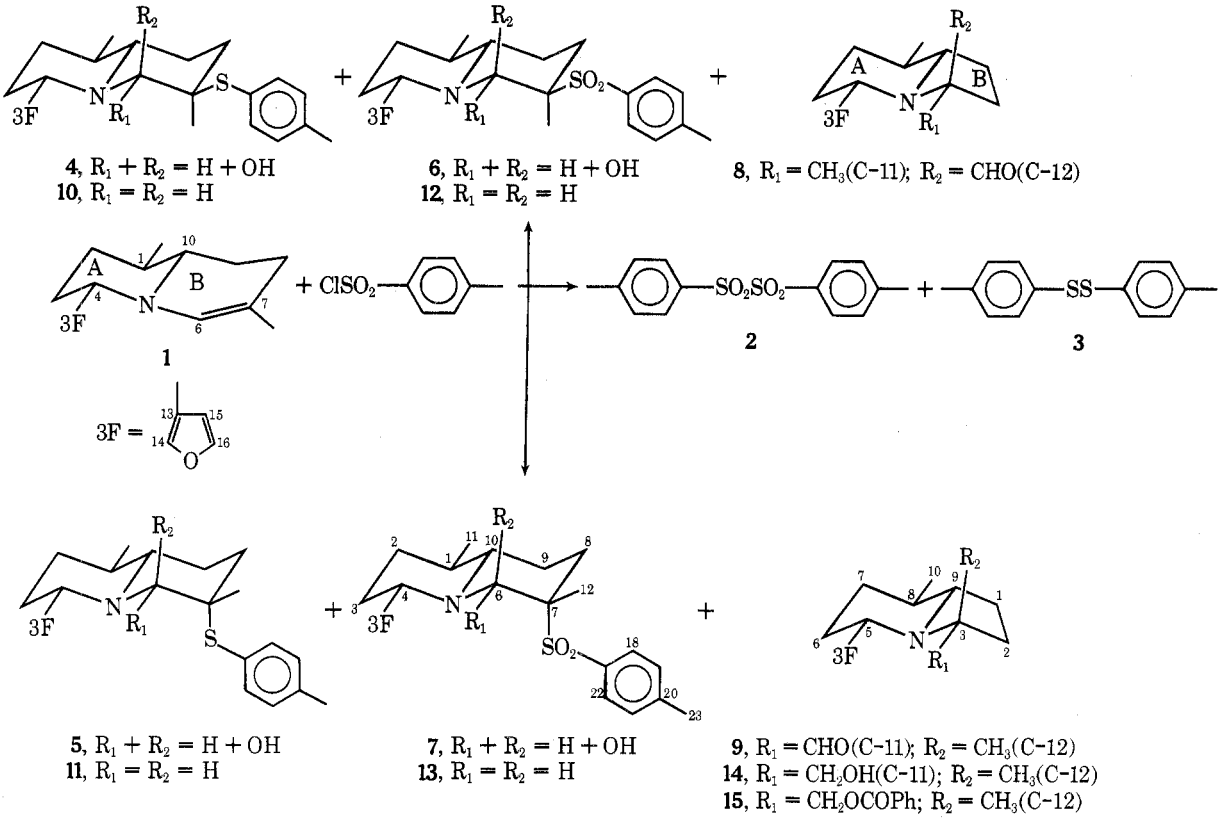
We wished to prepare a group of α-arenesulfonylhemiaminals for the purpose of comparing their metal hydride reductions with those of α-arylthiohemiaminals. Therefore we carried out the reaction of *p*-toluenesulfonyl chloride with 6-dehydrodeoxynupharidine (**1**). No less than eight products, including *p*-tolyl disulfone (**2**), *p*-tolyl disulfide (**3**), and three pairs of diastereomers, result from this reaction which takes the unusual course, outlined in Scheme I, in producing the rearranged indolizidines **8** and **9** and the α-thiohemiaminals **4** and **5** in addition to affording the desired and expected α-sulfonylhemiaminals **6** and **7**. Because of the unusual course of this reaction we wish to present the evidence for the formation of the six compounds **4–9**; the procedures for the isolation of five of them (**4–7** and **9**); and the structure determination of **4–7** and **9** as the principal topics of this paper. *p*-Tolyl disulfone (**2**)[2,3,4] and *p*-tolyl disulfide (**3**)[5,6] have long been known and their identification needs no further treatment beyond what is given in the Experimental Section. Finally a brief discussion regarding product formation is presented. The features of α-sulfonyl- and α-thiohemiaminal reductions will be treated in a separate paper at a later date.

The Indolizidines. Although only one of the two indolizidine aldehydes, **9**, could be isolated for study, there was evidence that both diastereomers **8** and **9** were formed. Thus the ^1H NMR of a chromatographic fraction showing two spots on TLC revealed a pair of singlets at δ 0.92 and 1.07, the lower field signal being the more intense. These signals were attributed to C-11, the methyl group attached to C-3 of **8** or **9**. Moreover the same spectrum exhibited a pair of aldehyde protons at δ 9.04 and 9.79 whose integrated intensities were in the ratio of 8:1.

Chromatographic refinement of this same fraction gave the pure diastereomer **9** but failed to separate the minor diastereomer **8** in a state completely free of **9**. The ^1H NMR of **9** revealed the C-8 methyl (C-10) doublet at δ 0.91, the C-5 proton double doublet at δ 3.36, and the 3-furyl multiplets at δ 6.36 and 7.26, the last two signals representing three protons. Consequently neither the furan ring nor ring A of the starting enamine had been altered since these ^1H NMR characteristics agree with those of the corresponding protons[7,8] in deoxynupharidine and 7-epideoxynupharidine (**1**, 6,7β- and 6,7α-dihydro, respectively). This conclusion was supported by the ^{13}C NMR spectrum, which exhibited the C-10 quartet at 18.5 ppm, the C-8 doublet at 37.0 ppm, and the C-9 doublet at 67.5 ppm in addition to the normal 3-furyl signals at 109.8, 127.0, 140.0, and 142.9 ppm, all in accord with the ^{13}C chemical shifts of corresponding carbons in deoxynupharidine and 7-epideoxynupharidine.[9]

The appearance of the ir absorption at 5.79 μm and the ^1H NMR singlet at δ 9.04 indicated the presence of the aldehyde function. The aldehyde group must be attached to a quaternary carbon which also bears the second methyl group since the latter appears at δ 1.07 as a singlet. The quaternary carbon was linked to the nitrogen since the higher field singlet in the ^{13}C NMR appeared at 70.5 ppm. The second carbon attached to nitrogen gave the 67.5-ppm doublet as already mentioned above. The third carbon attached to nitrogen, as yet unaccounted for, appeared as a doublet at 52.9 ppm and was assigned to C-5. Therefore, of the total 15 carbons indicated by

Scheme I. Products from the Reaction of *p*-Toluenesulfonyl Chloride and 6-Dehydrodeoxynupharidine and Subsequent Transformations



the mass spectrum and the elemental analysis of the corresponding primary alcohol (see the Experimental Section), the two remaining carbons were incorporated into the structure as C-1 and C-2 to complete a five-membered B ring as shown in **8** and **9**. The remaining features of the ^{13}C NMR are consistent with the structure; the 28.6-ppm triplet corresponds to the C-9 chemical shift in deoxynupharidine and one of the triplets at 34.6, 33.2, or 31.6 ppm agrees with the 30.6-ppm chemical shift of C-8 in deoxynupharidine. Therefore two of the three signals at 34.6, 33.2, and 31.6 ppm remain for C-6 and C-7.

The mass spectrum is consistent with the indolizidine aldehyde structure. In addition to the molecular ion, of special significance is the appearance of the base peak at *m/e* 218, corresponding to the loss of CHO, and *m/e* 110, accounted for by the loss of all carbon, hydrogen, and oxygen comprising the original six-membered ring and the transfer of a single hydrogen from the remaining five-membered ring, which carries the charge.

Reduction of the indolizidine aldehyde afforded a primary alcohol as indicated by the appearance of the hydroxyl group at 2.92 μm in the ir, a two-proton AB quartet at δ 2.62 in the ^1H NMR, and a triplet at 67.2 ppm in the ^{13}C NMR. The base peak at *m/e* 218 in the MS corresponds to the loss of CH_2OH from the parent ion. The ir revealed the presence of Bohlmann bands in the region of 3.62 μm showing that the indolizidine was trans fused.[10] A cis-fused indolizidine would possess no α hydrogens which are anti diaxial to the nitrogen lone pair and therefore Bohlmann bands would not be expected in such a case. Infrared spectral examination of the indolizidine alcohol in carbon tetrachloride solutions as dilute as 1.4×10^{-2}M revealed the presence of an intramolecular hydrogen bonded hydroxyl at 3438 cm^{-1} but no free hydroxyl was observed in the region of 3500–3650 cm^{-1}. Therefore the simultaneous occurrence of Bohlmann bands and intramolecular hydrogen bonding is evidence for assigning the structure **14** to the indolizidine alcohol and structure **9** to the corresponding aldehyde. A recent x-ray crystallographic study of the benzoate, **15**, hydrobromide confirms the structure of **14**.[11]

The α-Arylthiohemiaminals. The spectral data indicated that no skeletal alteration had occurred in the transformation of enamine **1** to hemiaminals **4** and **5**. For example, the MS peaks at *m/e* 248, 246, 231, 228, 218, 216, and 214 showed that the entire carbon, nitrogen, and oxygen skeleton of the enamine had been preserved in **4** and **5**. The unaltered ring A and attached 3-furyl group were confirmed in the presence of peaks at *m/e* 136, 107, 94, and 81. Both series of peaks have been observed in the MS of other α-thiohemiaminals derived from the enamine **1**.[12,13] Also, the unaltered presence of the C-1 methyl and 3-furyl group attached to the quinolizidine system at C-4 was confirmed by the ^1H NMR; the C-1 methyls appeared as doublets in the δ 0.93 region while the 3-furyl groups gave rise to the resonance of three of the seven protons observed in the δ 6.4–7.4 region and resulted in the C-4 protons appearing as a double doublet at δ 3.6–3.8.

The presence of the hemiaminal function in **4** and **5** was indicated by the appearance of the hydroxyl absorption in the 2.8–2.9-μm region of the ir and the carbinyl (C-6) proton in the region of δ 4.2–4.3 in the ^1H NMR. Conversion with perchloric acid of **4** to a crystalline immonium perchlorate exhibiting absorption at 6.05 μm supported the hemiaminal presence in **4**.

The incorporation of sulfur as aryl sulfide, rather than aryl sulfone, was first revealed in the parent ions at *m/e* 371 in the MS but was supported later in a number of ways, most interesting among them being the acidic solution uv which revealed several new absorption bands in the 260–280-nm region not observed in the neutral solution uv nor in the neutral nor acidic solution uv of the sulfone hemiaminals, **6** and **7**. Moreover, the acidic solution CD of **4** exhibited a positive CD band at 282 nm while the CD of **5** gave a negative band at 289 nm as illustrated in Figure 1. The appearance of these bands is generally characteristic of acidic solutions of hemiaminals possessing sulfide substituents at α or β carbons.[14,15] A specific

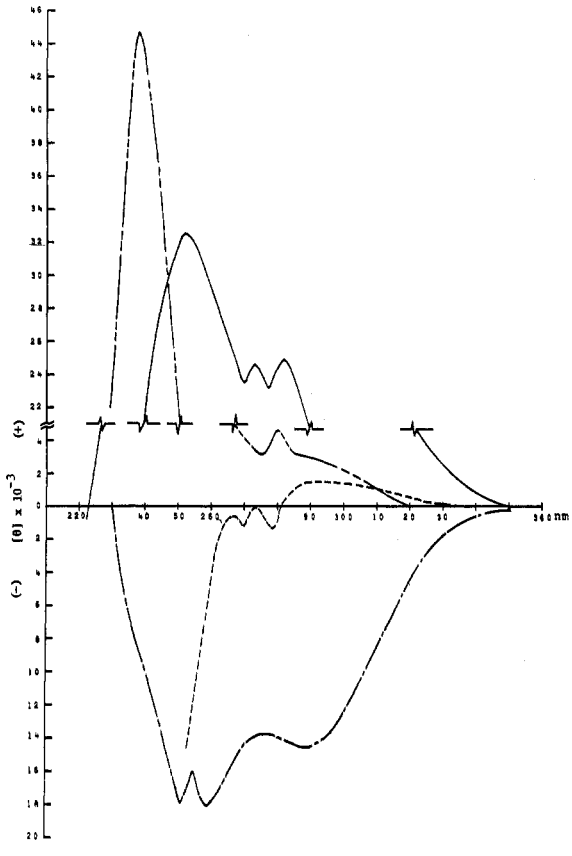


Figure 1. The circular dichroism of 7β-*p*-tolylthiodeoxynupharidin-6-ol, **4** (—); 7α-*p*-tolylthio-7-epideoxynupharidin-6-ol, **5** (— · —); 7β-*p*-toluenesulfonyldeoxynupharidin-6-ol, **6** (— - —); 7α-*p*-toluenesulfonyl-7-epideoxynupharidin-6-ol, **7** (- - -), in EtOH with added $HClO_4$.

case in point is the pair 7β-phenylthiodeoxynupharidin-6-ol and 7α-phenylthio-7-epideoxynupharidin-6-ol; in neutral solution both have low-intensity bands in the 240–280-nm region but in acidic solution both show high-intensity bands ($[\theta] > 4000$) at 295 nm, the 7β isomer giving a positive band and a 7α isomer a negative band.[16] Therefore the positive negative bands exhibited by **4** and **5**, respectively, establish the configuration of C-7 in **4** and **5** when these results are compared to those of earlier studies.[14]

Reduction of the hemiaminal function with sodium borohydride in methanol converted **4** and **5**, respectively, to **10** and **11** whose spectral data and elemental analyses are consistent with C-7 substituted aryl sulfide derivatives, but not sulfones. Oxidation of **10** and **11**, in acidic solution, with hydrogen peroxide gave the sulfones **12** and **13**, respectively, which were employed to correlate the C-7 configuration of α-thiohemiaminals **4** and **5** with the same center in α-sulfonylhemiaminals **6** and **7**.

The α-Arenesulfonylhemiaminals. The detailed spectral properties of **6** and **7** presented in the Experimental Section generally are similar to those of the α-thiohemiaminals **4** and **5** already discussed and demonstrate the preservation of the unaltered skeleton of the starting enamine and the hemiaminal character. However, the MS of **6** and **7** showed parent ions at *m/e* 403 indicating the incorporation of two additional oxygens not possessed by the sulfides and the ir exhibited strong bands in the regions 8.6–8.9 and 7.4–7.7 μm characteristic of sulfones.[17] Another significant property difference was observed in the acidic solution CD which are included for comparison in Figure 1. The CD bands in the 280–300-nm region for the α-sulfonylhemiaminals were much less intense than those of the α-thiohemiaminals.

Attempts to correlate the α-sulfonylhemiaminals with the α-thiohemiaminals by reduction of **12** and **13** to sulfides with lithium aluminum hydride in refluxing ether were unsuccessful; only unconverted starting sulfones were recovered. However, reduction of **6** with sodium borohydride in methanol gave the sulfone **12** which was identical with the sulfone obtained from the α-thiohemiaminal **4** through the latter's reduction followed by sulfide to sulfone oxidation, as discussed above. In a similar manner **7** gave **13** identical with the sulfone obtained from **5**. These correlations establish the configurations of **6** and **7** at C-7.

Interestingly, the ir of **12** and **13** in solution both show Bohlmann bands, the intensity of the absorptions being slightly greater for **13** than **12**. Furthermore, the ^{13}C NMR of **12** reveals the C-7 methyl (C-12) at 17.1 ppm which appears at 4–5 ppm higher field than the chemical shift of the C-7 methyl in **13**. These results, in conjunction with those from earlier ^{13}C studies of methyl decalins[18] and quinolizidines,[19] and the known stereochemical requirements needed for Bohlmann band appearance,[10] define the stereochemistry of ring fusion and conformation of the quinolizidine B ring. Thus in both **12** and **13** ring B is trans fused to ring A and possesses a chair conformation. The C-7 methyl is axial in **12** but equatorial in **13**.

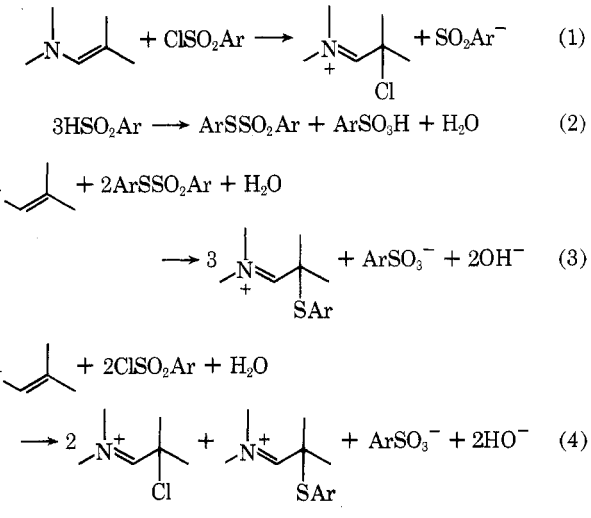
The above conclusion regarding ring B stereochemistry in **13** was not clearly predictable since the larger free-energy difference ($\Delta G^\circ = -2.5$ kcal/mol) between an axial and equatorial sulfonyl group,[20] relative to that of the methyl group, might have forced the arylsulfonyl group into an equatorial conformation with the consequent development of a trans-fused twist boat or a cis-fused chair ring B, a prediction inconsistent with results. Presently no completely satisfactory explanation can be offered for the axial conformational preference of the bulky sulfonyl group in **13**.

Discussion

Since the purpose of this paper is to point out the exceptional products resulting from treatment of an enamine with a sulfonyl chloride, some attention should be given to the manner in which these products are formed.

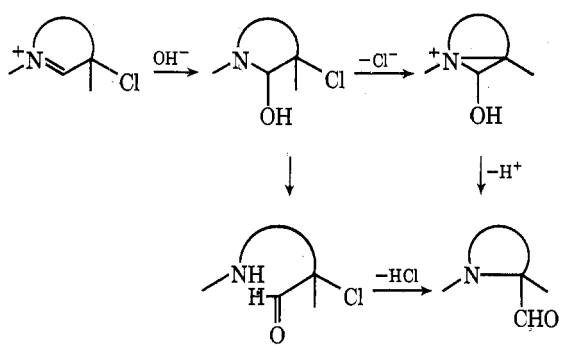
The action of arenesulfonyl halides on enamines is reported[21] to generate sulfones in the straightforward manner expected for the reaction of an electrophilic sulfur derivative on a nucleophilic enamine. However, among one of these reports there is mentioned[22] in a footnote that in addition to the predominating sulfone a sulfide also results and that the latter was observed even when analytically pure arenesulfonyl chloride was used. In our studies no *p*-toluenesulfenyl chloride nor *p*-tolyl *p*-toluenethiosulfonate could be detected in the sulfonyl chloride employed.

For the moment, we suggest that the exceptional products



result from the processes in eq 1–4. Attack of enamine on chlorine rather than sulfur of the sulfonyl chloride leads to the α-chloroimmonium ion and the formation of sulfinate anion as indicated in eq 1. In turn, the arenesulfinate anion becomes protonated giving the arenesulfonic acid, a weak acid, which undergoes disproportionation to arenesulfonic acid and aryl arenethiosulfonate, according to eq 2. The aryl arenethiosulfonate serves as an electrophilic thiating agent which competes for enamine and converts it to an α-thioimmonium ion that subsequently gives α-thiohemiaminal. Such electrophilic attack of thiosulfonate produces additional arenesulfinate whose fate is also disproportionation. Equation 3 sums up both the reaction of enamine with aryl arenethiosulfonate and the disproportionation of arenesulfonic acid. The indolizidine aldehydes likely result, at least in part, from the chlorine-containing immonium ion (eq 1) through routes depicted in Scheme II.

Scheme II. Possible Routes from the Chlorine-Containing Immonium Ion to Aldehyde



There is close analogy or precedent for each of the steps indicated by eq 1–3. The behavior of arenesulfonyl chlorides as ambident electrophiles capable of furnishing positive chlorine, as required in eq 1, is demonstrated in reactions with the sodium enolates of β-keto esters.[23] The disproportionation of sulfinic acids to thiosulfonates and sulfonic acids, eq 2, is well known[24] and there is ample precedent for the electrophilic thiating capability of aryl and alkyl arenethiosulfonates on enamines[12,22,25] and aromatic amines[26] as required by eq 3.

Combining eq 1–3 and including a trivial equation for the conversion of sulfinate anion to sulfinic acid with water gives eq 4 which clearly indicates the overall requirement for water in order that the enamine be oxidized and the sulfur reduced. In our experimental procedure, water was not added. But in all but one of the several experiments, no precaution was taken to dry the solvents nor to exclude water from the reaction mixtures. In one experiment the solvents were dried and still the same quinolizidine and indolizidine derivatives were obtained. However, all product mixtures were separated on columns of hydrated alumina. Therefore the hydration of α-chloro- and α-arenesulfonyl immonium salts and sulfinate ion and the subsequent rearrangement very likely have taken place to some extent on columns of hydrated alumina in addition to that which might have occurred in wet benzene solution.

Regarding the formation of the disulfide, the hydrolysis of an unstable arenesulfinic acid is known to yield disulfide and arenesulfonic acid.[27] The generation of *p*-tolyl disulfide may take place by a similar process. As for *p*-tolyl disulfone, its generation most likely comes from the reaction of *p*-toluenesulfinate anion with *p*-toluenesulfonyl chloride.

This proposal for the formation of the unexpected products resulting from the action of *p*-toluenesulfonyl chloride with an enamine is not intended to be the last word on the subject but rather a working hypothesis to be tested by further study.

Experimental Section

Spectra were determined as follows. ^1H NMR at 60 MHz in $CDCl_3$, 2% Me_4Si (δ 0.0) on a Varian A-60 spectrometer unless otherwise indicated, symbols, br, s, d, and m refer to broad, singlet, doublet, and multiplet, respectively; ^{13}C NMR at 25.16 MHz and ^1H NMR at 100 MHz in $CDCl_3$, both relative to Me_4Si (δ 0.0) on a Varian XL100 spectrometer operating in the pulsed Fourier mode. Fourier transformations were based on 8192 data points and employed the absorption spectrum; field/frequency lock was established on deuterium of $CDCl_3$, between 1 and 5K transients were used for fully decoupled ^{13}C spectra and three–four times that many for off-resonance decoupled spectra used to assist the assignment of ^{13}C resonance lines. Ir spectra were determined in the phase indicated on Perkin-Elmer 137 and 621 spectrometers, w, m, s refer to weak, medium, and strong, respectively; mass spectra were determined on a Hitachi Perkin-Elmer RMU6E using a direct inlet probe at 110 °C, unless indicated otherwise, and at 70 eV. High-resolution mass spectra were run on an AEI MS-9. Melting points were determined on a Köfler micro hot stage and/or a Mel-Temp apparatus and are uncorrected. The circular dichroism was determined on a Jasco Model 5 spectropolarimeter in solution at the concentrations indicated. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Thin layer chromatography was performed on microscope slides uniformly coated with Al_2O_3 (GF_{254}) using the solvent systems indicated; the spots were developed with Dragendorff reagent.

The *p*-tosyl chloride was freshly recrystallized[28] and its mass spectra, run prior to use, showed no peaks corresponding to the presence of the sulfenyl chloride (M^+, *m/e* 190) nor *p*-tolyl *p*-toluenethiosulfonate (M^+, *m/e* 278).

Reaction of 6-Dehydrodeoxynupharidine (1) with *p*-Toluenesulfonyl Chloride and the Isolation of *p*-Tolyl Disulfone and *p*-Tolyl Disulfide. The following is typical of several reactions carried out between the title reactants. A solution of 1072 mg (4.64 mmol) of 1 and 885 mg (4.64 mmol) of *p*-tosyl chloride in 20 ml of C_6H_6 was kept under N_2 at 0 °C for 1.5 h and thereafter a −20 °C for 4 days.[29] The frozen contents were warmed to 25 °C, and the persisting solid filtered and washed with CH_2Cl_2–C_6H_6, yielding 53 mg of *p*-tolyl disulfone (**2**): mp 204 °C dec (lit. 212 °C dec[2]); ir 6.05 (w), 6.27 (m), 7.48 (s), 7.71 (m), 8.82 (s), 9.41 (m), 12.43 (m), 14.46 μm (m); MS (110 °C) *m/e* (rel intensity) 310 (7) (M^+), 262 (9), 155 (73), 139 (100), 92 (53).

The filtrate was concentrated and then chromatographed on 75 g of Al_2O_3 (activity 3). The chromatography was monitored by TLC on Al_2O_3 (GF_{254}). The column was eluted with 350 ml of C_6H_6, 360 ml of 8:1 C_6H_6–Et_2O, 200 ml of 5:3 C_6H_6–Et_2O, 100 ml of 1:1 C_6H_6–Et_2O, 60 ml of 1:3 C_6H_6–Et_2O, 100 ml of CH_2Cl_2, 100 ml of 17:3 CH_2Cl_2–MeOH, and 100 ml of MeOH in the order given in 37 30–40-ml fractions (A1–A37). According to TLC, mixtures of unconverted enamine (**1**), indolizidine aldehydes (**8** and **9**), 7β-*p*-tolylthiodeynupharidin-6-ol (**4**), and *p*-tolyl disulfide (**3**) emerged in the C_6H_6 fractions A1–A5, the indolizidine aldehydes in the C_6H_6 fractions A6–A8, and a mixture of indolizidine aldehydes and 7α-(*p*-tolylthio)-7-epideoxynupharidin-6-ol (**5**) in 8:1 C_6H_6–Et_2O fractions A9–A15. Mixtures of **6** and **7** emerged in fractions A22–A26, fractions eluted at the end of the 8:1 C_6H_6–Et_2O elution and with later eluents richer in Et_2O.

Fractions A1 and A2, eluted with C_6H_6, yielded a total of 95 mg of material showing on TLC two spots, one Dragendorff active and uv inactive and the other Dragendorff inactive but uv active. The former corresponded to unconverted **1**. Rechromatography of this two-component mixture on 15 g of Al_2O_3 (activity 2) with 150 ml of hexane afforded 17 mg of *p*-tolyl disulfide: mp 47–48 °C (lit. 41,[5] 47–48 °C[6]); TLC uv active; MS *m/e* 246 (M^+).

7α-(*p*-Tolylthio)-7-epideoxynupharidin-6-ol (5). Fractions A10–A15 were recombined (73 mg) and chromatographed on 15 g of Al_2O_3 (activity 3) with 100 ml of 19:1 C_6H_6–Et_2O, 100 ml of 9:1 C_6H_6–Et_2O, 100 ml of 3:2 C_6H_6–Et_2O, and 60 ml of MeOH. Ten 20-ml fractions, B1–B10, and then five 30–35 ml fractions, B11–B15, were collected. Fractions B8–B10 combined consisted of 13 mg of **5** (0.035 mmol, 0.76%), an oil: TLC (C_6H_6) R_f 0.125; TLC (8:1 C_6H_6–Et_2O) R_f 0.33; TLC (8:3 C_6H_6–Et_2O) R_f 0.55; ^1H NMR δ 0.93 (s superposed on d, 6 H, C-1 and C-7 CH_3), 2.29 (s, 3 H, $ArCH_3$), 3.60 (d of d, J = 4 and 8 Hz, 1 H, C-4 H), 4.30 (m, 1 H, C-6 H), 6.45 (m, 1 H, 3-furyl β H), 6.83–7.37 (m, 6 H, 3-furyl α H and ArH); ir (liquid film) 2.86 (m), 5.82 (w), 6.04 (w), 6.23 (w), 6.70 (m), 6.89 (m), 7.28 (m), 11.47 (s), 12.3 (s), 12.6 μm (m); uv (neutral 95% EtOH) λ_{sh} 268 nm (ε 2050), λ_{max1} 262 nm (ε 2800), λ_{max2} 254 nm (ε 2940), λ_{max3} 248 nm (ε 2510), λ_{max4} 242 nm (ε 2270); uv (95% EtOH, $HClO_4$ added) λ_{sh1} 275 nm (ε 2800), λ_{sh2} 267 nm (ε 2570), λ_{sh3} 254 nm (ε 3260), λ_{sh4} 247 nm (ε 3850), λ_{sh5} 242 nm (ε 4420), λ_{sh6} 237 nm (ε 4670); CD (*c* 0.18 mg/ml, neutral 95% EtOH, *l* = 0.1 dm) $[\theta]_{330}$ +74°, $[\theta]_{320}$ + 144°, $[\theta]_{312}$ +186°, $[\theta]_{310}$ +

173°, $[\theta]_{300}$ +82°, $[\theta]_{295}$ 0°, $[\theta]_{293}$ −21°, $[\theta]_{290}$ +21°, $[\theta]_{275}$ + 907°, $[\theta]_{258}$ −12°, $[\theta]_{250}$ +194°, $[\theta]_{240}$ + 1030°, $[\theta]_{235}$ + 3960°; CD (*c* 0.18 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{360}$ 0°, $[\theta]_{290}$ −14 500°, $[\theta]_{288}$ −14 500°, $[\theta]_{275}$ − 13 800°, $[\theta]_{259}$ −18 100°, $[\theta]_{255}$ −15 900°, $[\theta]_{251}$ −17 900°, $[\theta]_{240}$ −9690°; MS *m/e* (rel intensity) 371 (7) (M^+), 353 (20), 342 (2), 248 (21), 246 (73), 231 (100), 230 (51), 229 (47), 228 (22), 218 (74), 216 (33), 214 (27), 202 (12), 200 (12), 192 (10), 188 (12), 186 (10), 176 (21), 174 (14), 164 (15), 136 (21), 124 (79), 123 (67), 107 (39), 96 (68), 95 (46), 94 (81), 91 (94), 82 (29), 81 (20).

7β-(*p*-Toluenesulfonyl)deoxynupharidin-6-ol (6). The A series chromatography yielded, in fractions A23–A26, a 102-mg mixture of 7α-(*p*-toluenesulfonyl)-7-epideoxynupharidin-6-ol (**7**) and 7β-(*p*-toluenesulfonyl)deoxynupharidin-6-ol (**6**), 45 mg of which was chromatographed on 15 g of SiO_2 (activity 2) with 100 ml of C_6H_6, 330 ml of 10:1 C_6H_6–Et_2O, 270 ml of 8:1 C_6H_6–Et_2O, 140 ml of 6:1 C_6H_6–Et_2O, 200 ml of 3:2 C_6H_6–Et_2O, 100 ml of 1:1 C_6H_6–Et_2O, and 50 ml of EtOH in the order given in 39 35-ml fractions (C1–C39). Combined fractions C1–C6 contained 9 mg of **6** (0.0223 mmol, 0.48%), an oil: TLC (3:2 C_6H_6–Et_2O) R_f 0.30; mp 114–118 °C; ^1H NMR δ 0.97 (m, 3 H, C-1 CH_3), 1.19 (s, 3 H, C-7 CH_3), 2.45 (s, 3 H, Ar CH_3), 3.67 (m, C-4 H), 3.80 (br s, OH), 4.26 (br s, 1 H, C-6 H), 6.31 (m, 1 H, 3-furyl β H), 7.09–7.46 (ArH and 3-furyl α H), 7.54 (ArH), 7.68 (ArH); ir (KBr) 2.88 (m), 6.24 (m), 6.69 (m), 6.89 (m), 6.97 (m), 7.16 (w), 7.30 (w), 7.86 (s), 8.76 (s), 11.44 (m), 12.27 (m), 12.56 (m), 12.92 μm (m); MS *m/e* (rel intensity) 403 (6) (M^+), 385 (2), 374 (1), 248 (6), 229 (100), 228 (24), 214 (46), 200 (16), 107 (19), 96 (20), 94 (30), 91 (46), 81 (14); CD (*c* 0.58 mg/ml, neutral 95% EtOH, *l* = 0.1 dm) $[\theta]_{285}$ +69°, $[\theta]_{277}$ +919°, $[\theta]_{272}$ +503°, $[\theta]_{270}$ +694°, $[\theta]_{265}$ +381°, $[\theta]_{263}$ +503°, $[\theta]_{260}$ +381°, $[\theta]_{250}$ −139°; CD (*c* 0.58 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{320}$ +208°, $[\theta]_{290}$ +3120°, $[\theta]_{285}$ +3120°, $[\theta]_{280}$ +4570°, $[\theta]_{275}$ +3120°, $[\theta]_{260}$ +6240°, $[\theta]_{238}$ +44 720°, $[\theta]_{220}$ −13 520°, $[\theta]_{213}$ +4160°.

7α-(*p*-Toluenesulfonyl)-7-epideoxynupharidin-6-ol (7). Fractions C37–C39 were combined (24 mg) and chromatographed on 15 g of Al_2O_3 (activity 2) with 100 ml of C_6H_6, 90 ml of 8:1 C_6H_6–Et_2O, 220 ml of 8:3 C_6H_6–Et_2O, 150 ml of 2:1 C_6H_6–Et_2O, 150 ml of 2:1 C_6H_6–Et_2O containing 4% MeOH in the order given in 27 35-ml fractions (D1–D27). Fractions D16–D27 (13 mg) were combined with fractions C26–C36 (14 mg) and chromatographed on 10 g of SiO_2 (activity 2) with 455 ml of CH_2Cl_2 in 13 35-ml fractions and then with 10% MeOH in CH_2Cl_2 in a single fraction which yielded 15 mg of material which was applied to a 20 × 20 cm plate coated with 0.25 mm of SiO_2. This was developed twice with 3:2 C_6H_6–Et_2O and the R_f 0.44 band was removed to obtain 12 mg of **7** (0.0298 mmol, 0.64%), an oil: ^1H NMR δ 0.88 (m, 6 H with δ 0.90 s, C-1 CH_3), 0.90 (s superposed on δ 0.88 m, 6 H with 0.88 m, C-7 CH_3), 2.45 (s, 3 H, Ar CH_3), 3.53–3.95 (m, 2 H, 1 H on addition of D_2O, C-4 H and C-6 OH), 5.03 (br s becoming narrow on addition of D_2O, 1 H, C-6 H), 6.74 (m, 1 H, 3-furyl β H), 7.2–7.8 (m, 6 H, 3 furyl α H and Ar H); ir (CCl_4) 2.85 (w), 5.79 (w), 6.00 (w), 6.24 (m), 6.68 (m), 6.87 (s), 6.27 (m), 7.64 (s), 7.71 (s), 8.66 (s), 8.77 (s), 8.93 (s), 11.48 μm (s); MS (130 °C) *m/e* (rel intensity) 403 (4), 385 (12), 374 (0.4), 370 (0.6), 357 (5), 321 (6), 248 (6), 229 (100), 228 (41), 214 (40), 200 (21), 107 (36.3), 94 (53), 91 (34), 81 (25); CD (*c* 0.46 mg/ml, neutral 95% EtOH, *l* = 0.1 dm) $[\theta]_{298}$ 0°, $[\theta]_{287}$ −386°, $[\theta]_{280}$ −2280°, $[\theta]_{277}$ −2630°, $[\theta]_{275}$ −2720°, $[\theta]_{274}$ −2630°, $[\theta]_{270}$ −3160°, $[\theta]_{265}$ −2630°, $[\theta]_{262}$ −2670°, $[\theta]_{252}$ −1400°, $[\theta]_{250}$ −1580°, $[\theta]_{244}$ −2630°, $[\theta]_{240}$ −4120°; CD (*c* 0.26 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{340}$ 0°, $[\theta]_{324}$ +307°, $[\theta]_{310}$ +843°, $[\theta]_{297}$ +1530°, $[\theta]_{287}$ +1380°, $[\theta]_{281}$ 0°, $[\theta]_{279}$ −1380°, $[\theta]_{274}$ 0°, $[\theta]_{270}$ −1230°, $[\theta]_{268}$ −613°, $[\theta]_{264}$ −1070°, $[\theta]_{258}$ −7820°, $[\theta]_{253}$ −14 600°; CD (*c* 0.13 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{238}$ −61 300°; high-resolution mass spectrum (70 eV, 110 °C) obsd/calcd mass (formula) 385.1709/385.1712 and 385.1740/385.1712 ($C_{22}H_{27}NO_3$, $[M - H_2O]^+$).

Indolizidine Aldehyde 9. The initial chromatography (A′ series) of a reaction mixture from 685 mg of enamine (2.96 mmol) and 546 mg of *p*-tosyl chloride (2.96 mmol) yielded 673 mg of a mixture of unconverted enamine, 7β-(*p*-tolylthio)deoxynupharidin-6-ol (**4**), and indolizidine aldehydes (**8** and **9**) in the C_6H_6 eluent comprising the second through ninth 40-ml fractions (A′2–A′9). This 673-mg mixture was chromatographed (B′ series) on 30 g of Al_2O_3 (activity 2). Elution with C_6H_6 resulted in fractions B′1–B′11 (10 ml each) of which fractions B′9–B′11 yielded 38 mg of a mixture of the indolizidine aldehyde **8** (0.154 mmol, 5.2%) and its C-3 epimer, **9**: TLC (C_6H_6) R_f 0.33; TLC (3:2 C_6H_6–Et_2O) R_f 0.55; ^1H NMR δ 0.92 (s, C-3 CH_3), 1.07 (s, C-3 CH_3), 9.04 (s, C-3 CHO), 9.79 (s, C-3 CHO, δ 9.04:9.79 8:1), ^1H NMR (C_6D_6) δ 0.90 (s, C-3 CH_3), 1.00 (s, C-3 CH_3), 9.14 (s, C-3 CHO), 9.64 (s, C-3 CHO). Repeated chromatography of earlier and later fractions yielded an additional 28 mg of material which when combined with the 38 mg (0.267 mmol total, 9.0%) and thereafter chromatographed yielded pure indolizidine aldehyde **9**, an oil: TLC (C_6H_6) R_f 0.33; ^1H NMR δ 0.91 (d, *J* = 5 Hz, C-8 CH_3), 1.07 (s, 3 H, C-3 CH_3), 3.36 (d of d, *J* = 5 and 9 Hz, 1 H, C-5 H), 6.36 (m, 1 H, 3-furyl β H), 7.26 (m, 2 H, 3-furyl α H), 9.04 (s, 1 H, CHO); ^1H NMR (C_6D_6) δ 0.75 (d, *J* = 5 Hz, C-8 CH_3), 1.00 (s, 3 H, C-3 CH_3), 3.06 (d of d, *J* = 5 and 9 Hz, 1 H, C-5 H), 6.14 (m, 1 H, 3-furyl β H), 7.02 (m, 2 H, 3-furyl α H), 9.14 (s, 1 H, CHO); ^{13}C NMR δ 12.5 (C-11), 18.5 (C-10), 28.6 (C-1), 33.2 (C-6, C-7, or C-2), 34.6 (C-6, C-7, or C-2), 31.6 (C-6, C-7, or C-2), 37.0 (C-8), 52.9 (C-5), 70.5 (C-3), 67.5 (C-9), 109.8 (C-15), 127.0 (C-13), 140.4 (C-14), 142.9 (C-16); ir (liquid film) 3.57 (m), 5.79 (s), 7.30 (m), 11.45 μm (m); MS *m/e* (rel intensity) 247 (24) (M^+), 232 (27), 218 (100), 204 (35), 110 (62), 82 (63).

7β-(*p*-Tolylthio)deoxynupharidin-6-ol (4). Continuing the B′ series chromatography by eluting with benzene gave fractions B′12–15 (20 ml each) and B′16–20 (35 ml each). Fractions B′12–19 recombined consisted of a mixture of indolizidine aldehydes (**8** and **9**), the title hemiaminal (**4**), and the 7β-tolysulfone hemiaminal, **6**, according to TLC. This mixture was rechromatographed (C′ series, 10 g of Al_2O_3, activity 2) using first benzene and collecting four 20-ml fractions (C′1–C′4) and six 35-ml fractions (C′5–C′10). Fractions C′4–C′8 contained a total of 90 mg of the pure title compound, **4** (0.242 mmol, 8.2%), an oil: TLC (C_6H_6) R_f 0.25; ^1H NMR δ 0.92 (d, *J* = 5 Hz, 3 H, C-1 CH_3), 1.14 (s, C-7 CH_3), 2.33 (s, 3 H, $ArCH_3$), 3.12 (br s, 1 H, C-6 OH), 3.75 (d of d, *J* = 4 and 8 Hz, 1 H, C-4 H), 4.03 (br s, 1 H, C-6 H), 6.29 (m, 1 H, 3-furyl β H), 6.93–7.53 (m, 6 H, 3-furyl α H and ArH); ir (liquid film) 2.86 (m), 6.23 (w), 6.72 (m), 6.94 (m), 7.20 (m), 7.34 (m), 11.48 (s), 12.34 (m), 12.72 μm (m); uv (neutral 95% EtOH) λ_{max} 264 nm (ε 452); uv (95% EtOH, $HClO_4$ added) λ_{max1} 283 nm (ε 3270), λ_{max2} 274 nm (3350), λ_{max3} 242 nm (5900); CD (*c* 0.43 mg/ml, neutral 95% EtOH, l = 0.1 dm) $[\theta]_{310}$ +128°, $[\theta]_{262}$ + 3600°, $[\theta]_{240}$ +940°, $[\theta]_{232}$ +2830°, $[\theta]_{230}$ +2310°, $[\theta]_{225}$ +3770°; CD (*c* 0.086 mg/ml, 95% EtOH, $HClO_4$ added, *l* = 0.1 dm) $[\theta]_{340}$ +860°, $[\theta]_{282}$ +24 830°, $[\theta]_{277}$ +23 120°, $[\theta]_{273}$ +24 620°, $[\theta]_{270}$ +23 540°, $[\beta]_{252}$ +32 530°, $[\theta]_{225}$ +300°; MS *m/e* (rel intensity) 371 (43) (M^+), 355 (7), 342 (8), 248 (100), 246 (4), 231 (4), 228 (30), 218 (10), 216 (10), 214 (20), 192 (19), 176 (7), 164 (19), 124 (17), 123 (19), 107 (42), 96 (25), 94 (31), 91 (35), 81 (25).

Conversion of 7β-(*p*-Tolylthio)deoxynupharidin-6-ol (4) to Its Immonium Perchlorate. A solution of 27 mg of the title hemiaminal in 2 ml of absolute EtOH was treated with 0.36 ml of 0.2 M aqueous $HClO_4$. The bulk of the solvent was vacuum evaporated, and the solid was separated by filtration and then recrystallized from $(CH_3)_2CO$–Et_2O to obtain 18 mg of white needles: mp 222.5–225 °C; ir (KBr) 3.21 (w), 6.05 (m), 6.26 (w), 6.74 (m), 6.94 (m), 7.30 (m), 9.2–9.5 (s), 11.46 (s), 12.38 μm (s).

Anal. Calcd for $C_{22}H_{30}NO_6SCl$: C, 58.21; H, 6.22; N, 3.09; S, 7.06. Found: C, 58.03; H, 6.30; N, 2.96, S, 7.06.

7β-(*p*-Tolylthio)deoxynupharidine (10). A gentle stream of CO_2 was bubbled through a solution of 40 mg of 7β-(*p*-tolylthio)deoxynupharidin-6-ol in MeOH. Thereafter 90 mg of $NaBH_4$ was added and the resulting mixture was kept at 25 °C for 48 h, at the end of which time TLC indicated that greater than 90% of the starting hemiaminal had been consumed. Thereafter the MeOH was vacuum evaporated, the residue mixed with C_6H_6, the solids removed by filtration, and the filtrate concentrated and added to a column of 15 g of Al_2O_3 (activity 2) which was eluted successively with 100 ml of C_6H_6, 50 ml of 9:1 C_6H_6–Et_2O, and 50 ml of 3:2 C_6H_6–Et_2O in 20-ml fractions. Fraction 1 yielded 26 mg of **10**: mp 88–89 °C; TLC (8:2 C_6H_6–Et_2O) R_f 0.9; ^1H NMR δ 0.84 (br s, 3 H, C-1 CH_3), 1.22 (s, 3 H, C-7 CH_3), 1.77 (d, *J* = 11 Hz, C-6 ax H), 2.29 (s, 3 H, $ArCH_3$), 2.75 (d, *J* = 11 Hz, 2 H with δ 2.88 d of d, C-6 eq H), 2.88 (d of d, *J* = 4 and 8 Hz, 2 H with δ 2.75, C-4 H), 6.17 (m, 1 H, 3-furyl β H), 6.78–7.37 (m, 6 H, 3-furyl α H and ArH); ir (liquid film) 3.66 (m), 6.26 (w), 6.68 (m), 6.72 (m), 7.24 (m), 7.28 (m), 11.42 μm (s); MS *m/e* (rel intensity) 355 (17) (M^+), 267 (12), 232 (92), 231 (43), 220 (16), 178 (20), 136 (34), 107 (23), 96 (49), 94 (100), 84 (56), 81 (22).

Anal. Calcd for $C_{22}H_{29}NOS$: C, 74.32; H, 8.23; N, 3.94; S, 9.02. Found: C, 74.56; H, 8.15; N, 3.95; S, 8.85.

7α-(*p*-Tolylthio)-7-epideoxynupharidine (11). A solution of 4 mg 7α-(*p*-tolylthio)-7-epideoxynupharidin 6-ol in 5 ml of MeOH was treated with 19 mg of $NaBH_4$ at 25 °C for 10 days. The reaction mixture was concentrated and chromatographed on 7 g of Al_2O_3 (activity 2) which was eluted successively with 30 ml of C_6H_6, 100 ml of 9:1 C_6H_6–Et_2O, and 100 ml of 4:1 C_6H_6–Et_2O in seven 30–35-ml fractions. Fraction 1 yielded 3 mg of **11**: mp 170–172 °C; TLC (7:3 C_6H_6-Et_2O) R_f 0.8; ^1H NMR (100 MHz) δ 0.96 (d, *J* = 5 Hz, 6 H with δ 0.97 s, C-1 CH_3), 0.97 (s superposed on δ 0.96 d, 6 H with 0.96 d, C-7 CH_3), 1.75 (d, *J* = 12.4 Hz, C-6 ax H), 2.35 (s, 3 H, $ArCH_3$), 2.90 (d, *J* = 12.4 Hz, 2 H with δ 2.94, d of d, C-6 eq H), 2.94 (d of d, *J* = 3 and 8 Hz, C-4 H), 6.54 (m, 3-furyl β H), 6.95–7.25 (m, 3-furyl α H and Ar H); ir (liquid film) 3.62 (w), 6.00 (w), 6.23 (w), 6.69 (m), 6.90 (m), 7.29 (m), 11.42 (s), 12.28 (s), 12.69 μm (s); MS *m/e* (rel intensity) 355 (6)

(M^+), 233 (74), 232 (38), 231 (45), 220 (15), 178 (30), 136 (30), 107 (34), 96 (100), 94 (61), 81 (45).

Anal. Calcd for $C_{22}H_{29}NOS$: C, 74.32; H, 8.23; N, 3.94. Found: C, 74.07; H, 8.12; N, 3.76.

7β-(p-Toluenesulfonyl)deoxynupharidine (12). A solution of 13 mg of 7β-(p-toluenesulfonyl)deoxynupharidin-6-ol (**6**) in MeOH was acidified to pH 4 with a gentle stream of gaseous HCl and then treated portionwise with a total of 50 mg of $NaBH_3CN$. Periodically HCl was bubbled into the solution to maintain the pH between 4 and 6. When TLC indicated that >90% hemiaminal had been consumed, the solution was concentrated under vacuum and the residue was treated with aqueous KOH and extracted with CH_2Cl_2. The extract was dried (Na_2SO_4), concentrated under vacuum, and chromatographed on 10 g of Al_2O_3 (activity 2) with 50 ml of C_6H_6, 150 ml of 19:1 C_6H_6–Et_2O, 150 ml of 9:1 C_6H_6–Et_2O, and 50 ml of 3:1 Et_2O–MeOH in 20-ml fractions for fractions 1–6 and 35-ml fractions for fractions 7–11. Fractions 2–4 combined yielded 7 mg of **12** in white needles: mp 170–172.3 °C; TLC (developed three times with 19:1 C_6H_6–Et_2O) R_f 0.65; ^1H NMR (100 MHz) δ 0.88 (d, J = 5.8 Hz, 3 H, C-1 CH_3), 1.28 (s, 3 H, C-7 CH_3), 2.08 (d, J = 11.8 Hz, C-6 ax H), 2.42 (s, 3 H, Ar CH_3), 2.80 (d of d, J = 11.8 and 2.4 Hz, 2 H with 2.98 d of d, C-6 eq H), 2.98 d of d, J = 2 and 8 Hz, C-4 H), 6.23 (m, 1 H, 3-furyl β H), 7.15–7.40 (m, 4 H, ArH), 7.63 (m, 2 H, 3-furyl α H); ir (KBr) 3.62 (w), 6.26 (m), 6.69 (m), 6.84 (m), 6.89 (m), 7.22 (m), 7.28 (m), 7.79 (s), 8.72 (s), 8.89 (m), 9.08 (m), 9.32 (s), 9.38 (m), 9.66 (m), 9.79 (m), 11.43 (s), 12.26 (s), 12.34 μm (s); ^{13}C NMR δ 17.1 (C-12), 19.1 (C-11), 21.7 (C-23), 26.6 (C-9), 29.0 (C-8), 33.6 (C-2), 35.4 (C-3), 36.6 (C-1), 55.7 (C-6), 60.2 (C-4), 62.8 (C-7), 68.7 (C-10), 109.2 (C-15), 129.6 (C-18 and C-22 or C-19 and C-21), 130.7 (C-18 and C-22 or C-19 and C-21), 139.8 (C-14), 143.5 (C-16); MS m/e (rel intensity) 387 (6) (M^+), 252 (11), 232 (51), 231 (100), 216 (5), 136 (15), 107 (9), 96 (26), 94 (37), 91 (11), 81 (12).

Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.18; H, 7.54; N, 3.62. Found: C, 68.33; H, 7.59; N, 3.50.

7α-(p-Toluenesulfonyl)-7-epideoxynupharidine (13). A solution of 32 mg of 7α-(p-toluenesulfonyl)-7-epideoxynupharidin-6-ol (**7**) in MeOH was treated with one portion of 39 mg of $NaBH_4$ at 25 °C for 12 h. The solution was concentrated and thereafter chromatographed on 10 g of Al_2O_3 (activity II) which was eluted with 50 ml of C_6H_6, 40 ml of 3:1 C_6H_6–Et_2O, 50 ml of 3:2 C_6H_6–Et_2O, and 30 ml of Et_2O. Fractions 1–6 consisted respectively of 20, 10, 25, 30, 30, and 60 ml portions of eluent. Fractions 5 and 6 were predominantly unconverted hemiaminal sulfone but fractions 3 and 4 combined yielded 17 mg of pure title sulfone **13:** mp 136–137 °C; TLC (7:3 C_6H_6–Et_2O) R_f 0.7; ^1H NMR (100 MHz) (d, J = 5.6 Hz, 3 H, C-1 CH_3), 1.10 (s, 3 H, C-7 CH_3), 2.42 (s, 3 H, $ArCH_3$), 3.12 (d of d, J = 2 and 10 Hz, 1 H, C-4 H), 3.41 (d, J = 12 Hz, 1 H, C-6 eq H), 6.50 (m, 1 H, 3-furyl β H), 7.15–7.50 (m, 4 H, ArH), 7.70 (m, 2 H, 3-furyl α H); ^1H NMR (C_6D_6) δ 0.70 (d, J = 5 Hz, 3 H, C-1 CH_3), 0.99 (s, 3 H, C-7 CH_3), 1.74 (d, J = 12 Hz, C-6 ax H), 1.90 (s, 3 H, $ArCH_3$), 2.92 (d of d, J = 4 and 10 Hz, 1 H, C-4 H), 3.59 (d, J = 12 Hz, 1 H, C-6 eq H), 6.55, 6.70, 6.82 (3 H, Ar H and 3-furyl H), 7.64, 7.89 (2 H, ArH and 3-furyl H); ^{13}C NMR δ 19.0 (C-11), 21.6 (C-12 or C-23), 22.7 (C-23 or C-12), 25.2 (C-9), 29.3 (C-8 or C-3), 31.5 (C-3 or C-8), 31.8 (C-1), 34.1 (C-2), 58.8 (C-6), 60.3 (C-4), 62.3 (C-7), 67.2 (C-10), 110.6 (C-15), 128.3 (C-13), 129.4 (C-17 or C-20), 130.7 (C-20 or C-17), 140.1 (C-14), 143.2 (C-16), 144.0 (C-18 and C-22 or C-19 and C-21), 144.5 (C-18 and C-22 or C-19 and C-21); ir (CCl_4) 3.69 (w), 6.29 (m), 6.71 (m), 6.96 (m), 7.02 (m), 7.35 (m), 7.71 (s), 7.80 (s), 8.76 (s), 8.87 (s), 11.60 μm (s); MS m/e (rel intensity) 387 (5) (M^+), 252 (12), 232 (46), 231 (100), 216 (5), 136 (16), 107 (8), 96 (29), 94 (40), 91 (7), 81 (10).

Anal. Calcd for $C_{22}H_{29}NO_3S$: C, 68.18; H, 7.54; N, 3.62; S, 8.27. Found: C, 67.93; H, 7.29; N, 3.58; S, 7.94.

Reduction of Indolizidine Aldehyde 9 to Primary Alcohol 14. A solution of 68 mg of **9** in 5 ml of MeOH was treated with 80 mg of $NaBH_4$ at 25 °C for 5 min at which time TLC (Al_2O_3, C_6H_6) indicated the complete consumption of aldehyde (R_f 0.33). The solution was concentrated and chromatographed on 10 g of Al_2O_3 (activity 3) which was eluted with 50 ml of C_6H_6. Vacuum evaporation of the C_6H_6 gave 78 mg of alcohol **14,** an oil: TLC (7.5:2.5 C_6H_6–Et_2O) R_f 0.42; ^1H NMR (100 MHz) δ 0.96 (d, J = 6.2 Hz, 3 H, C-8 CH_3), 1.02 (s, 3 H, C-3 CH_3), 2.62 (A or B of AB q, J = 10 Hz, 1 H, CH_2OH), 2.91 (B or A of AB q, J = 10 Hz, 1 H, CH_2OH), 3.52 (d of d, J = 6 and 8 Hz, 1 H, C-4 H), 6.52 (m, 1 H, 3-furyl β H), 7.28–7.52 (m, 3-furyl α H); ^{13}C NMR δ 18.4 (C-10 or C-12), 18.5 (C-12 or C-10), 28.8 (C-1), 33.1 (C-6, C-7, or C-2), 36.7 (C-6, C-7, or C-2), 36.8 (C-6, C-7, or C-2), 37.1 (C-8), 52.9 (C-5), 65.0 (C-3), 67.2 (C-11), 69.3 (C-9), 109.5 (C-15), 127.9 (C-13), 139.3 (C-14), 142.8 (C-16); ir (liquid film) 2.92 (m), 3.62 (w), 6.72 (m), 6.92 (m), 7.20 (m), 7.33 (m), 11.48 μm (s); ir (6.5, 4.8, 3.0, 2.2, 1.7, 1.4 × 10^{-2} M in CCl_4) 3438 (intramolecular bonded OH), 3500–3650 cm^{-1} (free OH) absent; MS m/e (rel intensity) 249 (1), 248 (2), 247 (2), 246 (1), 234 (4), 218 (100), 164 (11), 136 (6), 107 (16), 96 (9), 94 (36), 91 (6), 82 (21), 81 (26).

Anal. Calcd for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62. Found: C, 72.47; H, 9.17; N, 5.44.

Conversion of the Primary Alcohol 14 to Its Benzoate 15. A solution of 29 mg of **13** in 0.5 ml of CH_2Cl_2 was treated at 25 °C for 1 h with 9 drops of benzoyl chloride and 12 drops of pyridine. Thereafter the resulting solution was kept at 0 °C for 14 h at the end of which TLC (7.5:2.5 C_6H_6–Et_2O) showed **14** (R_f 0.42) had been consumed and **15** (R_f 0.75) present. The solvent was evaporated at reduced pressure and the residual oil was taken up in 5 ml of Et_2O. The Et_2O solution was shaken with 5 ml of 0.5% aqueous HCl, separated, and washed with H_2O. The combined aqueous and aqueous HCl washings were basified (pH 14) with MeOH, saturated with NaCl, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried (Na_2SO_4) and the solvent was evaporated at reduced pressure. The resulting residue was chromatographed on 5 g of Al_2O_3 (activity 2) by eluting with 5% Et_2O–hexane. The first fraction (1 ml), containing no Dragendorff active material, was discarded. Fraction 2 (40 ml) yielded 18 mg of pure **15,** an oil: TLC (7.5:2.5 C_6H_6–Et_2O) R_f 0.75; ir (CCl_4) 3.60 (w), 5.80 (s), 11.45 μm (s); ^1H NMR δ 0.93 (d, J = 5.5 Hz, 3 H, C-8 CH_3), 1.14 (s, 3 H, C-3 CH_3), 3.56 (m, 1 H, C-5 H), 3.71 (s, 2 H, C-3 CH_2O), 6.48 (m, 1 H, 3-furyl β H), 7.3–7.65 (m, 5 H, 3-furyl α H and benzoyl ArH), 8.03 (q, 2 H, J = 2 and 7 Hz, benzoyl ortho Ar H); ^1H NMR (C_6D_6) δ 0.83 (d, J = 5.5 Hz, 3 H, C-8 CH_3), 1.02 (s, 3 H, C-6 CH_3), 3.86 (s, 2 H, C-3 CH_2O).

Conversion of the Benzoate Ester 15 to Its Hydrobromide Salt. A solution of 18 mg of the benzoate **15** (0.05 mmol) in 0.5 ml of MeOH was treated with 0.6 ml of 0.1 M aqueous HBr (0.06 mmol). The solvent was evaporated under vacuum and the solid residue was recrystallized over the course of several weeks from MeOH at 0 °C. One-half of the resulting prism-shaped crystals (14 mg) was recrystallized from C_6H_6 to obtain needles: mp 212–213 °C; MS (130 °C) m/e (rel intensity) 353 (0.6) (M^+), 338 (1.1), 231 (6), 218 (100), 203 (0.6), 187 (0.7), 176 (0.6), 174 (0.6), 161 (1.1), 136 (1.9), 122 (1.6), 107 (2.7), 105 (89), 94 (7). The remaining half of the original crystals was recrystallized from wet MeOH to obtain prisms: mp partially 94–110 °C and completely 208–219 °C.

TLC of the base liberated from the salt showed R_f 0.75 (7.5:2.5 C_6H_6–Et_2O).

Transformation of 7β-(p-Tolylthio)deoxynupharidine (10) to 7β-(p-Toluenesulfonyl)deoxynupharidine (12). A solution of 5 mg of **10** in 0.45 ml of acetic acid was treated with 0.05 ml of 30% H_2O_2 at 25 °C. After 1 h TLC (7:3 C_6H_6–Et_2O) exhibited the starting sulfide spot (R_f 0.82) and a new spot (R_f 0.53). After 20 h both R_f 0.82 and R_f 0.53 spots disappeared and a second new spot at R_f 0.71 appeared. After 21 h the reaction mixture was evaporated to dryness under vacuum and a drop of pyridine was added. The excess pyridine was removed at reduced pressure and the residue was chromatographed on 1 g of Al_2O_3 (activity 3) with C_6H_6, the first 20 ml of which yielded 1.6 mg of **12:** TLC (7:3 C_6H_6–Et_2O) R_f 0.71; ir (CCl_4) identical with that of **12** isolated from the reaction of p-toluenesulfonyl chloride and 6-dehydrodeoxynupharidine as described elsewhere above.

Transformation of 7α-(p-Tolylthio)deoxynupharidine (11) to 7α-(p-Toluenesulfonyl)deoxynupharidine (13). A solution of 3.6 mg of **11** in 0.45 ml of acetic acid was treated with 0.05 ml of 30% H_2O_2 at 25 °C for 25 h. The solvent was removed at reduced pressure and the residue basified with a drop of pyridine. Excess pyridine was removed at reduced pressure and the residue was chromatographed on 1 g of Al_2O_3 with C_6H_6, the first 5 ml of which was discarded. Continued elution with 20 ml of CH_2Cl_2 yielded 2.2 mg of **13:** TLC (7:3 C_6H_6–Et_2O) R_f 0.69; ir ($CHCl_3$ or CCl_4) identical with those of **13** obtained in the reaction of 6-dehydrodeoxynupharidine with p-toluenesulfonyl chloride as described elsewhere above.

Registry No.—**1,** 32468-93-4; **2,** 10409-07-1; **3,** 103-19-5; **4,** 59187-39-2; 4 perchlorate, 59187-40-5; **6,** 59187-41-6; **8,** 59187-42-7; **9,** 59246-19-4; **10,** 59187-43-8; **11,** 59187-44-9; **12,** 59187-45-0; **13,** 59187-46-1; **14,** 59187-47-2; **15,** 59187-48-3; 15 HBr, 59246-20-7; p-toluenesulfonyl chloride, 98-59-9.

References and Notes

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(29) When the reaction solution was kept at 25 °C in benzene, conditions previously used to good advantage in the reaction of **1** with arylthiosulfonates (see ref 16), dark-colored intractable material resulted. Therefore the typical procedure consisted in mixing the reactant at 25 °C and cooling immediately thereafter.

Reactions of Activated Arenesulfonates with Oxygen and Nitrogen Nucleophiles. Hydroxide Ion and Micellar Catalysis

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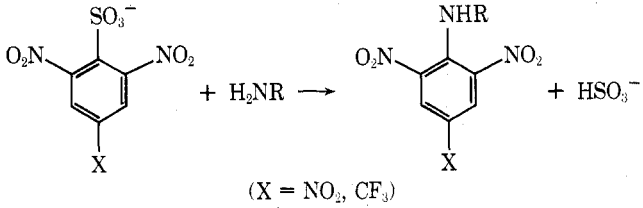
The reactions of 2,4,6-trinitrobenzenesulfonate ion (TNBS) and 2,6-dinitro-4-trifluoromethylbenzenesulfonate ion (TFBS) with OH^- are catalyzed by OH^- as are the reactions with aniline and glycinate ion, and the kinetic parameters have been evaluated in terms of a mechanism in which a tetrahedral intermediate decomposes to products spontaneously or with hydroxide ion catalysis. Decomposition of the tetrahedral intermediate can be followed spectrophotometrically for reaction of TNBS with OH^- in aqueous Me_2SO. At relatively low pH (<10.5), cationic micelles of cetyltrimethylammonium bromide (CTABr) catalyze the reactions of TNBS by the following factors: glycinate, 6; leucinate, 38; phenylglycinate, 174; aniline, 30. The reaction of glycineamide is slightly inhibited by CTABr. In CTABr the hydroxide ion catalysis of reactions of TNBS with aniline or OH^- is considerably less than at relatively low pH. The reaction of phenoxide ion with TNBS is catalyzed by a factor of 2000 by CTABr.

Activated arenesulfonates, e.g., 2,4,6-trinitrobenzenesulfonate ion (TNBS) and 2,6-dinitro-4-trifluorobenzenesulfonate ion (TFBS), react readily with primary and secondary amines and are useful protein modifying agents.[1] The reaction of TNBS with amino acid anions is reportedly cleanly second order.[1a,b] Aromatic nucleophilic substitution by uncharged



(X = NO_2, CF_3)

and anionic nucleophiles is catalyzed by cationic micelles,[2-5] which also speed formation of the tetrahedral intermediate.[6,7] Addition to give the tetrahedral intermediate is generally rate limiting for reactions of halonitrobenzenes in polar hydroxylic solvents.[13,14]

The polarities of micellar surfaces are similar to those of many proteins,[10] so that nucleophilic aromatic substitution catalyzed by a micelle should be a better model for protein modification than reaction in water, and the effects of cationic micelles of cetyltrimethylammonium bromide (CTABr) upon reactions of TFBS and 2,4-dinitrofluorobenzene were examined.[15] For both reagents micellar catalysis increases with increasing hydrophobicity of the nucleophile, as is generally found,[8-12] but the effect is much more marked for reactions of TFBS.

In this paper we extend the investigation to reactions of TNBS and we show that for reactions with hydroxide and glycinate ion and aniline there is a base-catalyzed reaction suggesting that the breakdown of the tetrahedral intermediate can become rate limiting, which complicates discussion of the micellar catalysis. However, reaction of phenoxide ion with TNBS is very strongly catalyzed by CTABr, showing the role of substrate hydrophobicity in a non-base-catalyzed nucleophilic aromatic substitution.

Experimental Section

Materials. The preparation of the surfactants and most of the reagents followed methods already described.[4,5,15] The tertiary amines were treated with tosyl chloride to remove secondary or primary amines and then distilled.

Kinetics. All the reactions were followed spectrophotometrically in water, at 25.0 °C, using Gilford spectrophotometers[15] at the following wavelengths: amino acid derivatives, 420 nm; phenoxide ion, 446 nm; OH^-, 430 nm; aniline, 435 nm.

The nucleophile was in large excess over the arenesulfonate, which was $1–4 \times 10^{-5}$ M, and the integrated first-order rate constants, k_ψ, are in s^{-1}, and the second-order rate constants, k_2^{obsd}, $M^{-1}\ s^{-1}$, were calculated by dividing k_ψ by the reagent concentration. It was necessary to use low concentrations of TNBS because otherwise there was precipitation during reactions with aniline in the absence of surfactant. The rate constants for reactions with amines in water were unaffected, within experimental error, by up to threefold changes in reagent concentration or for reaction with aniline by increases in pH from 7.5 to 10.

The pH was such that the amino acids were wholly in the reactive anionic form, and 0.027 M carbonate buffer was used, except for re-