Conversion of the Carboxyl Group to the Corresponding Trichloromethyl Group in the Quinoline Series

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Various substituted quinaldinic acids were treated with phosphorus pentachloride in an excess of thionyl chloride. Carboxyl groups of quinaldinic acid, 6-methyl-, 6-chloro-, 4-phenyl- and 4-(*p*-chlorophenyl)quinaldinic acids and benzo[*f*]quinoline-3-carboxylic acid were converted to the trichloromethyl group, while those of 8-methyl-, 4-(3,4-dichlorophenyl)-, 4-(*p*-nitrophenyl)-quinaldinic acids and benzo[*h*]quinoline-2-carboxylic acid were not. The difference is discussed on the basis of the effects of the basicity of ring nitrogen and steric factors.

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In our previous papers (1,2), it has been reported that the carboxyl group attached to the carbon atom α to the unsaturated ring nitrogen of the imidazole and the pyridine systems can be converted to the trichloromethyl group by treatment with phosphorus pentachloride in thionyl chloride, and the reaction mechanism was proposed as in Figure 1.

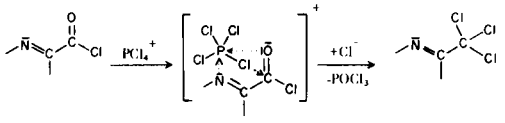


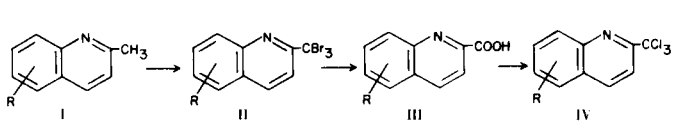
Figure 1

The proposed mechanism suggested that the conversion would be affected by either the basicity of the ring nitrogen or steric factors in the molecule of the substrate. The conversion has been further applied to various substituted picolinic acids, and it was found that the acids successful in this conversion must have a higher basic p*K*a of the unsaturated ring nitrogen than 3.5 and those with a p*K*a value less than 3.5 could be hardly converted (3). However, the steric effect on the conversion has been ambiguous with a series of substituted picolinic acids.

In the present work, the conversion was applied to various substituted quinaldinic acids and, as a result, the effects of steric hindrance and of basicity on the conversion were clarified.

Various substituted quinaldinic acids were prepared and then treated with phosphorus pentachloride (Scheme 1). The convertibility to the corresponding trichloromethyl derivatives is shown in Table I, together with the basic p*K*a value of the ring nitrogen atom as determined potentiometrically.

Scheme 1



Ra = H; b = 6-CH_3; c = 8-CH_3; d = 6-Cl; e = 4-C_6H_5; f = 4-(*p*-ClC_6H_4); g = 4-(3,4-$Cl_2C_6H_3$); h = 4-(*p*-$NO_2C_6H_4$); i = benzo[*f*]; j = benzo[*h*]

(A) Influence of Basicity of Unsaturated Ring Nitrogen.

For the conversion in the series of imidazole- and pyridinecarboxylic acids in the previous paper (3), the p*K*a has been shown to be necessarily higher than about 3.5. Table I shows that also in a series of quinaldinic acids the p*K*a should be higher than about 3.7, although the quantitative interpretation of these limit values cannot be presented until the kinetic studies on the conversion has been completed.

(B) Influence of the Steric Factor.

As seen in Table I, 6-methylquinaldinic acid (p*K*a, 4.74) and benzo[*f*]quinoline-3-carboxylic acid (p*K*a, 4.92) gave the corresponding trichloromethyl derivatives, while their isomers, 8-methylquinaldinic acid (p*K*a, 4.35) and benzo-[*h*]quinoline-2-carboxylic acid (p*K*a, 4.25), failed in spite of sufficient basicity. Such a difference is evidently explainable on the basis of the steric effect of the 8-methyl and benzo[*h*] groups to hinder the formation of the intermediate in Figure 1.

In a comparison of quinaldinic acid with picolinic acid, the hydrogen atom at position 8 in the former must have a steric effect on the conversion to some extent. The quantitative investigation on the effect of the 8-hydrogen atom will be reported in a subsequent paper. However, it may be concluded that substituted quinaldinic acids can

Table I

Basic p*K*a and Convertibility of Substituted Quinaldinic Acids

Quinaldinic acids	p*K*a	Convertibility of -COOH to -CCl_3
IIIa	4.72	○
IIIb	4.74	○
IIIc	4.35	X
IIId	3.96	○
IIIe	4.75	○
IIIf	4.28	○
IIIg	3.61	X
IIIh	2.98	X
IIIi	4.92	○
IIIj	4.25	X

Table III

Reaction Product of Quinaldinic Acids with Phosphorus Pentachloride

Product	M.p. (°C)	Elementary Analysis (%) Found C	H	N	Cl	Calcd. C	H	N	Cl
IVb	88-89	50.44	3.05	5.30	40.94	50.67	3.07	5.37	40.88
IVd	84-85	42.72	1.78	4.86	50.08	42.70	1.78	4.98	50.53
IVe	96-98	59.62	3.11	4.22	33.07	59.53	3.10	4.34	33.02
IVf	117-119	53.81	2.59	3.96	39.95	53.78	2.52	3.92	39.78
IVi	121-122	56.48	2.97	4.89	35.62	56.66	2.70	4.72	35.92

Table II

Compound	M.p. (°C)	Elementary Analysis (%) Found C	H	N	Cl	Br	Calcd. C	H	N	Cl	Br
Substituted Quinaldines											
If	108-110	75.47	4.99	5.58	14.01		75.74	4.73	5.52	14.00	
Ig	96-98	66.95	3.88	4.96	24.39		66.67	3.82	4.86	24.65	
Ih	191-192	72.84	4.41	10.56			72.73	4.55	10.61		
Substituted 2-Tribromomethylquinolines											
IIc	98-100	33.60	1.97	3.36		60.84	33.50	2.03	3.55		60.91
IId	64-65	28.83	1.18	3.36			28.95	1.21	3.38		
IIe	98-99	42.05	2.23	2.85		52.74	42.11	2.19	3.07		52.63
IIf	131-132	39.01	1.72	2.76			39.14	1.83	2.85		
IIg	136-137	36.46	1.24	2.70			36.57	1.52	2.67		
IIh	181-182	38.60	1.74	5.26		47.70	38.32	1.80	5.59		47.90
IIi	153-155	38.88	1.73	3.05		55.59	39.07	1.86	3.26		55.81
IIj	159-160	39.28	1.87	3.04		55.68	39.07	1.86	3.26		55.81
Substituted Quinaldinic Acids (H_2O)											
IIIf	148-150	63.76	3.64	4.34	11.43		63.68	3.98	4.64	11.77	
IIIg	156-157	56.70	2.89	4.07	21.21		57.14	3.27	4.17	21.13	
IIIh	191-193	61.72	3.66	8.84			61.54	3.85	8.97		

also be converted to the corresponding trichloromethylquinolines by treatment with phosphorus pentachloride, if the ring nitrogen atom has sufficient basicity ($pKa > ca.$ 3.7) and if it is not sterically hindered by a bulky group at the 8-position. Consequently, the proposed mechanism is most likely.

EXPERIMENTAL

Melting points and elementary analyses of each compound prepared are summarized in Table II and III. All melting points are uncorrected.

Preparation of the Substituted Quinaldines (I).

Known quinaldines were prepared by the Doebner-Miller method (4). Compounds If, Ig and Ih were prepared from substituted acetophenones, paraldehyde and aniline by the Beyer method (5).

4-(*p*-Chlorophenyl)quinaldine (If).

Compound If was obtained in a yield of 6 g. (24%) from 15.5 g. of *p*-chloroacetophenone; nmr (carbon tetrachloride): δ 2.55 (s, 3H), δ 6.7-7.7 (m, 9H); ir (potassium bromide): 1600 (s), 1485 (s), 1410 (m), 1375 (m), 1190 (m), 1085 (s), 1010 (s), 835 (s), 765 (s) cm^{-1}.

4-(3,4-Dichlorophenyl)quinaldine (Ig).

Compound Ig was obtained in a yield of 2.5 g. (8.7%) from 18.9 g. of 3,4-dichloroacetophenone; nmr (carbon tetrachloride): δ 2.52 (s, 3H), δ 6.6-7.6 (m, 8H); ir (potassium bromide): 1600 (m), 1465 (s), 1400 (m), 1365 (m), 1130 (m), 1030 (m), 820 (m), 770 (s), 760 (s) cm^{-1}.

4-(*p*-Nitrophenyl)quinaldine (Ih).

Compound Ih was obtained in a yield of 7 g. (26.5%) from 16.5 g. of *p*-nitroacetophenone; nmr (deuteriochloroform): δ 2.65 (s, 3H), δ 6.8-7.9 (m, 9H); ir (potassium bromide): 1590 (s), 1510 (s), 1350 (s), 1195 (m), 1105 (m), 860 (s), 830 (s), 765 (s) cm^{-1}.

Preparation of Substituted 2-Tribromomethylquinolines (II).

6-Methylquinaldine (Ib), 1.57 g. (0.01 mole), was dissolved in 10 ml. of acetic acid containing 3 g. of anhydrous sodium acetate and one ml. of acetic anhydride at 70-80°. Bromine (1.6 ml.) in 7

ml. of acetic acid was added dropwise into the solution and the mixture was kept at 70-80° with stirring for 5 hours. Then the reaction mixture was concentrated to dryness, and the resulting residue was washed with aqueous sodium carbonate and extracted with benzene. After drying over anhydrous sodium sulfate, the benzene was distilled, yielding the crude solid, which was recrystallized from *n*-hexane to give 2-tribromomethyl-6-methylquinoline (IIb), yield 1.62 g. (41%), m.p. 129-130° (lit. (6) 132-133°); ir (potassium bromide): 1585 (m), 1485 (m), 1370 (m), 970 (m), 885 (m), 830 (s), 730 (s), 715 (s) cm^{-1}.

Compounds IIc, IId, IIe, IIf, IIg, IIh, IIi and IIj were prepared by a similar method.

2-Tribromomethyl-8-methylquinoline (IIc).

This compound was obtained in a yield of 25 g. (63.5%) from 15.7 g. of Ic; ir (potassium bromide): 1590 (m), 1570 (m), 1495 (m), 1075 (m), 930 (m), 865 (m), 835 (s), 765 (s), 740 (s), 720 (s) cm^{-1}.

2-Tribromomethyl-6-chloroquinoline (IId).

This compound was obtained in a yield of 2 g. (51.9%) from 1.65 g. of Id; ir (potassium bromide): 1580 (m), 1490 (s), 1380 (m), 1295 (m), 1075 (m), 960 (m), 875 (m), 825 (s), 725 (s), 710 (s) cm^{-1}.

2-Tribromomethyl-4-phenylquinoline (IIe).

This compound was obtained in a yield of 2.05 g. (81.7%) from 1.2 g. of Ie; ir (potassium bromide): 1585 (m), 1575 (m), 1485 (m), 1440 (m), 1410 (m), 1025 (m), 920 (m), 870 (m), 770 (s), 730 (s), 720 (s), 695 (m) cm^{-1}.

2-Tribromomethyl-4-(*p*-chlorophenyl)quinoline (IIf).

This compound was obtained in a yield of 3.82 g. (77.9%) from 2.54 g. of If; ir (potassium bromide): 1590 (m), 1575 (m), 1485 (s), 1410 (m), 1085 (m), 1010 (m), 920 (m), 875 (m), 830 (m), 820 (m), 770 (s), 735 (s), 725 (s) cm^{-1}.

2-Tribromomethyl-4-(3,4-dichlorophenyl)quinoline (IIg).

This compound was obtained in a yield of 1 g. (78.4%) from 0.7 g. of Ig; ir (potassium bromide): 1580 (m), 1540 (m), 1470 (s), 1410 (m), 1125 (m), 1030 (m), 940 (m), 830 (s), 785 (m), 765 (s), 720 (s) cm^{-1}.

2-Tribromomethyl-4-(*p*-nitrophenyl)quinoline (IIh).

This compound was obtained in a yield of 1 g. (79.8%) from 0.66 g. of Ih; ir (potassium bromide): 1600 (m), 1575 (m), 1510 (s), 1340 (s), 1100 (m), 935 (m), 860 (s), 800 (s), 775 (s), 700 (m) cm^{-1}.

3-Tribromomethylbenzo[*f*]quinoline (IIi).

This compound was obtained in a yield of 1.3 g. (58.3%) from 1 g. of Ii; ir (potassium bromide): 1600 (m), 1584 (m), 1485 (m), 1450 (m), 1405 (m), 1250 (m), 990 (m), 955 (m), 840 (s), 800 (s), 775 (s), 700 (m) cm^{-1}.

2-Tribromomethylbenzo[*h*]quinoline (IIj).

This compound was obtained in a yield of 1.7 g. (38.2%) from 2 g. of Ij; ir (potassium bromide): 1590 (m), 1500 (m), 1390 (s), 1340 (m), 1235 (m), 960 (m), 840 (s), 800 (s), 750 (s), 730 (s), 690 (s) cm^{-1}.

Preparation of Substituted Quinaldinic Acids (III).

2-Tribromomethyl-6-methylquinoline (IIb), 3.94 g. (0.01 mole), was hydrolyzed with 100 ml. of concentrated hydrochloric acid under reflux for 3 days. The reaction mixture was concentrated to dryness, and the residual solid was recrystallized from water to give 6-methylquinaldinic acid (IIIb), yield 0.75 g. (40.1%), m.p. 200° dec., (lit. (7) 204°); ir (potassium bromide): 1950 (broad), 1695 (s), 1640 (s), 1625 (s), 1585 (s), 1490 (m), 1385 (s), 1360 (s), 1310 (s), 1285 (s), 1265 (m), 1230 (m), 1145 (s), 995 (m), 830 (m), 820 (m), 800 (m), 795 (m), 775 (m), 755 (m), 745 (m), 705 (s) cm^{-1}.

Compounds IIIc, IIId, IIIe, IIIf, IIIg, IIIh, IIIi and IIIj were prepared by a similar method.

8-Methylquinaldinic Acid (IIIc).

This compound was obtained in a yield of 4.2 g. (84.3%) from 10.5 g. of IIc, m.p. 127-128° (lit. (8) 132°); ir (potassium bromide): 1700 (s), 1470 (s), 1440 (m), 1410 (m), 1380 (m), 1325 (m), 1300 (s), 1210 (m), 1200 (m), 1145 (s), 910 (broad), 850 (s), 770 (s) cm^{-1}.

6-Chloroquinaldinic Acid (IIId).

This compound was obtained in a yield of 0.4 g. (53.3%) from 1.5 g. of IId, m.p. 224-225° (lit. (9) 228°); ir (potassium bromide): 1950 (broad), 1690 (s), 1640 (s), 1615 (s), 1580 (s), 1470 (s), 1380 (s), 1360 (s), 1315 (s), 1280 (m), 1260 (m), 1240 (m), 1205 (m), 1145 (m), 985 (m), 955 (m), 900 (m), 865 (m), 830 (m), 820 (m), 790 (m), 750 (m) cm^{-1}.

4-Phenylquinaldinic Acid (IIIe).

This compound was obtained in a yield of 0.15 g. (30%) from 0.19 g. of IIe, m.p. 167-168° (lit. (10) 171°); ir (potassium bromide): 1720 (broad), 1590 (s), 1510 (m), 1495 (m), 1460 (m), 1385 (broad), 1225 (broad), 895 (m), 770 (s), 765 (s), 705 (s) cm^{-1}.

4-(*p*-Chlorophenyl)quinaldinic Acid Hydrate (IIIf).

This compound was obtained in a yield of 0.2 g. (33%) from 1 g. of IIf; ir (potassium bromide): 1720 (broad), 1650 (s), 1620 (m), 1595 (s), 1510 (m), 1490 (m), 1460 (m), 1395 (s), 1365 (s), 1335 (m), 1225 (m), 1085 (m), 1010 (m), 765 (m) cm^{-1}.

4-(3,4-Dichlorophenyl)quinaldinic Acid Hydrate (IIIg).

This compound was obtained in a yield of 0.2 g. (31.3%) from 1 g. of IIg; ir (potassium bromide): 1770 (s), 1590 (m), 1470 (m), 1385 (s), 1340 (m), 1310 (m), 1135 (m), 1030 (m), 910 (m), 825 (m), 775 (s) cm^{-1}.

4-(*p*-Nitrophenyl)quinaldinic Acid Hydrate (IIIh).

This compound was obtained in a yield of 0.1 g. (32.1%) from 0.5 g. of IIh; ir (potassium bromide): 1710 (broad), 1595 (m), 1510 (s), 1455 (m), 1345 (s), 1130 (m), 1100 (m), 855 (m), 830 (m), 765 (m), 700 (m) cm^{-1}.

Benzo[*f*]quinoline-3-carboxylic Acid (IIIi).

This compound was obtained in a yield (acetic acid) of 0.17 g. (25.5%) from 1.3 g. of IIi, m.p. 185-186° (lit. (11) 187°); ir (potassium bromide): 1950 (broad), 1655 (s), 1615 (s), 1590 (m), 1380 (s), 1340 (s), 980 (m), 830 (m), 810 (m), 775 (m), 750 (m) cm^{-1}.

Benzo[*h*]quinoline-2-carboxylic Acid Hydrate (IIIj).

This compound was obtained in a yield of 0.2 g. (23.8%) from 1.5 g. of IIj, m.p. 180-181° (lit. (12), 182-183°); ir (potassium bromide): 1765 (s), 1680 (s), 1500 (m), 1430 (m), 1395 (m), 1355 (m), 1320 (m), 1270 (m), 1150 (m), 850 (m), 740 (m), 710 (m) cm^{-1}.

Reaction of Substituted Quinaldinic Acid with Phosphorus Pentachloride.

Quinaldinic acid (IIIa), 500 mg. (2.9 mmoles), and phosphorus

pentachloride, 1.8 g. (8.7 mmoles), in 20 ml. of thionyl chloride were heated under reflux for 40 hours. The reaction mixture was concentrated to give a solid, into which ice cubes and sodium carbonate were added. The mixture was then extracted with chloroform and the solvent layer was dried over anhydrous sodium sulfate and concentrated to dryness. The residue was passed through silica gel column using *n*-hexane as a solvent, and then the elute was evaporated to dryness, yielding the solid, which was recrystallized from *n*-hexane to give 400 mg. (69%) of 2-trichloromethylquinoline (IVa), m.p. 54° (lit. (13) 56°); ir (potassium bromide): 1595 (m), 1565 (m), 1505 (m), 1425 (m), 1300 (m), 965 (m), 915 (m), 825 (s), 790 (s), 780 (s), 770 (s) cm^{-1}.

Compounds IVb, IVd, IVe, IVf and IVi were obtained in a similar method.

2-Trichloromethyl-6-methylquinoline (IVb).

This compound was obtained in a yield of 570 mg. (81.8%) from 500 mg. of IIIb; ir (potassium bromide): 1590 (m), 1555 (m), 1495 (m), 1375 (m), 1300 (m), 1220 (m), 1120 (m), 970 (m), 965 (m), 935 (m), 885 (m), 860 (s), 830 (s), 825 (s), 810 (s), 790 (s), 760 (s), 750 (s), 710 (s) cm^{-1}.

2-Trichloromethyl-6-chloroquinoline (IVd).

This compound was obtained in a yield of 110 mg. (24.5%) from 300 mg. of IIId; ir (potassium bromide): 1590 (m), 1490 (m), 1380 (m), 1300 (m), 1185 (m), 1070 (m), 970 (m), 885 (m), 835 (s), 820 (s), 790 (s), 755 (s) cm^{-1}.

2-Trichloromethyl-4-phenylquinoline (IVe).

This compound was obtained in a yield of 69 mg. (40%) from 123 mg. of IIIe; ir (potassium bromide): 1585 (m), 1570 (m), 1490 (m), 1440 (m), 1410 (m), 1255 (m), 930 (m), 855 (m), 810 (s), 790 (s), 770 (s), 760 (s) cm^{-1}.

2-Trichloromethyl-4-(*p*-chlorophenyl)quinoline (IVf).

This compound was obtained in a yield of 6.5 mg. (5.5%) from 100 mg. of IIIf; ir (potassium bromide): 1595 (m), 1580 (m), 1480 (s), 1410 (m), 1375 (m), 1250 (m), 1080 (m), 1010 (m), 930 (m), 855 (m), 825 (s), 805 (s), 790 (s), 770 (s) cm^{-1}.

3-Trichloromethylbenzo[*f*]quinoline (IVi).

This compound was obtained in a yield of 10 mg. (4.4%) from 170 mg. of IIIi; ir (potassium bromide): 1600 (m), 1490 (m), 1455 (m), 1410 (m), 1260 (m), 965 (m), 870 (m), 845 (m), 835 (s), 820 (s), 810 (s), 770 (s), 755 (s), 720 (m) cm^{-1}.

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