1,3-Bridged Aromatic Systems. VII. Quinolines[1,2]

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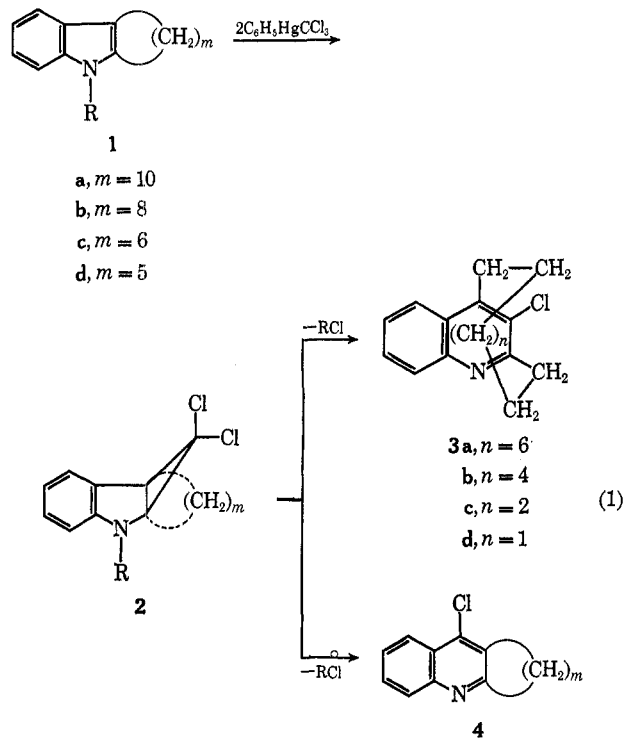
Received February 25, 1970

The preparation of 1,3-bridged quinolines of type **3** are described. As the value of n in these pyridinophanes is reduced, the methylene bridge is more constrained and the pyridine ring is strained; such strain is reflected by changes in spectral and chemical behavior. The asymmetry of the quinolines **3** was established by conversion of **3a** to the epimeric alcohols **6a** and **6b** in which the hydroxyl functions are at carbon-1 of the bridge. The pK_a of representative examples of **3** are compared with that of the model 3-chloro-2,4-dimethylquinoline. The pyridinophane **3a** undergoes only monobromination with *N*-bromosuccinimide to give **15**; by contrast the dechloro derivative **8a** readily gives the dibromide **17**. These reactions, and the lack of reactivity of **17**, are discussed in terms of steric requirements for reaction.

In a preliminary communication[4] we described the preparation of the 1,3-bridged quinolines **3a–c** (48–76% yield) by addition of dichlorocarbene to the indoles **1** (R = H or R = C(O)CH$_3$), as summarized in eq 1.



1

a, $m = 10$
b, $m = 8$
c, $m = 6$
d, $m = 5$

2

3 a, $n = 6$; b, $n = 4$; c, $n = 2$; d, $n = 1$

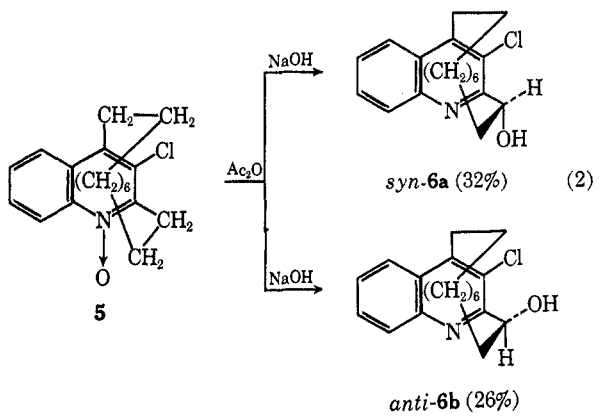
4

(1)

The limiting value of m for the preparation of **3** was found to be 6; when $m = 6$ the quinoline **4** ($m = 6$) was formed as a minor compound (2.7% yield) together with **3c**, and, when $m = 5$, the quinoline **4** ($m = 5$) was the only product characterized (11.6% yield).[5,6]

In this paper we describe experimental procedures for these syntheses, and report additional studies bearing on the physical and chemical properties of these heterocyclic metacyclophanes.

Reaction of 12,13-Benzo-16-chloro[10](2,4)pyridinophane *N*-Oxide (5) with Acetic Anhydride.—Comparision of the nmr spectra of the cyclophanes **3a–b** with the dechlorinated analogs **8** suggested that in the former the methylene bridge cannot pass over the halogen to the other face of the aromatic ring; thus, molecules **3a–c** are asymmetric and exist as *dl* pairs. This conclusion was confirmed by a study of the reaction of the *N*-oxide **5**, derived from **3a** (96% yield) by oxidation with hydrogen peroxide, with acetic anhydride (eq 2). The products,



5

syn-**6a** (32%)

anti-**6b** (26%)

(2)

obtained subsequent to hydrolysis of the intermediate acetates, were the *syn*-alcohol **6a** (32%) and the *anti*-alcohol **6b** (26%). The conversion of 2-alkylpyridine *N*-oxide to the corresponding pyridinemethanols is well known;[7] the nonequivalence of the α-benzyl hydrogen atoms leading to the diastereomeric alcohols **6a** and **6b** confirms the asymmetry of the metacyclophane structure. This reaction is also attractive as a route for derivatives of **3** with functionality in the methylene side chain.

Both isomers of **6** are oxidized to the same ketone **7** with chromium trioxide in pyridine, which confirms the diastereomeric relationship of the isomeric alcohols. The hydroxyl group of the syn isomer (**6a**) was found to be completely intramolecular hydrogen bonded to nitrogen (ν_{OH} 3440 cm^{-1}), while the anti isomer exists entirely as free hydroxyl (ν_{OH} 3615 cm^{-1}). A model compound, *o*-chlorobenzyl alcohol, displayed no significant intramolecular hydrogen bonding.

Reduction of **7** with sodium borohydride gave predominantly the syn isomer (79% **6a**, 4.4% **6b**). The

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(1) Supported by the National Science Foundation, Grants GP-6169X and GP-11918.

(2) For the preceding article in this series, see W. E. Parham and R. W. Davenport, *J. Org. Chem.*, **35**, 0000 (1970).

(3) In part from the thesis of R. W. Davenport, The University of Minnesota, 1969.

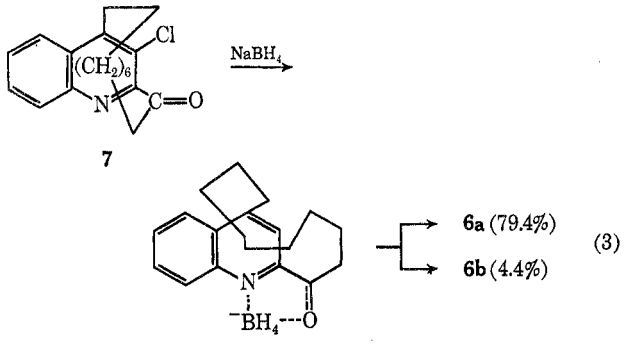
(4) W. E. Parham, R. W. Davenport and J. B. Biasotti, *Tetrahedron Lett.*, **7**, 557 (1969).

(5) W. E. Parham, D. R. Johnson, C. T. Hughes, M. K. Meilahn, and J. K. Reinhart, *J. Org. Chem.*, **35**, 1048 (1970).

(6) The mechanism for the conversion of **2** to **4** is thought to occur by phenyl migration in the intermediate carbonium ion prior to disrotatory ring opening, as discussed in ref 5 for cyclopropanes derived from related indenes.

(7) (a) V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954); (b) K. Biemann, G. Büchi, and B. H. Walker, *ibid.*, **79**, 5558 (1957).

most probable transition state is shown in eq 3, in which the boron is partially bonded to both oxygen and ni-

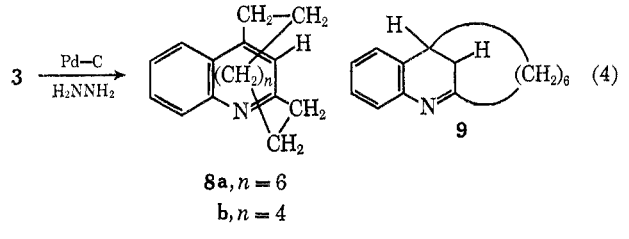


(3)

trogen to become part of a five-membered ring. In order to obtain such a transition state, the carbonyl group must orient itself in the plane of the aromatic ring, and hydride attack is from the side opposite to the methylene chain.

Reduction.—As the value of n in **3** is reduced progressively from 6 to 4 to 2, the nitrogen-containing aromatic ring becomes more strained and distorted from its normal planar configuration by the methylene bridge.[8] Chemical evidence for this conclusion was obtained by studies of the reduction of **3a–c**.

Both **3a** and **3b** were reduced (eq 4) with hydrazine on



(4)

charcoal to the corresponding dechlorinated pyridinophanes **8a** and **8b** in 88 and 96% yield, respectively. Removal of the chlorine atom from **3a** and **3b** permits the methylene bridge to invert to either face of the aromatic ring.[9,10] The nitrogen containing ring in **3c** is evidently more strained and reactive, for, under identical conditions used for **3a** and **3b**, the nitrogen ring is reduced to give **9** (~100%). The structure of **9** was assigned on the basis of the composition of the derived picrate, and by its spectra (see Experimental Section, $\nu_{C=N}$ at 1622 cm^{-1}).

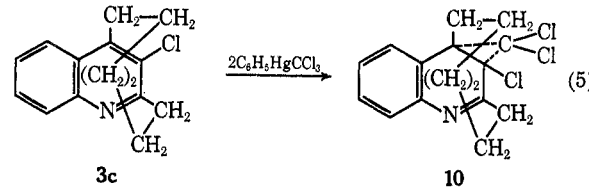
Reaction of 3 with Phenyl(trichloromethyl)mercury.—Deformation and increased reactivity of the aromatic ring in **3c** was also evidenced by comparison of the reaction of **3c** and **3a** with phenyl(trichloromethyl)-mercury as shown in eq 5 and 6. The cyclopropane **10** was first isolated as a minor product from the reaction of **1c** with phenyl(trichloromethyl)mercury, and its structure was assigned on the basis of the composition and spectra, and by its facile preparation (46%) by reaction of **3c** with phenyl(trichloromethyl)mercury.

(8) This conclusion is supported by comparisons of nmr spectra and ultraviolet spectra as discussed in ref 4.

(9) This conclusion is supported by the nmr spectra of **3a–b** and **8a–b**; see Experimental Section.

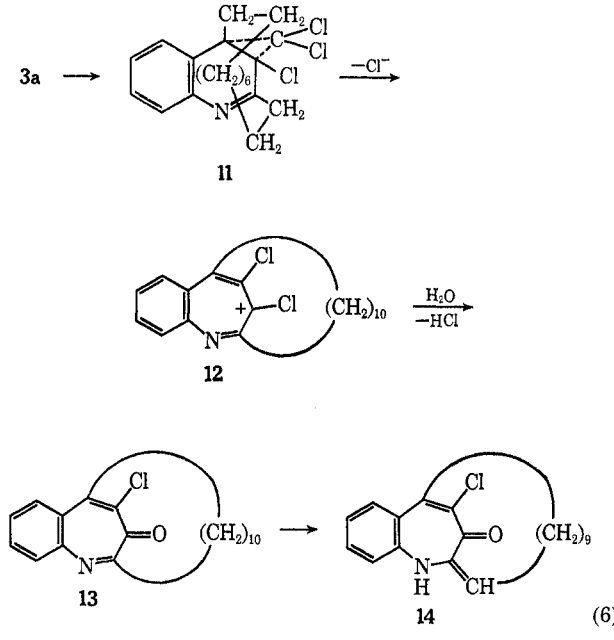
(10) Similar results are described in ref 5 for the corresponding naphthalene analogs.

The cyclopropane **10** was quite stable in polar solvents and showed no tendency to undergo ring expansion, a conclusion consistent with the high degree of strain in products projected by normal ring expansion of the cyclopropane ring in **10**.



(5)

The only product isolated (8% yield by liquid chromatography) from a similar reaction of **3a** with phenyl-(trichloromethyl)mercury, other than unchanged **3a** (31%), was assigned structure **14** on the basis of its composition and spectra, coupled with the logic of its formation as shown in eq 6. The derivative **13** is as-



(6)

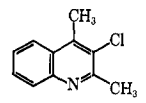
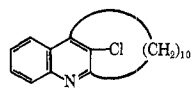
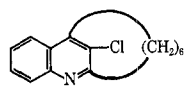
sumed to be formed from the adduct **11**, which is analogous to **10** formed from **3c**. In this case, however, the system is less strained by the larger methylene bridge; normal ring expansion with hydrolysis of the derived ion **12** would be expected to produce the ketone **13**. It is assumed that the initial product **13** undergoes prototropic isomerization to **14**, since **14**, but not **13**, is consistent with the observed spectral data.

Effect of Ring Strain on the Basicity of 3.—Although factors determining the basicity of amines have been thoroughly investigated,[11] there have been no studies which correlate base strength of aromatic heterocyclic amines with deformation of the nitrogen-containing ring.

The acid dissociation constants (pK_a) of **3a**, **3c**, and 3-chloro-2,4-dimethylquinoline were determined by potentiometric titration in 70% ethanol and are listed in Table I. The results suggest that deformation of the ring has no appreciable effect on basicity. As the process involved is one of equilibrium, these results suggest

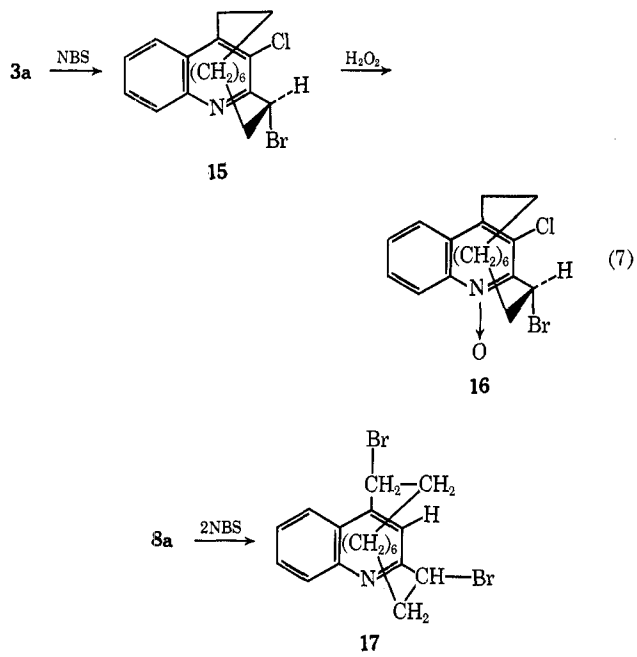
(11) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, Chapter 7.

TABLE I

Compd	pK_a
 3-Chloro-2,4-dimethylquinoline	3.04 ± 0.03
 3a	2.88 ± 0.03
 3c	3.03 ± 0.03

that the energy difference between the protonated and unprotonated forms of these three amines is small.[12]

Reaction of 3a and 8a with *N*-Bromosuccinimide.—The reaction **3a** with 1 equiv of *N*-bromosuccinimide gave a monobromo derivative (23% yield) which was assigned structure **15** (eq 7). Assignment of structure



(7)

15 as the syn isomer shown was made partially on the basis of steric considerations. Models showed that the alternate methylene position (C-10) to be hindered by the peri hydrogen and the chlorine atoms, respectively, and the epimeric anti position by the bridge and by the chlorine atom. Support for this conclusion was obtained by failure to detect a dibromo derivative when **3a** was treated with 2 equiv of *N*-bromosuccinimide; the yield of **15** was increased slightly to 30% in this case. Similarly, **15** was recovered unchanged (>69%) subsequent to attempted reaction with *N*-bromosuccinimide. Further support for structure **15** was the observation that the *N*-oxide **16**, derived from **15**, was recovered unchanged when heated with hot acetic anhydride under conditions identical with those used for the conversion of **5** to **6**. Lack of reactivity of the *N*-oxide is reasonable for **16**, but unlikely if the bromine atom was at the alternate methylene position (C-10).

One would expect that removal of the chlorine atom from **15** would sufficiently reduce the steric constraint of the pyridinophane to permit dibromination, and this was shown to be the case; **8a** reacted readily with 2 equiv of *N*-bromosuccinimide to give the dibromo derivative **17**, which was isolated in 47% yield. The bromine atoms in **15** and **17** are unreactive; **17** was recovered (88%) after 10 hr in hot acetic acid containing 5 mol equiv of potassium acetate.[13] The properties of halides of type **15** and **17** will be the subject of a subsequent report; however, these preliminary studies suggest that they can be compared qualitatively with bridgehead halides. Thus, there is steric interference to SN2 attack, and ionization of halogen is inhibited by the additional steric demands imposed when the ring methylene carbon changes from sp^3 to sp^2 hybridization.

Experimental Section

All nmr spectra, unless otherwise stated, were determined at 20% concentration (wt/v) on a Varian A-60 spectrophotometer; ultraviolet spectra were determined in 95% ethanol.

General Procedure for the Preparation of 3. 12,13-Benzo-16-chloro[10](2,4)pyridinophane (3a). A.—Phenyl(trichloromethyl)mercury (17.1 g, 43.2 mmol) and 2,3-cyclododecenoindole[14] (**1a**, 5.03 g, 19.7 mmol) were heated under a nitrogen atmosphere in refluxing anhydrous benzene (200 ml) for 44 hr. The mixture was cooled, filtered to remove phenylmercuric chloride (12.2 g, 90.2%), and concentrated to a dark brown oil (7.63 g). The residue was shaken with petroleum ether, filtered to remove additional phenylmercuric chloride, and chromatographed on alumina (200 g) using petroleum ether as initial eluent. Elution of the column with petroleum ether–ether (10%) gave the pyridinophane **3a** as a yellow oil (4.11 g, 69.1% yield) which solidified (mp 75.0–78.0°). The material was purified by conversion to the hydrochloride (3.83 g, 57.5%), white needles (mp 187–197°). The hydrochloride was suspended in water and ether and aqueous sodium hydroxide was added dropwise until the solution was alkaline. The ether layer was dried ($MgSO_4$) and concentrated to give nearly pure **3a** (3.29 g, 55.2% yield, mp 77–81.5°). Pure **3a** showed mp 81.5–82.5° (from methanol); uv max 235 mμ (ε 44,100), 285 (4250), 296 (4160), 309 (3980), and 323 (4200); ir (Nujol) 1579 (m), 1501, 1030 (m), and 771 cm^{-1} (s); nmr (CCl_4) τ 1.90–2.76 (m, 4.1, aromatic **H**) and 6.04–10.40 (very complex, 19.9, CH_2).

Anal. Calcd for $C_{19}H_{24}ClN$: C, 75.60; H, 8.01; Cl, 11.75; N, 4.64. Found: C, 75.87; H, 7.93; Cl, 11.95; N 4.59.

Picrate of 3a had mp 177–178° (from methanol).

Anal. Calcd for $C_{25}H_{27}ClN_4O_7$: C, 56.55; H, 5.13; Cl, 6.68; N, 10.55. Found: C, 56.57; H, 5.19; Cl, 6.84; N, 10.36.

Hydrochloride of 3a had mp 194–221° (from anhydrous ether–ethanol).

Anal. Calcd for $C_{19}H_{25}Cl_2N$: C, 67.45; H, 7.45; Cl, 20.96; N, 4.14. Found: C, 67.19; H, 7.58; Cl, 21.14; N, 3.99.

This procedure was employed to prepare **3a–3c**[4] and the properties of these pyridinophanes have been reported.

B.—1-Acetyl-2,3-cyclododecenoindole (1a, R = CH_3CO) was prepared by a modification of the procedure[15] by Atkinson, *et al.* The crude product (65% yield, mp 82–92°) was difficult to purify by recrystallization (petroleum ether at −78°, then petroleum ether and finally methanol) and considerable loss was encountered. Pure **1a** (R = CH_3CO) (4.6 g, 15.8%, mp 113–

(12) The basicity of the amines is determined by the availability of the lone pair on nitrogen. Either the ring deformation is not enough to overcome other factors such as inductive effects of the alkyl groups, or there are compensating effects in base and conjugate acid. One would not expect *a priori* that these effects would be the same. Another possibility suggested by a referee, that has not been explored, is that the solvent may be introducing compensating errors.

(13) This is a general procedure for converting benzyl bromides to benzyl acetates: *cf.* W. Wenner, *J. Org. Chem.*, **17**, 523 (1952).

(14) Ng. Ph. Buu-Hoï, *J. Chem. Soc.*, 2882 (1949); L. M. Rice, E. Hertz, and M. E. Freed, *J. Med. Chem.*, 7, 313 (1964); Ng. Ph. Buu-Hoï, P. Jacquigon, and T. B. Loc, *J. Chem. Soc.*, 738 (1958).

(15) C. M. Atkinson, J. C. E. Simpson, and A. Taylor, *ibid.*, 165 (1954).

114°) showed uv max 246 mμ (ε 15,900), 266 (sh) (11,100), 291 (sh) (5630), and 302 (5460); ir (Nujol) 1702 cm^{-1} (C=O); nmr ($CDCl_3$) τ 2.08–2.80 (m, 4.1, aromatic H), 6.76–7.39 (2 t and s, 6.8, allylic CH_2 and $COCH_3$), and 7.88–8.90 (m, 6.1, CH_2).

Anal. Calcd for $C_{20}H_{27}NO$: C, 80.76; H, 9.15; N, 4.71. Found: C, 80.91; H 9.06; N, 4.68.

The acetyl derivative **1a** (13.5 mmol) was reacted with phenyl(trichloromethyl)mercury (29.6 mmol) essentially as described above. The pyridinophane was eluted essentially pure (mp 81.0–81.5°, 75.8% yield) with petroleum ether–ether (10%).

When 1-acetyl-2,3-dimethylindole was employed, the crude 3-chloro-2,4-dimethylquinoline (55%, mp 64–68°) was easily purified (35.3%, mp 70–72.8°); when 2,3-dimethylindole was used, as in procedure A, the yield of pure 3-chloro-2,4-dimethylquinoline, mp 71–72.5°, was 35% (lit.[16] mp 73°).

C. Isolation of 10 and 4 (m = 6).—The dark brown residue obtained from 2,3-cyclooctenoindole[14] (**1c**, 20.0 g, 0.10 mol, procedure A) was chromatographed on alumina (800 g).

The adduct **10** was eluted from the column with petroleum ether–ether (5–8%) as a light brown solid (2.17 g, 6.6%) which melted at 125–126° (from petroleum ether, bp 30–60°): uv max 230 mμ (ε 23,100), 236 (sh) (20,300), 294 (5140), and 305 (sh) (3910); ir (Nujol) 1625 (s) (C=N), 1591 (m), 1565 (m), 1121 (m), 1050 (m), 1035 (m), 981 (s), 855 (m), 821 (m), 738 (m), and 755 cm^{-1} (s); nmr ($CDCl_3$) τ 2.64 (unresolved m, 3.9, aromatic H), 7.03–7.57 (m, 1.8, allylic CH_2), and 7.91–9.27 (m, 10.2, CH_2); mass spectrum m/e 327 (calcd mol wt, 327).

Anal. Calcd for $C_{16}H_{16}Cl_3N$: C, 58.47; H, 4.91; Cl, 32.36; N, 4.26. Found: C, 58.30; H, 5.00; Cl, 32.20; N, 4.19.

Elution of the column with petroleum ether–ether (15%) gave a mixture of **3c** and **4** (m = 6). The crude product was dissolved in petroleum ether, bp 30–60°, treated with charcoal, filtered through Celite, and crystallized at −78°. The pyridinophane **3c** melted at 60–65° (6.40 g, 26%) and at 67–68° after additional recrystallization. The mother liquor was recrystallized (petroleum ether at −78°) to give additional **3c** (1.48 g, 6.0% yield, mp 61–64°). The mother liquor was reprocessed to give 4-chloro-2,3-cyclooctenoquinoline (**4**) as yellow crystals (0.66 g, 2.7% yield, mp 73–77.5°). Pure **4** (m = 6) showed mp 82.5–83.0°; uv max 233 mμ (ε 53,500), 283 (5040), 288 (4980), 294 (4960), 299 (4230), 307 (5170), 311 (sh) (3320), 316 (sh) (3010), and 320 (6340); ir (Nujol) 1590, 1560, and 770 cm^{-1}; nmr ($CDCl_3$) τ 1.75–2.70 (m, 4.1, aromatic H), 6.67–7.10 (m, 3.6, benzylic CH_2), and 7.90–8.93 (m, 8.3, CH_2).

Anal. Calcd for $C_{15}H_{16}ClN$: C, 73.31; H, 6.56; Cl, 14.43; N, 5.70. Found: C, 73.35; H, 6.57; Cl, 14.39; N, 5.57.

12,13-Benzo-16-chloro[10](2,4)pyridinophane *N*-oxide (5) was obtained in 96% yield (mp 103–110°) by oxidation of **3a** with hydrogen peroxide[7] and showed mp 125–127° [chromatography (25–55% petroleum ether–ether) and recrystallization (petroleum ether)]; uv max 349 mμ (log ε 3.88), 334 (3.95), 250 (4.61), 241 (sh) (4.47), 234 (sh) (4.40), and 224 (4.32); nmr (25% $CDCl_3$) τ 0.74–0.99 (m, 1, aromatic H), 1.99–2.71 (m, 3, aromatic H), and 6.07–7.01 (m, 4, benzylic CH_2), and 7.45–10.03 (m, 16 CH_2).

Anal. Calcd for $C_{19}H_{24}ClNO$: C, 71.80; H, 7.61; N, 4.41; Cl, 11.15. Found: C, 72.05; H, 7.46; N, 4.15; Cl, 11.25.

12,13-Benzo-16-chloro[10](2,4)pyridinophan-1-ol (6).—The reaction of **5** (5.00 g) with acetic anhydride (20 ml) was effected for 15 hr at 100° by a procedure similar to that described by Biemann, Büchi, and Walker.[7b] The crude acetate was heated (reflux) in methanol (100 ml) containing aqueous (20%) potassium hydroxide and the crude alcohols (4.6 g, 92% yield, mp 139–158°) were chromatographed on neutral alumina (500 g) using petroleum ether–ether (15%) as initial eluent.

syn-**6a** (1.54 g, 30.8% yield, mp 154–158°) eluted first and showed mp 160–162° (petroleum ether–chloroform); uv max 323 mμ (log ε 3.82), 308 (3.78), 296 (3.81), 286 (3.83), 241 (sh) (4.80), 236 (4.84), and 216 (4.71); nmr (10% $CDCl_3$) τ 1.82–2.63 (m, 4, aromatic H), 4.40–5.05 (broad s, 2, CHOH, 4 lines when D_2O used as solvent), 6.22–6.92 (m, 2, benzylic CH_2), and 7.12–10.41 (m, 16, CH_2).

Anal. Calcd for $C_{19}H_{24}ClNO$: C, 71.80; H, 7.61; N, 4.41; Cl, 11.15. Found: C, 72.01; H, 7.76; N, 4.32; Cl, 10.91.

anti-**6b** (1.21 g, 24.2% yield, mp 202–204.5°) showed mp 205.5–207° (from petroleum ether–chloroform); uv max 326 mμ (log ε 3.62), 311 (3.58), 297 (sh) (3.62), 283 (3.68), 236 (4.73), and 218 (sh) (4.55); nmr (7% $CDCl_3$) τ 1.80–2.50 (m, 4, aromatic H), 4.67–5.20 (broad s, 2, CHOH, 4 lines when D_2O used as solvent), and 6.0–10.33 (m, 18, CH_2).

Anal. Found: C, 71.59; H, 7.60; N, 4.24; Cl, 10.95.

12,13-Benzo-16-chloro[10](2,4)pyridinophan-1-one (7).—Oxidation of **6a** or **6b** (500 mg) was effected with chromium trioxide in pyridine as described for related compounds.[7] The crude ketone was purified by chromatography on alumina (PF_{254}, eluent ether) and the ketone was purified (38.5 and 50% yield, respectively) from petroleum ether (bp 30–60°) to give pure **7**: mp 136–137.5; ir $\nu_{C=O}$ 1712 cm^{-1}; uv max 324 mμ (log ε 3.56), 310 (sh) (3.62), 291 (3.72), 236 (4.71), and 212 (4.54); nmr (10% $DCCl_3$) τ 1.75–2.67 (m, 4, aromatic H) and 6.45–10.30 (m, 18, CH_2).

Anal. Calcd for $C_{19}H_{22}ClNO$: C, 72.25; H, 7.02; Cl, 11.22; N, 4.43. Found: C, 72.15; H, 6.93; Cl, 11.43; N, 4.19.

Preparation of 8. General Procedure.—The pyridinophane **3a** (0.579 g, 1.91 mmol) was reduced with hydrazine (5 ml) and palladium on charcoal (0.200 g, 10%) in absolute ethanol (50 ml) for 35 min according to the procedure of Mosby.[17] The crude product obtained from the ethanol showed one spot on tlc [R_f 0.29, silica gel HF254, petroleum ether–ether (10%)] and was chromatographed on alumina (50 g) using petroleum ether–ether (10%) as eluent to give **8a** (mp 60–61°) in 88% yield. Pure **8a** showed mp 62–63°; hydrochloride mp 230–234°; uv max 229 mμ (ε 45,100), 232 (sh) (41,100), 279 (4930), 289 (sh) (4660), 302 (3950), and 316 (4370); nmr (CCl_4) τ 1.87–2.88 (m, 4.0, aromatic H), 2.98 (s, 1.0, 16-H), 6.87–7.22 (m, 4.1, benzylic CH_2), and 7.88–9.40 (m, 15.9, CH_2).

Anal. Calcd for $C_{19}H_{25}N$: C, 85.34; H, 9.42; N, 5.24. Found: C, 85.36; H, 9.64; N, 5.20.

Anal. Calcd for $C_{19}H_{26}ClN$ (hydrochloride): C, 75.09; H, 8.63; Cl, 11.67; N, 4.61. Found: C, 75.05; H, 8.53; Cl, 11.44; N, 4.57.

The yield of **8b** was 96%; the properties of **8b** have been reported.[4]

4,5,6,7,8,9-Hexahydro-2,9-methano-3*H*-1-benzazacycloundecine (9).—Reduction of **3c** (0.500 g, 2.04 mmol) with hydrazine as described above for **3a** gave a yellow oil (0.422 g, 98.0% yield) of essentially pure **9**. The ir spectrum of the product was essentially identical with that of a sample further purified by preparative tlc [alumina PF254, petroleum ether–ether (10%) as eluent] and showed ir $\nu_{C=N}$ 1622 cm^{-1}; nmr (CCl_4) τ 2.67–3.15 (m, 3.8, aromatic H) and 7.00–9.00 (m, 15.2, CH and CH_2).

The amine **9** was unstable and was converted into the corresponding picrate: mp 167–169° (from methanol); mass spectrum m/e (relative intensity) 213 (30), 229 (10) (calcd mol wt of **12**, 213; of picric acid, 229). The mass spectrum of picric acid showed m/e 213 (1), 229 (10).

Anal. Calcd for $C_{21}H_{22}N_4O_7$: C, 57.01; H, 5.01; N, 12.66. Found: C, 56.74; H, 5.09; N, 12.69.

Preparation of 10.—The pyridinophane **3c** (0.500 g, 2.04 mmol) was treated with phenyl(trichloromethyl)mercury (0.806 g, 2.04 mmol) in dry benzene (80 ml) for 39 hr as described for the preparation of **3a**. The residue was extracted with chloroform and filtered to remove additional phenyl mercuric chloride; preparative tlc [silica gel PF254, petroleum ether–ether (5%) as eluent] gave crude **10** (0.305 g, 45.7% yield, brown oil), recovered **3c** (0.140 g, 28%) and four other minor products. The amine **10** was obtained with considerable loss of product by recrystallization from petroleum ether, bp 30–60° (mp 126–127°, mmp (with **10** from **1c**) 126–127°).

Reaction of 3a with Phenyl(trichloromethyl)mercury.—Chromatography [preparative tlc, silica gel PF254, petroleum ether–ether (10%)] of the crude product obtained by reaction of **3a** (0.400 g, 1.32 mmol) with phenyl(trichloromethyl)mercury (0.528 g, 1.33 mmol) as described above showed at least nine products. The major components were removed with chloroform–methanol (10%) and were A, recovered **3a** (30.8%) and B, a solid (mp 184–186°, 8% yield, from petroleum ether) which was assigned **14**: uv max 236 mμ (ε 19,400), 240 (19,700), 254 (17,200), 298 (6290), 312 (5740), and 325 (5200); ir (Nujol) ν_{NH} 3325 (broad), $\nu_{C=O}$ 1681 cm^{-1}; nmr ($CDCl_3$) τ 1.52–3.10 (m, 4.7, NH and aromatic H), 4.52–5.09 (m, 0.8, C=C—H), and 6.30–9.80 (m, 18.4, CH_2).

Anal. Calcd for $C_{20}H_{24}ClNO$: C, 72.82; H, 7.34. Found: C, 72.90; H, 7.61.

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Basicity Studies.—Carefully purified samples of 3-chloro-2,4-dimethyl quinoline, **3a** and **3c**, were weighed into 50-ml volumetric flasks and dissolved in 35.00 ml of 95% USP ethanol. Water (carbonate free) was added to the mark and the solution was thermostated at 25° and titrated with 0.1 *N* ethanolic hydrochloric acid using a Radiometer automatic titration apparatus (type TTT1c), glass and calomel electrodes. The pK_a values were calculated from eq 8,[18] where C = initial concentration of

$$pK_a = pH + \log \frac{C/2 + [H^+]}{C/2 - [H^+]} \quad (8)$$

base; the values of pH and $[H^+]$ are those measured at the calculated half-neutralization point. No correction was made for the presence of ethanol in the solutions.

12,13-Benzo-1-bromo-16-chloro[10](2,4)pyridinophane (15).—A mixture of **3a** (2.0 g, 6.64 mmol), *N*-bromosuccinimide (1.18 g, 6.64 mmol), and carbon tetrachloride (30 ml) was heated at the reflux temperature and benzoyl peroxide (80 mg) was added in portions every 0.5 hr for 1.5 hr, and the mixture was heated at the reflux temperature under nitrogen for an additional 4 hr. The solid obtained by removal of solvent was chromatographed [neutral alumina, 250 g, petroleum ether–ether (10%) as eluent] to give **15** (23.5%): mp 149.5–151° (from petroleum ether, bp 30–60°); uv max 330 mμ (log ε 3.58), 316 (3.68), 303 (3.72), 295 (sh) (3.71), 240 (4.70), and 217 (4.58); nmr (15% in $CDCl_3$) τ 1.70–2.54 (m, 4, aromatic **H**), 3.78–4.10 (q, 1, CHBr), 6.30–6.70 (m, 2, benzylic CH_2), 7.03–10.42 (m, 16, CH_2).

Anal. Calcd for $C_{19}H_{23}ClBrN$: C, 59.93; H, 6.09; N, 3.68. Found: C, 60.19; H, 6.10; N, 3.64.

The yield of **15** was 30.5% when 2 equiv of *N*-bromosuccinimide was employed. Attempt to further brominate **15** with *N*-bromosuccinimide gave only **15** (69.3% recovered, mp and mmp 149–150°).

The *N*-oxide 16 was prepared from **15** (2.5 g, 6.6 mmol) and hydrogen peroxide as described above for **5**. The crude product (1.9 g) was chromatographed on neutral alumina (220 g) using petroleum ether–ether as eluent. There was obtained 1.3 g (52%) of recovered **15** and the *N*-oxide **16** (412 mg, 15.8%): mp 186–188° (from petroleum ether–chloroform); uv max 364 mμ (sh) (log ε 3.64), 345 (sh) (3.74), 333 (3.77), 258 (4.38), 244 (sh) (4.33), and 226 (sh) (4.23); nmr ($CDCl_3$) τ 1.09–1.30 (m, 1, aromatic **H**), 1.86–2.42 (m, 3, aromatic **H**), 3.77–4.09 (q, 1, CHBr), 6.30–7.00 (m, 2, benzylic CH_2), and 7.44–10.00 (m, 16, CH_2).

Anal. Calcd for $C_{19}H_{23}BrClNO$: C, 57.52; H, 5.84; N, 3.53. Found: C, 57.62; H, 5.94; N, 3.28.

12,13-Benzo-1,10-dibromo[10](2,4)pyridinophane (17).—Reaction of **8a** (6.70 g, 0.025 mol) with *N*-bromosuccinimide (8.9 g, 0.050 mol) was carried out as described for the preparation of **15**. The crude product was chromatographed on neutral alumina (750 g) using petroleum ether and petroleum ether–ether as eluent. There was obtained 5.0 g (47.1%) of the dibromo derivative (**17**): white crystals; mp 133.5–135° (from petroleum ether); uv max 322 mμ (log ε 3.51), 310 (3.61), 298 (3.64), 210 (sh) (3.54), 239 (4.51), and 213 (4.41); nmr ($CDCl_3$) τ 1.75–2.47 (m, 5, aromatic **H**), 4.06–4.33 (q, 1, CHBr), 4.62–4.90 (q, 1, CHBr), and 6.87–9.78 (m, 16, CH_2); picrate mp 183.5–185°.

Anal. Calcd for $C_{19}H_{23}Br_2N$: C, 53.67; H, 5.45; Br, 37.58; N, 3.29. Found: C, 53.70; H, 5.46; Br, 37.26; N, 3.12.

Anal. Calcd for $C_{25}H_{26}Br_2N_4O_7$ (picrate): C, 45.87; H, 3.98; N, 8.56. Found: C, 46.10; H, 3.85; N, 8.18.

Reduction of 7.—The pyridinophane **12** (1.0 g, 3.17 mmol) was treated with sodium borohydride (0.121 g, 3.17 mmol) in absolute ethanol (50 ml). The solution was heated (reflux) for 18 hr. Removal of solvent gave the crude product (0.92 g, 92.3%, mp 150–157°) of which 0.800 g was chromatographed [silica gel, 80 g, petroleum ether–ether (0–30%)] to give **6a** (0.635 g, 79.4% yield, mp and mmp 160.5–162.5°). Eluted second was **6b** (0.035 g, 4.4% yield, mp and mmp 205.5–207°).

Registry No.—**1a**, 25907-80-6; **3a**, 22200-39-1; **3a** picrate, 25866-33-5; **3a** HCl, 25866-34-6; **4**, 25866-35-7; **5**, 25907-81-7; **6a** *syn*, 25866-36-8; **6b** *anti*, 25907-82-0; **7**, 25859-31-8; **8a**, 22200-42-6; **8a** HCl, 25830-79-7; **9**, 25859-33-0; **9** picrate, 25859-34-1; **10**, 25859-35-2; **14**, 25859-36-3; **15**, 25859-37-4; **16**, 25859-38-5; **17**, 25859-39-6; **17** picrate, 25859-40-9.

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Stereochemistry of the Isomerization of *N*-Acyl-2,3-Disubstituted Aziridines to Δ^2-Oxazolines

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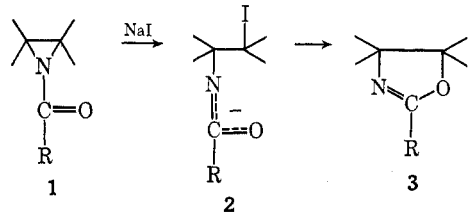
Received March 31, 1970

The iodide ion catalyzed isomerization of *cis*- and *trans*-1-acetyl and 1-aroyl-2,3-disubstituted aziridines to Δ^2-oxazolines has been studied. The rearrangement is stereoselective, the selectivity being greater with *trans*-aziridines than with *cis*-aziridines. The former yield 90–95% *trans*- and 10–5% *cis*-Δ^2-oxazolines while the latter give 40–90% *cis* and 60–10% *trans*. The selectivity of isomerization for *cis*-1-aroylaziridines was found to vary with the iodide ion concentration and the solvent system employed while the ratio of Δ^2-oxazolines formed from the corresponding *trans*-aziridines was unaffected. Using tetrabutylammonium iodide as the isomerization catalyst also affected the Δ^2-oxazoline isomer distribution. The stereochemical outcome of this reaction was found to be insensitive to the size of the 2,3-dialkyl substituents and to resonance effects. The ratio of isomers formed was determined by glpc, while stereochemical configurations were elucidated by means of nmr spectroscopy.

The rearrangement of *N*-acylaziridines (**1**) to the isomeric 2-aryl- or 2-alkyl-Δ^2-oxazoline ring system (**3**) by nucleophiles such as iodide ion and thiocyanate ion has been the subject of a number of studies.[2-6] The mechanism of the iodide-catalyzed isomerization has been postulated as occurring by attack of the nucleophile on a carbon atom of the aziridine ring to produce



R = aryl or alkyl

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