THE SKRAUP REACTION OF 3,4-DIHALOANILINES

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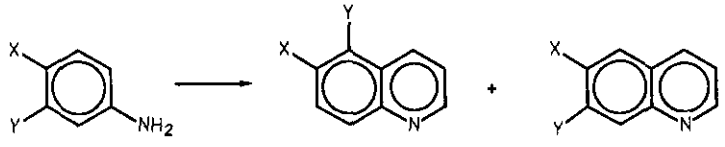
Abstract - Six 3,4-dihaloanilines (**1**) were converted by the sulfo-mix variation of the Skraup reaction to mixtures of 5,6- and 6,7-dihaloquinolines, **2** and **3** respectively. Inductive effects were the dominant influence on the course of cyclization: the more highly electron-withdrawing the substituents of **1**, the greater was the proportion of **3**. Steric effects were absent.

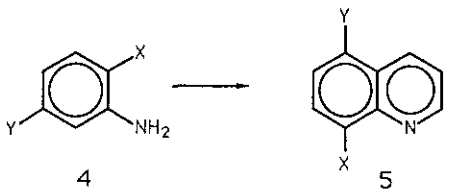
The Skraup reaction with 3-substituted anilines produces 5- and 7-substituted quinolines by an acid-catalyzed condensation with glycerol. The directing influences of a 3-halo substituent have been studied in detail and reviewed critically.[2] Palmer demonstrated that inductive effects are more important than resonance effects and that steric factors are without consequence.[3] The Skraup reaction of 3,4-dihaloanilines has, in contrast, received scant attention. Although such cyclizations afford 5,6- and 6,7-dihaloquinolines, there is only one reported value of a product ratio.[3] Palmer found that 3,4-dichloroaniline gave 5,6- and 6,7-dichloroquinolines in ratios of 58:42 and 67:33, depending on the conditions. The only other mention of such derivatives is early reports of isomeric products from 3,4-dibromoaniline which, based on results presented here, contained incorrect structural assignments.[4] In connection with other studies in this laboratory, we were interested in the generation of 6,7-didehydroquinoline. The preferrred route to the 6,7-dihaloquinoline precursors was the Skraup cyclization of 3,4-dihaloanilines (**1**), since halogenation of 6-haloquinolines leads to 5,6-dihalo derivatives.[5] In the present study we assess the influence of inductive, resonance, and steric effects on the title reaction (eq 1).



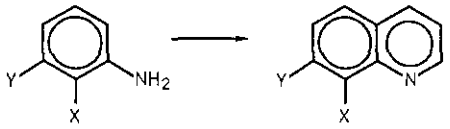
1 2 3 (1)

Of the many methods[6] reported for effecting this cyclization, the one of choice is the Utermohlen modification.[7] The process employs a "sulfo-mix" medium, prepared by the treatment of nitrobenzene with 30% oleum, in which 3-nitrobenzenesulfonic acid functions as the acid catalyst, dehydrating agent, and oxidizing agent. In the latter capacity it serves to aromatize the 1,2-dihydroquinoline intermediate, thereby generating 3-aminobenzenesulfonic acid which is too deactivated to participate in

subsequent quinoline formation (a side reaction observed when nitrobenzene is the oxidizing agent). We have recently prepared a series of 4-bromo-3-haloanilines by the treatment of 3-haloanilines with 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one and identified the minor components of the product mixtures.[8] Since some of our starting dihaloanilines (**1c-f**) contained lesser amounts of isomers **4** and **6**, the dihaloquinolines also included **5** and **7** (eq 2,3).



4 5 (2)



6 7 (3)

The latter two isomers combined always constituted a minor percentage of those product mixtures (7.5-11.7%) and they were usually not further identified. The crude product mixture was analyzed directly by gas liquid chromatography (glc) to obtain isomer ratios and was then chromatographed on a column of alumina. From the purified solids thus obtained the major products were isolated by preparative glc, and the pure compounds were characterized by their proton nuclear magnetic resonance (nmr) and high resolution mass spectra (ms). In passing, it should be noted that the original assignments of structures to **2e** and **3e** were reversed.[4]

Detailed nmr analysis served as the basis for isomer identification of all thirteen dihaloquinolines isolated in this work. Our results concurred with the one known example (**3b**) reported in the literature.[9] In addition to structure confirmation, the spectra of the eight compounds containing a 6-bromo substituent constituted a series from which chemical shift trends could be extracted. For the 6-bromo-5-haloquinolines (**2cdef**) the chemical shifts of protons H-2, H-3, and H-8 were unaffected by the nature of the 5-halo substituent. Proton H-7, however, moved upfield with the increasing electronegativity of the 5-substituent, with the exception of 5-iodo. That case (**2f**) involved the largest halogen and possibly reflected a buttressing effect. The shifts of H-8 moved in a complex pattern, probably indicating a composite of small effects from the 5-substituent; the shift varied by less than 0.15 ppm. The striking feature of the entire series of 5,6-dihaloquinolines was the small variability of the proton shifts.

The proton resonances of the 6-bromo-7-haloquinolines (**3cdef**) showed surprisingly localized influences. For protons H-2, H-3, and H-4 the shifts showed virtually no change. In contrast, both H-5 and H-8 changed significantly with the 7-halo substituent. Fluorine in the 7-position affected H-5 differently than did the other halogens. Proton H-8 (*ortho* to the 7-halo

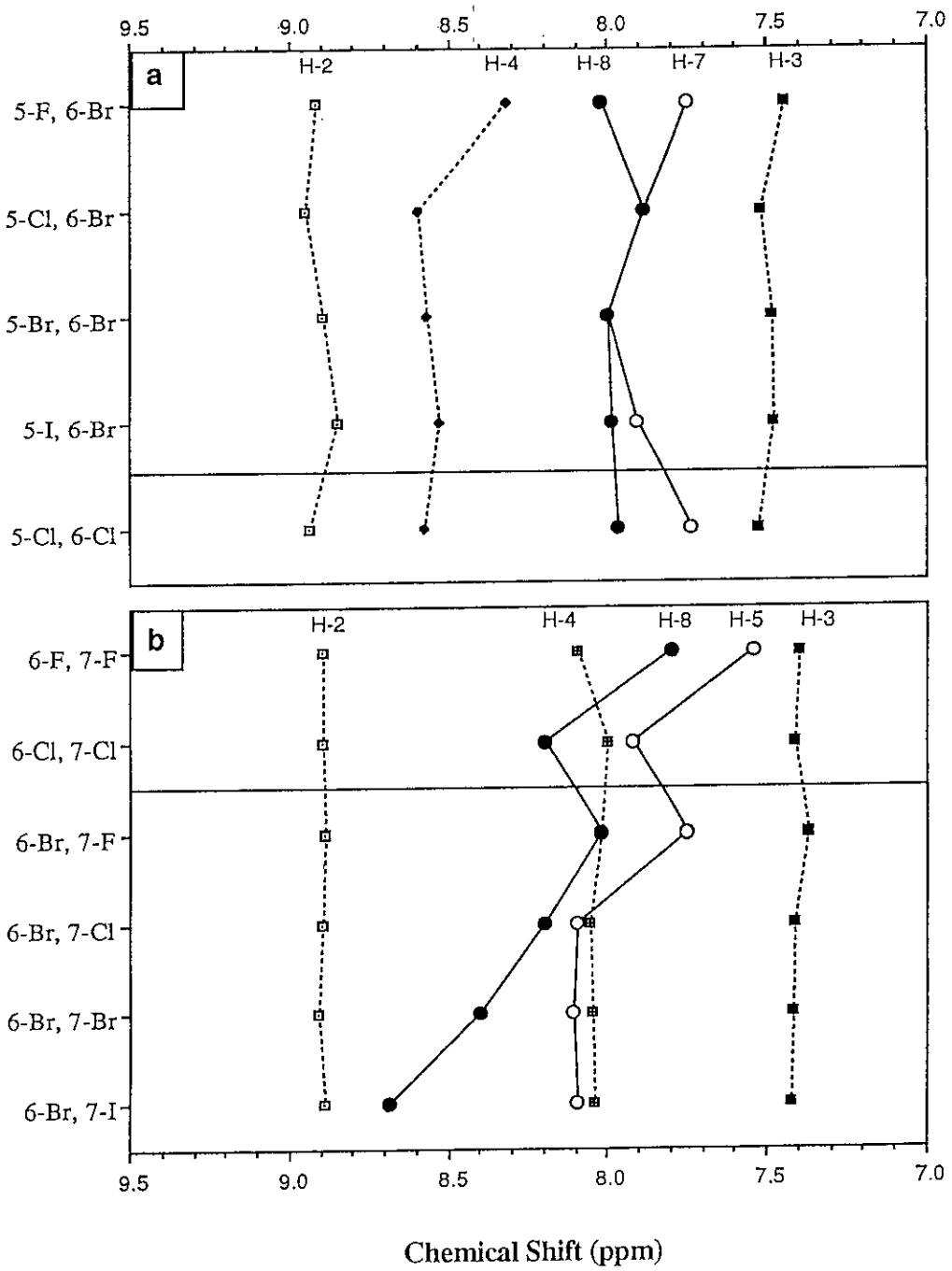


Figure 1. Proton nmr shifts of (a) 5,6-dihaloquinolines **2** and (b) 6,7-dihaloquinolines **3**.

substituent) shifted monotonically downfield as the change from fluorine to iodine occurred. In the **3** series, H-8 chemical shifts varied over 1 ppm and H-5 varied over 0.5 ppm.

Based on empirical relationships reported for the chemical shift effects of halogens on monosubstituted benzenes,[10] we estimate that, in the absence of interactions between substituents (i.e., values can be predicted by summing the effects of the two halogens), the largest changes should correspond to halogen substitutions *ortho* to the observed proton (0.7 ppm for a change of iodine for fluorine). The effects of *meta* substitution should be smaller (0.25 ppm) and those of *para* substitution should be smallest (0.19 ppm, with the effect of halogens other than fluorine nearly negligible). The present results are generally in accord with this simple empirical model. While there are anomolous effects (e.g., **2f**), overall the shifts are surprisingly similar to our predicted values.

The results for the conversion of **1** to **2** and **3** are shown in the Table. From a prior study of the Skraup reaction of 3-substituted anilines it was concluded that resonance effects were the dominant influence on the course of cyclization.[11] Palmer showed, however, that with 3-haloanilines inductive effects were dominant.[3] Both studies established the absence of steric effects. Our results reinforce those of Palmer. The more highly electron-withdrawing the halogen substituents of **1**, the greater is the proportion of **3**. This is most dramatic in the case of **1a**, but the correlation holds for **1c-f** in which the 4-substituent is constant. Steric effects were inconsequential, as demonstrated by the increasing proportion of **2** observed with the increasing size of the 3-substituent in **1**.

Table. Synthesis of dihaloquinolines from 3,4-dihaloanilines (**1**)

1	X	Y	**2** : **3**
a	F	F	< 1 : 99
b	Cl	Cl	54 : 46
c	Br	F	24 : 76
d	Br	Cl	51 : 49
e	Br	Br	59 : 41
f	Br	I	64 : 36

EXPERIMENTAL

Melting points were determined on a modified Hershberg apparatus with matched Anschutz thermometers. Column chromatography was carried out on ICN Alumina N-Super I. Analytical and preparative glc separations were performed on an Aerograph 202-1-B instrument, using a 1/8-inch x 6-ft 10% DC-710 silicone on Chromosorb W 100/120 mesh column (carrier gas: helium at 30 ml/min). ^{1}H Nmr spectra were obtained in deuteriochloroform on an IBM/Bruker WP-200 SY spectrometer; data are reported in δ (ppm) referenced to the chloroform resonance at 7.24 ppm. Mass spectra were determined by Mr. Eric Block at the Massachusetts Institute of Technology Mass Spectrometry Facility (funded by NIH grant RR0037 to Klaus Biemann) with a CEC 110-B high-resolution photoplate spectrometer, using an accelerating voltage of 8 kV, an ionizing voltage of 70 eV, and an ion source temperature of 180 °C. Compounds **1a** and **1b** were obtained from Aldrich; **1c-f** were previously reported mixtures.[8]

General Cyclization Procedure.

To a 50-ml round-bottomed flask, fitted with a stir bar and reflux condenser, containing cold sulfo-mix[6] (18 g, 10 ml) were added glycerol (3.9 g, 40 mmol) and water (6 ml). To the stirred mixture at 130 °C was added **1** (12 mmol), and the mixture was maintained at 120-140 °C for 7 h. The cooled mixture was basified with 25% sodium hydroxide solution (40 ml), diluted with water (20 ml), and the supernatant aqueous phase was transferred to a separatory funnel. Chloroform (3 x 10 ml) was used first to triturate the residual viscous organic phase and then to extract the aqueous phase. The combined chloroform extracts were washed with brine (10 ml) and extracted with 2 N hydrochloric acid (3 x 10 ml). The combined aqueous acidic extracts were basified with 25% sodium hydroxide (8 ml) and extracted with chloroform (3 x 10 ml). The combined chloroform extracts were washed with brine (10 ml), dried over sodium sulfate, and the solvent was removed under reduced pressure to yield a dark solid. The variability of crude yields reflected the ranges previously reported for such cyclizations.[2,6] Glc analysis of the crude reaction mixture established that it contained only unreacted starting material and expected products; the **2:3** ratio was calculated from these data. The crude mixture was chromatographed on alumina (chloroform eluent) to give crystalline product from which the separate isomers were isolated by preparative glc.

Difluoro derivative (entry a).

From **1a** (1.03 g, 8.0 mmol) was obtained crude product (0.87 g, 66%) which exhibited two peaks on glc analysis (column temp. 180 °C), retention time, structure, physical and spectral data: 2.0 minutes, **3a**, mp 111.2-111.9 °C; nmr: δ 8.88 (dd, 1, $J_{2,3}$ = 4.3 Hz, $J_{2,4}$ = 1.4 Hz, H-2), 8.10 (dd, 1, $J_{2,4}$ = 1.4 Hz, $J_{3,4}$ = 8.4 Hz, H-4), 7.84 (dd, 1, $J_{6,8}$ = 7.7 Hz, $J_{7,8}$ = 11.2 Hz, H-8), 7.54 (dd, 1, $J_{5,6}$ = 10.2 Hz, $J_{5,7}$ ≈ 8.4 Hz, H-5), 7.40 (dd, 1, $J_{2,3}$ = 4.3 Hz, $J_{3,4}$ = 8.4 Hz, H-3); ms (m/z): 165.0391 M^+ (calcd for $C_9H_5F_2N$ theoretical mass 165.0390); and 3.0 minutes (trace, unidentified).

Dichloro derivatives (entry b).

From **1b** (1.94 g, 12 mmol) was obtained crude product (2.13 g, 90%) which exhibited two peaks on glc analysis (214 °C): 3.2 minutes, **2b**, mp 84.4-85.1 °C (lit.[5] 82-84 °C); nmr: δ 8.94 (br d, 1, $J_{2,3}$ = *ca.* 3 Hz, H-2), 8.58 (ddd, 1, $J_{2,4}$ = 1.6 Hz, $J_{3,4}$ = 8.6 Hz, $J_{4,8}$ = 0.8 Hz, H-4), 7.97 (dd, 1, $J_{4,8}$ = 0.7 Hz, $J_{7,8}$ = 9.1 Hz, H-8), 7.74 (d, 1, $J_{7,8}$ = 9.1 Hz, H-7), 7.53

(dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.6 Hz, H-3); ms (m/z): 196.9808 M^+ (calcd for $C_9H_5{}^{35}Cl_2N$ 196.9799); and 3.7 minutes, **3b**, mp 131.6-131.9 °C (lit.[3] 132-134 °C); nmr: δ 8.90 (br d, 1, $J_{2,3}$ = *ca.* 4 Hz, H-2), 8.20 (s, 1, H-8), 8.06 (d, 1, $J_{3,4}$ = 8.3 Hz, H-3), 7.92 (s, 1, H-5), 7.41 (dd, 1, $J_{2,3}$ = 4.1 Hz, $J_{3,4}$ = 8.4 Hz, H-3); ms (m/z): 196.9795 M^+ (calcd for $C_9H_5{}^{35}Cl_2N$ 196.9799).

Bromofluoro derivatives (entry c).

From **1c** (2.28 g, 12 mmol) was obtained crude product (1.83 g, 67%) which exhibited four peaks on glc analysis (202 °C): 3.3 minutes, **2c**, nmr: δ 8.92 (br d, 1, $J_{2,3}$ = *ca.* 5 Hz, H-2), 8.32 (dd, 1, $J_{2,4}$ = 1.4 Hz, $J_{3,4}$ = 7.8 Hz, H-4), 8.05-7.99 (m, 1, H-8), 7.78-7.73 (m, 1, H-7), 7.45 (dd, 1, $J_{2,3}$ = 3.8 Hz, $J_{3,4}$ = 7.7 Hz, H-3); 3.7 minutes, **3c**, nmr: δ 8.99 (br d, 1, $J_{2,3}$ = *ca.* 4 Hz, H-2), 8.05-7.99 (m, 2, H-4, H-8), 7.78-7.73 (m, 1, H-5), 7.37 (dd, 1, $J_{2,3}$ = 4.0 Hz, $J_{3,4}$ = 7.9 Hz, H-3); 4.4 minutes, **5c**, mp 81.6-83.0 °C; nmr: δ 9.09 (dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{2,4}$ = 1.6 Hz, H-2), 8.45 (dd, 1, $J_{2,4}$ = 1.6 Hz, $J_{3,4}$ = 8.4 Hz, H-4), 7.98 (dd, 1, $J_{5,7}$ = 5.6 Hz, $J_{6,7}$ = 8.3 Hz, H-7), 7.52 (dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.5 Hz, H-3), 7.13 (t, 1, $J_{5,6} \approx J_{6,7}$ = 8.7 Hz, H-6); and 5.5 minutes, **7c**, nmr: δ 8.84 (dd, 1, $J_{2,3}$ = 4.0 Hz, $J_{2,4}$ = 1.5 Hz, H-2), 8.02 (dd, 1, $J_{2,4}$ = 1.4 Hz, $J_{3,4}$ = 7.4 Hz, H-4), 7.66 (dd, 1, $J_{5,6}$ = 8.1 Hz, $J_{6,7}$ = 5.2 Hz, H-6), 7.34 (dd, 1, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 8.1 Hz, H-3), 7.31 (d, 1, $J_{5,6}$ = 8.1 Hz, H-5). The mixture of **2c** and **3c**, collected as a single sample with mp 105.0-106.2 °C, gave discernible ^1H nmr spectra with the relative peak heights reflecting the 1:3 ratio of the components; mixture ms (m/z): 224.9606 M^+ (calcd for $C_9H_5{}^{79}BrFN$ 224.9589). Fractions **5c** and **7c** combined represented 11.7% of the product mixture.

Bromochloro derivatives (entry d).

From **1d** (2.50 g, 12 mmol) was obtained crude product (1.03 g, 35%) which exhibited four peaks on glc analysis (230 °C): 3.6 minutes, **2d**, mp 84.2-85.8 °C; nmr: δ 8.95 (br s, 1, H-2), 8.60 (d, 1, $J_{3,4}$ = 8.9 Hz, H-4), 7.89 (s, 2, H-7, H-8), 7.52 (dd, 1, $J_{2,3}$ = 4.4 Hz, $J_{3,4}$ = 8.9 Hz, H-3); ms (m/z): 240.9306 M^+ (calcd for $C_9H_5{}^{79}Br{}^{35}ClN$ 240.9294); 4.1 minutes, **3d**, mp 128.0-129.5 °C; nmr: δ 8.91 (br s, 1, H-2), 8.21 (s, 1, H-8), 8.12 (s, 1, H-5), 8.06 (d, 1, $J_{3,4}$ = 8.4 Hz, H-4), 7.41 (dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.4 Hz, H-3); ms (m/z): 240.9312 M^+ (calcd for $C_9H_5{}^{79}Br{}^{35}ClN$ 240.9294); 4.7 minutes and 6.1 minutes, **5d** and **7d** respectively (combined, 10% of product mixture).

Dibromo derivatives (entry e).

From **1e** (3.11 g, 12 mmol) was obtained crude product (0.70 g, 20%) which exhibited four peaks on glc analysis (230 °C): 6.4 minutes, **2e**, mp 75.6-76.6 °C (lit.[5] 77-79 °C); nmr: δ 8.90 (dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{2,4}$ = 1.5 Hz, H-2), 8.57 (ddd, 1, $J_{2,4}$ = 1.6 Hz, $J_{3,4}$ = 8.6 Hz, $J_{4,8}$ = 0.8 Hz, H-4), 8.09-7.84 (m, 2, H-7, H-8), 7.49 (dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.6 Hz, H-3); ms (m/z): 284.8768 M^+ (calcd for $C_9H_5{}^{79}Br_2N$ 284.8789); 7.3 minutes, **3e**, mp 134-136 °C (lit.[4] 135 °C); nmr: δ 8.91 (dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{2,4}$ = 1.6 Hz, H-2), 8.41 (s, 1, H-8), 8.11 (s, 1, H-5), 8.05 (d, 1, $J_{3,4}$ = 8.3 Hz, H-4), 7.43 (dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.3 Hz, H-3); ms (m/z): 284.8776 M^+ (calcd for $C_9H_5{}^{79}Br_2N$ 284.8789); 7.7 minutes and 9.2 minutes, **5e** and **7e** respectively (combined, 7.5% of the product mixture).

Bromoiodo derivatives (entry f).

From **1f** (2.72 g, 9.1 mmol) was obtained crude product (0.90 g, 30%) which exhibited four peaks on glc analysis (230 °C): 9.0 minutes, **2f**, mp 126.4-127.4 °C; nmr: δ 8.85 (d, 1, $J_{2,3}$ = *ca.* 3 Hz, H-2), 8.53 (dd, 1, $J_{2,4}$ = 0.8 Hz, $J_{3,4}$ = 8.5 Hz, H-4), 7.99 (d, 1, $J_{7,8}$ = 8.9 Hz, H-8), 7.91 (d, 1, $J_{7,8}$ = 9.0 Hz, H-7), 7.48 (dd, 1, $J_{2,3}$ = 4.3 Hz, $J_{3,4}$ = 8.4 Hz, H-3); ms (m/z): 332.8643 M^+ (calcd for $C_9H_5{}^{79}Br^{127}IN$ 332.8650); 10.5 minutes, **3f**, mp 164.2-165.2 °C; nmr: δ 8.89 (dd, 1, $J_{2,3}$ = 4.1 Hz, $J_{2,4}$ = 1.4 Hz, H-2), 8.69 (s, 1, H-8), 8.10 (s, 1, H-5), 8.04 (br d, 1, $J_{3,4}$ = *ca.* 7.5 Hz, H-4), 7.43 (dd, 1, $J_{2,3}$ = 4.2 Hz, $J_{3,4}$ = 8.3 Hz, H-3); ms (m/z): 332.8642 M^+ (calcd for $C_9H_5{}^{79}Br^{127}IN$ 332.8650); 11.2 minutes and 13.4 minutes, **5f** and **7f** respectively (combined, 8.4% of the product mixture).

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