The Swamping Catalyst Effect. VI. The Halogenation of Isoquinoline and Quinoline[1]

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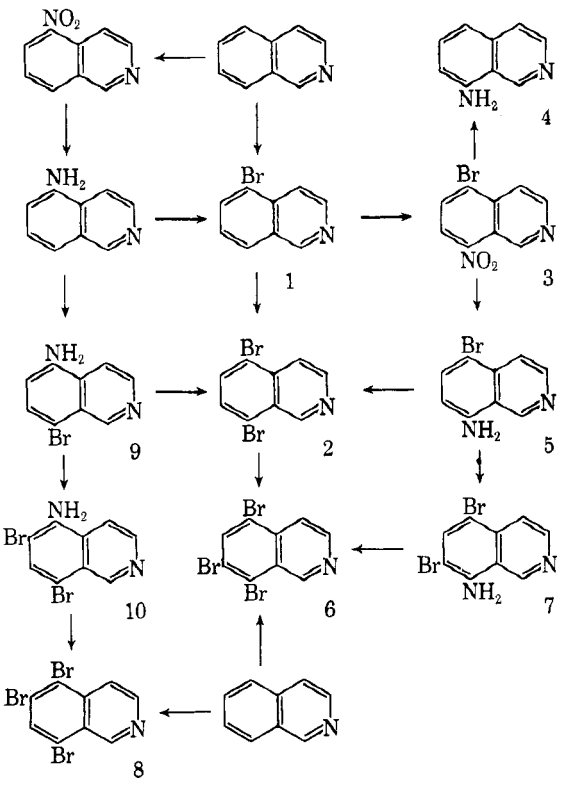
Halogenation of the aluminum chloride complexes of isoquinoline or quinoline gave in good yield halogen derivatives substituted in the benzenoid ring. Bromination of the aluminum chloride–isoquinoline complex gave the following sequence in substitution: 5-bromo-, 5,8-dibromo-, 5,7,8-tribromo-. To obtain good yields of 5,7,8-tribromoisoquinoline, it was necessary to brominate 5,8-dibromoisoquinoline, not isoquinoline itself. Bromination of the aluminum chloride complex of quinoline gave similar results except that 5,6,8-tribromoquinoline was obtained by bromination of 5,8-dibromoquinoline. Chlorination of the aluminum chloride complexes of both quinoline and isoquinoline gave results very similar to bromination. 5,6,7,8-Tetrabromo- and 5,6,7,8-tetrachloroquinoline were isolated also. Identification of many of these compounds was carried out by synthesis from known compounds as shown in the Scheme I.

In a previous communication[3] the complex of pyridine and aluminum chloride was shown to brominate in the 3-position. Only a 50% yield or less was obtained because the hydrogen bromide eliminated formed a new complex, probably $C_5H_5N\overset{+}{H}\cdot\overset{-}{A}lCl_3Br$, which was inert toward substitution. The question then arose whether isoquinoline and quinoline would behave in the same manner. Precedent was established for answering the question concerning the bromination of quinoline. De Le Mare and co-workers[4] had shown that the protonated form of quinoline (as obtained in concentrated sulfuric acid) is brominated by a mixture of silver sulfate and bromine to give 28% 5-bromo-, 29% 8-bromo-, and 43% 5,8-dibromoquinoline (Derbyshire–Waters procedure). A greater proportion of bromine gave higher yields of 5,8-dibromoquinoline and subsequently 5,6,8-tribromoquinoline. Quinoline as the free base, on the other hand, forms a complex with bromine which on heating is transformed to 3-bromoquinoline.[4,5] Eisch has attempted to explain this rather strange orientation.[6]

The aluminum chloride complexes of quinoline and isoquinoline were found to be brominated in a manner very similar to quinoline hydrogen sulfate[4] except that less 8-bromoquinoline was formed, perhaps indicating that the aluminum chloride complexes at the nitrogen atom serves as a hindering agent to 8-substitution. The yields were practically quantitative except for the distribution among mono-, di-, and trihalogenated products. Indeed the problem of selective halogenation became acute enough to warrant the development of a new method of introducing bromine in a diffused state. Dropwise addition led to momentary high concentrations of bromine which gave a spread of mono-, di-, and tribrominated products. The use of gaseous bromine, however, minimized the distribution of products and permitted an acceptable synthesis of a mono-, di-, or tribromoisoquinoline (or quinoline) depending on the amount of gaseous bromine added.

Since De La Mare concentrated on the halogenation of quinoline using the Derbyshire–Waters method, we concentrated on the halogenation of isoquinoline using the swamping catalyst method, leading us to many new compounds which remained to be identified. The sequence of substitution is interesting as shown in the middle column of Scheme I. The first bromine atom

SCHEME I



enters the 5-position, the second the 8-position, and the third predominantly the 7-. The latter compound is 5,7,8-tribromoisoquinoline (**6**). The results of bromination of quinoline are very similar except that bromination of 5,8-dibromoquinoline gave 5,6,8-tribromoquinoline in place of 5,7,8- as was found with isoquinoline. The orientation sequence could be explained as follows: the complex of aluminum chloride with the nitrogen atom deactivates the heterocyclic ring to such an extent that substitution occurs only in

(1) Paper V, D. E. Pearson, W. E. Stamper, and B. R. Suthers, *J. Org. Chem.*, **28**, 3147 (1963).

(2) Abstracted mainly from the Ph.D. thesis of M. G.

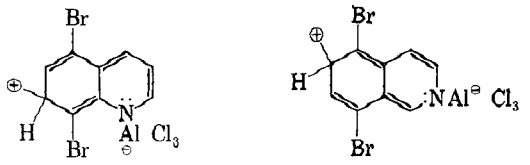
(3) D. E. Pearson, W. W. Hargrove, J. K. T. Chow, and B. R. Suthers, *J. Org. Chem.*, **26**, 789 (1961).

(4) P. B. D. De La Mare, M. Kiamud-din, and J. H. Ridd, *J. Chem. Soc.*, 561 (1960); *Chem. Ind.* (London), 361 (1958).

(5) A. Edinger, *J. prakt. Chem.*, [2] **54**, 357 (1896); E. H. Rodd, "Chemistry of Carbon Compounds," Vol. IVA, Elsevier Publishing Co., New York, N. Y., 1957, p. 654; H. E. Jansen and J. P. Wibaut, *Rec. trav. chim.*, **56**, 699 (1937). The latter authors state that, at 500°, 2-bromoquinoline is formed.

(6) J. J. Eisch, *J. Org. Chem.*, **27**, 1318, 4682 (1962).

the benzenoid ring. The 6- and 8-positions of the quinoline complex are the most deactivated viewing the benzenoid ring as benzene with a deactivated group attached.[7] The 5- should be more active than the 7-position, because it has some of the characteristics of the α-position in naphthalene. Thus, the first bromine atom should enter the 5-position. The second bromine atom should enter the 8-position because the 5-bromo atom controls the point of attack through resonance contributions. The orientation in bromination of the 5,8-dibromo- leading to 5,6,8-tribromoquinoline and of 5,8-dibromo-leading to 5,7,8-tribromoisoquinoline is remarkable insofar as it is predictable from the molecular orbital calculations of Dewar[8] for the protonated forms of quinoline and isoquinoline. These calculations show the 6- more active than the 7-position in quinoline and the reverse for isoquinoline. In terms other than molecular orbital calculations we can say that the orientation suggests that the following canonical forms are important enough contributors to the hybrid to favor 6-substitution for 5,8-dibromoquinoline and 7-substitution for 5,8-dibromoisoquinoline.[9]



The chlorination of the quinoline– and isoquinoline–aluminum chloride complexes followed much the same pattern as bromination except for the less selective action of the chlorinating agent. Indeed, it was reactive enough to form 5,6,7,8-tetrachloroquinoline, a new compound, in good yield on exhaustive chlorination.

Identification of the haloisoquinolines was carried out according to Scheme I, confirmation being obtained by cross references to known compounds as described in the Experimental. Essentially, the proofs of structure depended on the isolation of 5-bromo-8-nitro- and 8-bromo-5-nitroisoquinolines, their conversion to the identical compound, 5,8-dibromoisoquinoline, as a cross reference, and their further conversion to isomeric trihaloisoquinolines. The identification was simplified greatly by the elimination of all structures with halogen in the heterocyclic ring. The three hydrogen atoms in the heterocyclic ring of isoquinoline had very characteristic n.m.r. peaks [H_1 τ 1.05, H_3 (doublet) 1.7, H_4 (doublet) 2.35; $J_{34} = J_{43} = 5$ c.p.s.; the τ-values became uniformly smaller when halogen atoms were attached to the benzenoid ring]. When H_4 in the heterocyclic ring was substituted by bromine (*i.e.*, in 4-bromoisoquinoline), the H_3 doublet was reduced to a singlet (H_1 τ 0.65, H_3 1.3). All haloisoquinolines obtained by the swamping catalyst method retained the characteristic peaks for the unsubstituted heterocyclic ring. The spectra of the haloquinolines showed 12 peaks of a typical ABX grouping for the hydrogen atoms at the 2-, 3-, and 4-position.[10]

(7) The 8-position may be as active as the 5- judging from the results of nitration of quinoline using nitric–sulfuric acids.[8] In this case, the 8-position may be sterically hindered when the nitrogen atom is complexed with aluminum chloride.

(8) M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 2521 (1957).

(9) If substitution occurs through the free base, dissociated from the complex of aluminum chloride and the weakly basic 5,8-dibromoquinoline (or isoquinoline), canonical forms with negative charges at the 6- and 7-positions, respectively, must be invoked.

Experimental[11]

Purity of the Bromoquinolines.—In the bromination of isoquinoline in the presence of aluminum chloride the possibility exists that chlorine may substitute or replace one of the bromine atoms. The possibility is remote because bromine is always the positive end of the dipole moment in any combination with chlorine and because the temperatures are low enough to avoid any exchange. However, to make certain, the haloquinolines obtained by the swamping catalyst method were analyzed by gas chromatography (2-ft. silicon column at 200° with He flow rate of 40 ml./min. using thermal conductivity detector). The retention times were quinoline, 40 sec., 5,6-dichloro, 105 sec., 5-bromo-6-chloro, 165 sec., 5,6-dibromo, 222 sec. As can be noted, the replacement of a bromine atom by a chlorine atom lowers the retention time by at least 60 sec. Less than 1% of 5-bromo-6-chloroquinoline could be detected in a mixture with 5,6-dibromoquinoline. All bromoquinolines examined had single peaks in gas chromatography, and we conclude that chlorine in aluminum chloride does not substitute or exchange for bromine in the bromoquinolines or isoquinolines.

5-Bromoisoquinoline (1).—The apparatus and general procedure previously described[12] was used except that the addition funnel was changed to permit the introduction of gaseous bromine. The bromine was allowed to drip slowly from a separatory funnel into an attached glass tube (10 × 150 mm.), the bottom of which was closed by sintered-glass tip (porosity E, Ace Glass Co.). The sintered-glass tip was positioned just above the surface of the stirred, molten complex. The bromine dripped slowly into the glass tube, diffused as a vapor through the sintered glass, and was absorbed by the complex. The rate of addition was controlled by the rate of bromine dripping from the separatory funnel. The brown complex from 0.42 mole of isoquinoline and 0.85 mole of anhydrous aluminum chloride was brominated over a 4-hr. period at 75° by 0.28 mole of bromine and heated an additional hour after completion of the addition. The almost black, fluid complex was poured carefully on to vigorously hand-stirred cracked ice. The cold mixture was treated with enough concentrated aqueous sodium hydroxide to dissolve all the aluminum salts as sodium aluminate and the oily layer extracted with ether. After being dried with sodium sulfate and concentrated, the ether extract was distilled at 0.3 mm., all fractions boiling below 120° being discarded. The solid distillate (40.6 g.) was recrystallized from pentane to give 1 as white needles, 38 g., 78%, m.p. 79.5–80.5°, lit.[13] m.p. 82–84°.

Anal. Calcd. for C_9H_6NBr: Br, 38.42. Found: Br, 38.16.

The same compound prepared from 5-aminoisoquinoline by the method of Osburn[13] melted at 80–82°. Mixture melting point, infrared spectra, and n.m.r. patterns were identical.

5,8-Dibromoisoquinoline (2).—The bromination was carried out as before except that the second equivalent of bromine was added to the complex maintained at 110° rather than at 75°. The precipitate which resulted from decomposing the complex with water and ice was filtered, washed thoroughly with water, air-dried, and sublimed at 0.1 mm. giving a colorless sublimate, 44 g., 55%, m.p. 110–114°. Considerable 1 remained dissolved in the acidic filtrate. Further purification of 2 was accomplished by countercurrent extraction. Twenty-gram portions of the impure dibromide were dissolved in 200 ml. of benzene and extracted six times with 100-ml. portions of 2.5% by weight of hydrochloric acid, yielding 1.3 g. of impure 5-bromoisoquinoline in the acid fractions. The 6th acid extract contained very

(10) We are indebted to Dr. D. L. Tuleen for obtaining and interpreting these spectra. The spectra were recorded with a Varian Associates, A-60, spectrometer at 60 Mc. per second. Spectra were obtained in methylene chloride solution. Chemical shifts are expressed as shielding values, τ.

(11) All melting points are uncorrected. Analyses were by Galbraith Laboratories. All the di- or trihaloquinolines were isolated simply by filtration of the acidic mixture from aqueous decomposition of the aluminum chloride complexes. The monohaloquinolines were isolated by making the acidic mixtures strongly alkaline. The aluminum chloride used was an anhydrous resublimed grade.

(12) D. E. Pearson, H. W. Pope, and W. W. Hargrove, *Org. Syn.*, **40**, 7 (1960).

(13) A. R. Osburn, K. Schofield, and L. N. Short, *J. Chem. Soc.*, 4191 (1956).

little quinoline. The benzene layer was extracted sixteen times with 5% hydrochloric acid and six times with 10% hydrochloric acid. Compound **2**, 12.2 g., 61%, m.p. 114–115°, was isolated by neutralizing and filtering the 5% hydrochloric acid portions 5 through 12 and the 10% acid portions 3 and 4. Also, the isoquinoline remaining in the benzene layer after all these extractions was pure **2**.

Anal. Calcd. for C_9H_6NBr: Br, 55.7. Found: Br, 55.76.

Identification of 5,8-Dibromoisoquinoline (2).—Ring closures using typical isoquinoline procedures failed. Nitration of **1** by the procedure of Osburn, *et al.*,[13] gave a 96% yield of 5-bromo-8-nitroisoquinoline (**3**) as yellow needles, m.p. 138–140°. The orientation of the groups in **3** was ascertained by simultaneous catalytic hydrogenation and hydrogenolysis to give 8-aminoisoquinoline (**4**). **3** (5 g.) was dissolved in 150 ml. of acetic acid containing ammonium acetate (10 g.) and suspended catalyst (4 g., 5% palladium on calcium carbonate). The mixture was hydrogenated for several hours in the Parr apparatus, filtered to remove catalyst, and made alkaline. The dark precipitate was filtered, air-dried, and sublimed at 140° (0.1 mm.), yielding 1.9 g., 67%, of **4** as yellow crystals, m.p. 170–172°, lit.[14] m.p. 174°.

Compound **3** was reduced to 5-bromo-8-aminoisoquinoline (**5**) without hydrogenolysis by means of 5% palladium on Norit. **3** (4 g.) was dissolved in 100 ml. of glacial acetic acid containing 1 g. of the catalyst. Isolation similar to the previous hydrogenation yielded **5** as yellow crystals, 2.7 g., 77%, m.p. 185–187°.

Anal. Calcd. for $C_9H_7N_2Br$: Br, 35.82; N, 12.56. Found: Br, 35.88; N, 12.41.

Compound **5** (1.0 g.) was converted to crude **2**, m.p. 110–114°, after sublimation, by the Sandmeyer reaction. Recrystallization from acetone gave pure **2** (0.45 g., m.p. 114–115°).

Anal. Calcd. for $C_9H_5NBr_2$: Br, 55.70. Found: Br, 55.57.

The infrared spectrum, melting point, and mixture melting point were identical with 5,8-dibromoisoquinoline obtained by dibromination of isoquinoline.

5,7,8-Tribromoisoquinoline (6).—Tribromination of isoquinoline led to a mixture of **6** and 5,6,8-tribromoisoquinoline (**8**), but monobromination of **2** gave pure **6**. It is recommended that to obtain tribromoquinolines in good yields the monobromination of the dibromoquinolines should be carried out. A complex of **2** (16.5 g., 0.05 mole) and aluminum chloride (23 g., 0.17 mole), prepared by stirring together at 150°, was brominated with bromine vapors (9.2 g., 0.058 mole) over a period of 2 hr. at this temperature. The usual isolation procedure including sublimation yielded crude **6**, m.p. 195–200°. The crude **6** was purified by the countercurrent extraction procedure described previously using a saturated solution of **6** in benzene and omitting the 2.5% hydrochloric acid extraction. Pure **6**, m.p. 200–201°, was obtained in 75% over-all yield.

Anal. Calcd. for $C_9H_4NBr_3$: Br, 65.53. Found: Br, 65.65.

The structure of **6** was ascertained by its synthesis from 5-bromo-8-aminoisoquinoline (**5**). Aluminum chloride (4.6 g., 27 mmoles) and **5** (2 g., 9 mmoles) were complexed at 120° and brominated at 150° with gaseous bromine (0.8 g., 4.5 mmole). The bromine was made the limiting agent to avoid the formation of the $AlCl_3$–6–HBr complex which might not brominate *ortho* to the amino group.[15] The usual isolation procedure including the countercurrent extraction technique yielded 1 g. of **5** and 1.5 g. of a light orange solid, m.p. 285° dec., presumed for the present to be 5,7-dibromo-8-aminoisoquinoline (**7**).

Anal. Calcd. for $C_9H_6N_2Br_2$: Br, 52.92; N, 9.27. Found: Br, 53.05; N, 9.14.

Compound **7** was diazotized in concentrated hydrobromic acid and the diazonium salt treated with freshly prepared cuprous bromide. After standing overnight, the mixture was made basic and the precipitate filtered, air-dried, and sublimed at 1-mm. pressure. The 5,7,8-tribromoquinoline isolated proved to be identical with **6** by mixture melting point and infrared spectrum comparison. The only assumption in this synthesis is that bromination takes place *ortho* to the amino group.

5,6,8-Tribromoisoquinoline (8).—The tribromination of isoquinoline led to a mixture of products which by sublimatography[16] appeared to have roughly the following composition: 16% of **1**, m.p. 78–80°; 34% of **2**, m.p. 112–114°; 6% of **6**; and 6% of an unknown isomer, m.p. 184–186°, suspected to be **8**. This compound was synthesized, therefore, by a known route. 5-Aminoisoquinoline (10 g., 0.074 mole) was mixed with aluminum chloride (29.3 g., 0.22 mole) and heated to 80°. Bromine vapor (5.9 g., 0.037 mole) was added to the stirred mixture. The usual isolation procedure yielded a mixture of 5-aminoisoquinoline and 5-amino-8-bromoisoquinoline (**9**). They were separated by sublimatography[16]; the yield was 5.5 g. of pure **9**, as pale yellow crystals, m.p. 158–160°.

Anal. Calcd. for $C_9H_7N_2Br$: Br, 35.82; N, 12.56. Found: Br, 35.76; N, 12.50.

To confirm the structure of **9**, a small portion was converted by the Sandmeyer reaction to **2**; melting point and mixture melting point with authentic **2**, 114–115°. Pure **9** (5 g., 0.022 mole) and aluminum chloride (9 g., 0.067 mole) were brominated at 125° with bromine vapor (2.0 g., 0.011 mole). The usual isolation together with sublimatography gave 2.6 g. of yellow crystals, m.p. 203–205°, after recrystallization from ethyl acetate. These crystals were 6,8-dibromo-5-aminoisoquinoline (**10**), assuming that the bromine atom was substituted *ortho* to the amino group. Pure **10** (1 g.) was diazotized in 5 ml. of concentrated hydrobromic acid with 0.5 g. of sodium nitrite. The cold diazonium solution was added to approximately 1 g. of freshly prepared cuprous bromide in 10 ml. of hydrobromic acid held at 75°. The cooled mixture was made alkaline and the precipitate filtered and air-dried. Sublimation at 0.1 mm. gave 1.5 g. of white crystals, m.p. 183–185°.

Anal. Calcd. for $C_9H_4NBr_3$: Br, 65.53. Found: Br, 65.32.

The mixture melting point with **8**, obtained from tribromination of isoquinoline, was undepressed and the infrared spectra were identical. Another indication of the structures of **6** and **8** is that all starting materials were known compounds (or related to known compounds) with substituents in the 5- and 8-positions. Therefore, assuming no substitution in the heterocyclic part of the ring which is not likely judging from its deactivation, the third bromine atom could substitute only in the 6- or 7-position. Classical procedures then gave 6-substitution by one route as expected and 7-substitution by the second route as expected. The cross references in synthesis shown in Scheme I strengthen the arguments for the structures of 5,7,8- (**6**) and 5,6,8-tribromoisoquinoline (**8**).

5-Chloroisoquinoline.—The procedure for chlorination has been described.[12] The aluminum chloride–isoquinoline complex was chlorinated at 75° over a period of 14 hr. Fractionation of the crude product gave 15 g., 41%, of recovered isoquinoline, b.p. 57° (0.2 mm.), and 14.2 g. (31%) of 5-chloroisoquinoline as white needles from pentane, m.p. 72–74°, lit.[17] m.p. 73–74°.

Anal. Calcd. for C_9H_6NCl: Cl, 21.67. Found: Cl, 21.65.

Some 5,8-dichloroisoquinoline was found in the residue.

5,8-Dichloroisoquinoline.—Isoquinoline (0.14 mole) was chlorinated with 2 equiv. of chlorine at 90–130° over a period of 12 hr. The precipitate from the complex decomposed with ice and water was filtered, air-dried, and sublimed, yielding 78% crude 5,8-dichloroisoquinoline, m.p. 110–115°. Further purification using the countercurrent extraction technique described and recrystallization from acetone gave colorless crystals, 57% over-all yield, m.p. 115–116°, lit.[18] m.p. 117°.

Anal. Calcd. for $C_9H_5NCl_2$: Cl, 35.80. Found: Cl, 35.36.

Infrared and n.m.r. patterns of this compound and the following chloroisoquinolines were very similar to those of the corresponding bromo compounds.

5,7,8-Trichloroisoquinoline.—The complex of 5,8-dichloroisoquinoline (0.1 mole) and aluminum chloride (0.3 mole) was chlorinated at 145° over a period of 2 hr. The usual isolation followed by recrystallization from isopropyl acetate gave 20 g. (87%), of white needles, m.p. 177–178°.

Anal. Calcd. for $C_9H_4NCl_3$: Cl, 45.75. Found: Cl, 46.02.

Bromination of Quinoline.—The bromination of quinoline was undertaken before the method of introducing bromine vapors had been perfected. Therefore, the products showed a greater distribution of bromine as indicated in Table I.[19] The yields and distribution of products are similar to those of De La Mare and co-workers[10] using sulfuric acid, silver sulfate, and bromine.

(14) R. A. Robinson, *J. Am. Chem. Soc.*, **69**, 1944 (1947).

(15) B. R. Suthers, P. H. Riggins, and D. E. Pearson, *J. Org. Chem.*, **27**, 447 (1962).

(16) H. Sugisawa and K. Aso, *Chem. Ind.* (London), 781 (1961).

(17) R. H. F. Manske and M. Kulka, *Can. J. Research*, **27B**, 161 (1949).

(18) H. Andersag, "Medicine in Its Chemical Aspects," Vol. II, I. G. Farbenindustrie, A. G. Leverkusen, 1934, p. 359. This author gives no experimental details.

(19) We are indebted to Mr. G. W. Senter and Mr. R. Woodberry, Tennessee Agricultural and Industrial State College, Nashville, Tenn., for obtaining the results in Table I. The work was done under the auspices of a National Science Summer Research Grant, 1960.

TABLE I

PER CENT YIELD IN BROMINATION OF QUINOLINE–ALUMINUM CHLORIDE COMPLEX

Bromination process	5-Bromo-[a]	5,6-Dibromo-	5,8-Dibromo-	5,6,8-Tribromo-
Mono-	46	3	8	
Di-		9	62	
Tri-		10	41	9

[a] Appreciable amounts of 8-bromoquinoline were noted.

To demonstrate that the introduction of gaseous bromine gave better selectivity the following two compounds were synthesized.

5,8-Dibromoquinoline.—The complex of quinoline (0.56 mole) and aluminum chloride (1.7 moles) was brominated at 80° with bromine vapor (0.6 mole) for 6 hr. and at 110° with more bromine vapor (0.6 mole). The usual isolation gave 144 g. (86%) of 5,8-dibromoquinoline, m.p. 120–125°. Purification by the countercurrent extraction procedure gave the pure compound, m.p. 126–128°, in approximately 70% yield.

5,6,8-Tribromo- and 5,6,7,8-Tetrabromoquinoline.—The complex of 5,8-dibromoquinoline (0.07 mole) and aluminum chloride (0.21 mole) was brominated at 145° with gaseous bromine (0.08 mole) over a period of 2 hr. The usual isolation procedure gave the crude tribromo compound in 78% yield, m.p. 145–150°. The crude compound was sublimed. Since the compound did not dissolve in benzene, the finely ground crystals were leached with a series of 5% hydrochloric acid solutions, followed by a series of 10% hydrochloric acid solutions. The extracted samples of m.p. 157–159° obtained by neutralization of the acid and filtration were combined. The reported melting point of 5,6,8-tribromo[20] is 159° and of 5,7,8-tribromoquinoline[21] is 141°. The remaining crude product from the extraction was leached with 20% hydrochloric acid and yielded a new compound which was probably 5,6,7,8-tetrabromoquinoline, recrystallized from amyl acetate, m.p. 241–243°.

Anal. Calcd. for $C_9H_3NBr_4$: Br, 71.85. Found: Br, 71.37.

5,6,7,8-Tetrachloroquinoline.—The complex of 5,8-dichloroquinoline (m.p. 97–98°, 0.09 mole, made by the swamping catalyst method) and aluminum chloride (0.27 mole) was chlorinated at 150° with chlorine (0.18 mole) over a period of 4 hr. The usual isolation followed by sublimation gave 22 g. (91%) of white crystals, m.p. 185–187°. The usual absorption band for the three adjacent hydrogen atoms at 12.7 μ was found in the infrared.

Anal. Calcd. for $C_9H_3NCl_4$: Cl, 53.10. Found: Cl, 52.93.

Acknowledgment.—The authors are indebted to the National Science Foundation for a grant in support of this work.

(20) A. Claus, *J. prakt. Chem.*, [2] **53**, 30 (1896).

(21) A. Claus and A. Ammelburg, *ibid.*, [2] **50**, 35 (1894).

Quinazolines and 1,4-Benzodiazepines. XVIII.[1] The Acetylation of Chlordiazepoxide[2] and Its Transformation into 6-Chloro-4-phenyl-2-quinazolinecarboxaldehyde[3]

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Acetylation of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide gave three products, the normal N-acetyl derivative (II), a 3-acetoxy compound (III) produced by rearrangement of the N-oxide, and the diacetyl compound (IV). In acidic medium, 1,4-benzodiazepines bearing an oxygen in position 3 rearranged to the corresponding 2-quinazolinecarboxaldehyde. The structures of these compounds were proved and the general applicability of the reactions is discussed.

A study of the acetylation of chlordiazepoxide[2] (I) led to the discovery that under varying reaction conditions three different products could be obtained, the normal N-acetylated reaction product,[4] described earlier, an isomeric monoacetyl derivative, and a diacetyl derivative, respectively.

Acetylation of I with acetic anhydride in pyridine at room temperature yielded the N-acetylated product (II), while reaction with acetyl chloride in DMF[5] gave an isomeric monoacetyl derivative which has been found to be 3-acetoxy-7-chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine (III), formed by rearrangement of the N-oxide to a compound bearing an oxygen on the adjacent carbon atom. Under more energetic reaction conditions (heating with acetic anhydride, with or without pyridine), the diacetyl compound (IV) was obtained. (See p. 333, col. 1.)

The rearrangement of I to III is analogous to the Polonovski rearrangement of 7-chloro-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one 4-oxide to the corresponding 3-acetoxy compound VI.[6]

Assignment of structures II, III, and IV was readily made on the basis of the characteristic infrared spectra of the three compounds.[7] The absence of any bands in the NH region and the presence of an amide carbonyl band at 1683 cm.$^{-1}$ confirmed the chemical structural proof[4,8] of II, while a strong NH stretching band[9] at 3480 cm.$^{-1}$ and a typical ester carbonyl band at 1758 cm.$^{-1}$ were consistent with the structure postulated for III. The diacetyl derivative (IV) showed both an amide carbonyl band at 1680 cm.$^{-1}$ and an ester carbonyl band at 1758 cm.$^{-1}$.

The structure of the rearrangement products was confirmed by hydrolysis of the diacetyl derivative IV with one equivalent of acid to VI.[6] Hydrolysis of compound IV with 2 moles of alkali at room temperature led to the hydroxy derivative V [ν (cm.$^{-1}$) 3550 (OH), 3440 (NH)]. This compound could be reacetylated to yield compound III.

(1) Paper XVII, R. I. Eryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, in press.

(2) Generic name for 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (Librium(R)).

(3) (a) While this paper was being prepared, an abstract of a paper by S. C. Bell, C. Gochman, and S. J. Childress appeared in Abstracts of Papers, 145th National Meeting of the American Chemical Society, New York, N. Y., September, 1963, p. 37-O, indicating that its contents probably overlap, in part, the material described in this paper. (b) NOTE ADDED IN PROOF.—See S. C. Bell, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **28**, 3010 (1963).

(4) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

(5) DMF is N,N-dimethylformamide.

(6) S. C. Bell and S. J. Childress, *J. Org. Chem.*, **27**, 1691 (1962).

(7) All infrared spectra were determined in 3% solution in chloroform unless otherwise noted.

(8) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 4936 (1961).

(9) Chlordiazepoxide (I) itself shows a weak band in this region (3474 cm.$^{-1}$). The intensity of this absorption band increases with dilution (3% → 0.3%) indicating intermolecular bonding.