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The Preparation of 3-Halo-4-dialkylaminoalkylaminoquinoline Derivatives

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The present paper deals with the synthesis of several 3-halo-4-aminoquinoline derivatives as part of a general study[1,2] on the effect of the position of halogen atom substituents on the antimalarial action of 4-dialkylaminoalkylaminoquinoline compounds. Of all the compounds studied thus far, only the 7-halo derivatives show marked antimalarial activity. It has now been found that the introduction of a second halogen atom in the 3-position of the quinoline nucleus as well as in the benzene ring[2] results in a decrease of activity.

It seemed desirable to prepare the 3-halo derivatives in the present series from intermediates now available in large quantities. This proved to be possible, for, when ethyl 4-hydroxyquinaldate and ethyl 5-(and 7)-chloro-4-hydroxyquinaldates were treated in glacial acetic acid with sulfuryl chloride,[3] bromine[4,5] or iodine monochloride, the 3-chloro, 3-bromo and 3-iodo derivatives, respectively, were obtained in practically quantitative yields (Table I). A trace of iodine as a catalyst was used in the chlorinations and brominations. The 3-iodo-4-hydroxyquinoline derivatives were also prepared by direct iodination with iodine monochloride of the corresponding 4-hydroxyquinolines. This obviated the decarboxylation of the 3-iodoquinaldic acids, in which some iodine was always lost.

The value of iodine monochloride in halogenations has been demonstrated previously with 8-hydroxyquinoline,[6] where the 5-iodo and 5,7-diiodo derivatives were obtained; also with 4-hydroxyquinoline,[7] to yield a monoiodo compound of undetermined structure. In view of the present work it would seem that the latter compound was an impure sample of 3-iodo-4-hydroxyquinoline. The use of sulfuryl chloride in quinoline chemistry appears to have been limited mostly to the chlorination of N-oxides to yield the 2- and 4-chloro derivatives.[8] Recently, however, sulfuryl chloride has been used in the chlorination of 6-methoxy-8-nitroquinoline to yield a mixture of polychlorinated quinoline derivatives.[9]

In most instances, the proof of structure of the halogenated compounds was accomplished by permanganate oxidation of the 3-halo-4-hydroxyquinaldic acids to the corresponding 2-carboxyoxyanilic acids, followed by hydrolysis[10] to give either anthranilic acid, 4-chloroanthranilic acid or *m*-chloroaniline.[11] The last was obtained only from the 5-chloro compounds. Apparently the 6-chloroanthranilic acid, which is formed from the corresponding oxanilic acid, is decarboxylated under the conditions of the hydrolysis.

The structure of 4-hydroxy-3-iodoquinaldic acid could not be proved by the above procedure. Here a considerable amount of iodine was liberated upon acidification of its oxidation product. At this point iodination of the oxanilic acid derivative must have occurred since only an iodinated product was isolated on hydrolysis which was not identified. This difficulty was not encountered with the corresponding 5- and 7-chloro-3-iodo compounds.

The structure of 3-bromo-4-hydroxyquinoline was further substantiated by the identity of its melting point with the compound reported by Niementowski and Sucharda.[12,12a] They prepared this compound by treatment of 3-carbamyl-4-hydroxyquinaldic acid with hot potassium hypobromite followed by decarboxylation. Since the 3,4,5- and 3,4,7-trichloroquinolines obtained from the corresponding ethyl 4-hydroxyquinaldates differed from the 4-chloro-bz-dichloroquinolines already prepared,[2] no further proof of structure was undertaken.

The ethyl 3-halo-4-hydroxyquinaldate derivatives (Table II) were hydrolyzed to the corresponding acids, the latter decarboxylated in Dowtherm followed by treatment with phosphorus oxychloride[13] to give the 4-chloro-3-halo-Y-quinolines, (Table III, Y = H, 5-Cl or 7-Cl) which were condensed with 4-diethylamino-1-methylbutylamine (Table IV). Considerable decomposition occurred in the condensations of the diamine with the 4-chloro-3-iodo compounds at 180° and no product containing iodine was isolated. The con-

(1) Surrey and Hammer, THIS JOURNAL, **68**, 113 (1946).

(2) Surrey and Hammer, *ibid.*, **68**, 1244 (1946).

(3) Jaffe, *Z. physiol. Chem.*, **7**, 399 (1883), chlorinated kynurenic acid with potassium chlorate and hydrochloric acid and obtained an unidentified tetrachloro derivative.

(4) Knorr, *Ann.*, **236**, 91 (1886), and Chick and Wilsmore, *J. Chem. Soc.*, **97**, 1990 (1910), brominated 2-hydroxy-4-methylquinoline and obtained the 3-bromo compound.

(5) Meyer and Heinmann, *Compt. rend.*, **203**, 264 (1936), prepared 3-bromo-2,4-dihydroxyquinoline in a similar manner.

(6) Glen and Jagemann, *J. prakt. Chem.*, **145**, 257 (1936).

(7) Dittmar, *Ber.*, **18**, 1618 (1885).

(8) Meisenheimer, *ibid.*, **59**, 1848–1853 (1926).

(9) Schultz, Goldberg, Carsch and Ordas, *J. Org. Chem.*, **11**, 170 (1946).

(10) Kretschy, *Monatsh.*, **5**, 16 (1884).

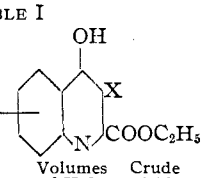
(11) Identified as the benzamide derivative.

(12) Niementowski and Sucharda, *J. prakt. Chem.*, **94**, 225 (1916).

(12a) After the present work had been completed, the preparation of 3-bromo-4-(4-diethylamino-1-methylbutylamino)-quinoline was reported by Riegel, Lappin, Albisetti, Adelson, Dodson, Ginger and Baker, THIS JOURNAL, **68**, 1229 (1946). These authors brominated 4-hydroxyquinoline and obtained 3-bromo-4-hydroxyquinoline. The hydroxyl group was replaced by both chlorine and bromine. They stated that the 3-bromo-4-chloroquinoline was extraordinarily unreactive toward amines in the coupling reaction. They also mention that 3,4-dihaloquinolines are difficult to prepare in quantity. We have found that the present work offers an excellent method for the preparation of 3,4-dihaloquinolines. In addition, 3-bromo-4-(4-diethylamino-1-methylbutylamino)-quinoline was prepared from 3-bromo-4-chloroquinoline without difficulty.

(13) In the preparation of 4,5-dichloro-3-iodoquinoline, some 4,5-dichloroquinoline was also obtained.

TABLE I

PREPARATION OF Y- 

Halogenating agent[a]	Volumes of acetic acid[b]	Temp. of addn.,[c]	Heating time on steam-bath	Volumes of H_2O added[b]	Crude yield, %	M. p., °C.[d]	Product X	Product Y
SO_2Cl_2	3[e]	45	30 min.[f]	5	93	210–213	Cl	H
SO_2Cl_2	6[g]	49	1 hr.	3	88	213–214	Cl	5-Cl
SO_2Cl_2	5[h]	45	30 min.[f]	1	94	230–232	Cl	7-Cl
Br_2	3	70	10 min.	5	95	244–245	Br	H
Br_2	6.5	70	25 min.	3	92	216–218	Br	5-Cl
Br_2	10	70	10 min.	8	94	244–245	Br	7-Cl
ICl	3	70	Heated to 80°[i]	5	94	246–247	I	H
ICl	5	70	Heated to 85°[i]	1	94	213–214	I	5-Cl
ICl	10	70	Heated to 80°[i]	4	90	239–240	I	7-Cl

[a] One mole of bromine and iodine monochloride, 1.1 mole of sulfuryl chloride. [b] All volumes based on the weight of ester used. [c] Where necessary, the ester was heated in the acetic acid to effect solution and then cooled to the desired temperature. [d] Melting points of the dried product directly from the reaction mixture. [e] Includes one-half volume of acetic anhydride. [f] Followed by heating at reflux for 5–10 minutes. [g] Includes one volume of acetic anhydride. [h] Includes one volume of acetic anhydride. At 45° there is incomplete solution. However, after addition of the sulfuryl chloride a clear solution is obtained. [i] Heating above 90° results in considerable discoloration.

densation product (40% yield) from 4-chloro-3-iodoquinoline was distilled to give 4-(4-diethylamino-1-methylbutylamino)-quinoline, that from 4,7-dichloro-3-iodoquinoline, without distillation, gave a 40% yield of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline.[1]

Even at lower temperatures (115–145°) iodine was lost in the condensation of 4-chloro-3-iodoquinoline with 3-diethylamino-2-hydroxypropylamine to give 4-(3-diethylamino-2-hydroxypropylamino)-quinoline. A somewhat analogous reductive dehalogenation was reported recently by Goldberg and Kelly.[14] Treatment of 2-chloro-4-nitrobenzoic acid with *p*-phenylenediamine at 140° gave a quantitative yield of *p*-nitrobenzoic acid. With 2-chloro-3-acetamidobenzoic acid and *p*-phenylenediamine at 140°, reductive dehalogenation also occurred. However, at 100°, the condensation product was obtained in good yield.

In order to further demonstrate the ease of reduction of the iodine in the three position, 4,7-dichloro-3-iodoquinoline was reduced catalytically with palladium-on-charcoal to yield 7-chloroquinoline. The latter was characterized by its picrate which had previously been prepared from the reduction product of 4,7-dichloroquinoline with Raney nickel.

The 4-chloro-3-iodoquinolines were finally converted to the 4-(3-diethylamino-2-hydroxypropylamino)-3-iodoquinoline bases by reaction with 3-diethylamino-2-hydroxypropylamine at temperatures of 115–125° for thirty to ninety minutes. Even under these conditions considerable iodine was lost but the desired iodo bases could be isolated in about 50% yields. The 3-iodo and 7-chloro-3-iodo bases were readily obtained as solids whereas the 5-chloro-3-iodo base remained as a viscous oil even after purification through its diphosphate salt.

(14) Goldberg and Kelly, *J. Chem. Soc.*, 102–111 (1946).

Experimental[15]

Ethyl 3-X-Y-4-hydroxyquinaldate (see Table I).—One mole of the halogenating agent was added to a well-stirred solution of one mole of the ethyl Y-4-hydroxyquinaldate in glacial acetic acid. For the chlorination and bromination, 0.01 mole of iodine was added to the original acetic acid solution. After heating the mixture for varying periods of time, a dilute aqueous sodium hydroxide solution (1 mole) was added, except in the chlorination where Y = H. The solid which separated was filtered off, washed with water and dried. All but the 3,7-dichloro ester were pure enough for use in the next step. The analytical samples were purified by one or more recrystallizations from acetic acid, alcohol or acetone (see Table II).

3-X-Y-4-Hydroxyquinaldic Acid.—One mole of ethyl 3-X-Y-4-hydroxyquinaldate was dissolved in six times its weight of a 5% sodium hydroxide (2 mole) solution. The solution was heated to boiling and filtered with charcoal. The hot filtrate was acidified with concentrated hydrochloric acid to congo red, and the solid which separated was filtered off, washed with water and dried. The yields were practically quantitative. Samples were purified for analysis by dissolving in sodium bicarbonate solution, filtering with charcoal and reprecipitating with hydrochloric acid (see Table II).

3-X-Y-4-Hydroxyquinoline.—In general, decarboxylation was carried out by heating a well-stirred mixture of one part of the acid in five volumes of Dowtherm. Where Y = H and X = Cl or Br, heating was continued for one hour at 180°; where Y = 7-Cl, and X = Cl or Br, heating was continued for one hour at 220°; where Y = 5-Cl and X = Cl or Br, heating was continued for thirty minutes at 160–70°.

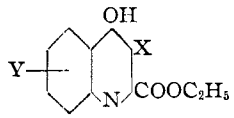
Decarboxylation of the iodo acids was carried out by adding the powdered acid to the hot Dowtherm (180° where Y = H, 160° where Y = 5-Cl, and 190° where Y = 7-Cl), maintaining the temperature for five to eight minutes, followed by rapid cooling.[16]

The product was filtered off from the cooled Dowtherm, washed with ether and dried. The yields were practically quantitative. Samples for analysis were purified by dissolving in hot dilute sodium hydroxide solution, filtering with charcoal and reprecipitating with acetic acid. The

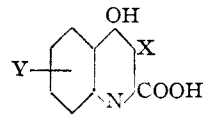
(15) All melting points are uncorrected.

(16) The iodo-hydroxyquinolines were best prepared by direct iodination of the hydroxyquinoline using a procedure similar to that described for the ester. This avoided the decarboxylation which was always accompanied by the liberation of some free iodine.

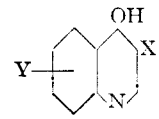
TABLE II



X	Y	M. p., °C.	Analyses, % Calcd.	Found
Cl	H	217–217.5	Cl, 14.09	14.15
Cl	5-Cl	219–220	Cl, 24.78	24.38
			N, 4.90	4.85
Cl	7-Cl	244–245	N, 4.90	4.70
Br	H	250–251	N, 4.73	4.85
Br	5-Cl	222–223	Cl, 10.73	10.84
			Br, 24.17	24.00
Br	7-Cl	244–245	N, 4.24	4.20
I	H	246–247	I, 36.99	36.81
			N, 4.08	4.27
I	5-Cl	217–218	Cl, 9.39	9.35
			I, 33.61	33.12
I	7-Cl	241–242	Cl, 9.39	9.28
			I, 33.61	33.25
			N, 3.71	3.68



M. p., °C.	Analyses, % Calcd.	Found
265–266	Cl, 15.86	16.10
	N, 6.26	6.31
373–375	Cl,[a] 25.69	25.89
	N, 5.07	5.11
381–382	Cl, 27.48	27.43
	N, 5.43	5.53
277–278	Br, 29.82	29.77
	N, 5.23	5.09
358–359	Br,[b] 26.42	26.05
	Cl, 11.72	11.71
355–356	Br,[b] 26.42	25.80
	Cl, 11.72	11.67
	N, 4.63	4.97
278–281	N, 4.44	4.66
302–304	Cl, 10.14	10.10
	I, 36.31	35.57
	N, 4.01	3.86
348–349	Cl, 10.14	10.02
	I, 36.31	36.03
	N, 4.01	3.93



M. p., °C.	Analyses, % Calcd.	Found
267–268	N, 7.80	7.91
378–380	Cl, 33.13	33.05
378–380	N, 6.54	6.55
385–386	N, 6.54	6.59
281–282	N, 6.25	6.31
358–359	Br, 30.91	30.49
	Cl, 13.72	13.79
353–354	C, 41.81	41.53
	H, 1.95	2.19
301–302	N, 5.17	5.22
315–316	Cl, 11.61	11.81
	I, 41.54	41.41
357–358	N, 4.58	4.65

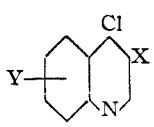
[a] Values calculated for one molecule of water of crystallization. [b] Obtained in the anhydrous form by drying at 125° at 10 mm. for eight hours. Ordinarily contains one molecule of water of crystallization.

products could then be recrystallized from alcohol or acetic acid or vacuum sublimed.

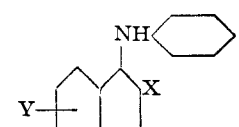
3-X-Y-4-Chloroquinoline.—The hydroxy compound was refluxed in three volumes of phosphorus oxychloride for five to ten minutes or until solution was effected. The iodo compounds, where Y = H and 7-Cl, were refluxed for one-half hour without solution occurring. About one-half of the phosphorus oxychloride was removed by distillation and the residue poured into ice water. The solution was made alkaline to litmus with dilute sodium hydroxide solution, and the precipitate taken up in chloroform. The product obtained after distillation of the chloroform was recrystallized from Skellysolve B or C to give colorless needles in better than 80% yields. The analytical samples were further purified by vacuum sublimation (see Table III).

A lower yield (55%) was obtained in the preparation of 4,5-dichloro-3-iodoquinoline. After refluxing the hydroxy compound with phosphorus oxychloride, the solution was poured into ice water. The solid which separated, was filtered off, taken up in chloroform and purified as above. On making the aqueous filtrate alkaline, more

TABLE III



PICRATE



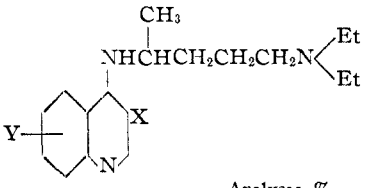
X	Y	M. p., °C.	Nitrogen, % Calcd.	Found	M. p., °C.	Calcd.	Found	M. p., °C.	Calcd.	Found
Cl	H	69–70	7.07	7.03	179–180	13.12	12.87	151–151.5	11.00	10.73
Cl	5-Cl	85–85.5	6.02	6.01	[a]	N, 10.23[b]	10.10	115–116	9.69	9.70
						NO_2, 19.80	19.80			
Cl	7-Cl	114–114.5	6.02	6.13	145.5–146.5	12.14	12.44	149–149.5	9.69	9.95
Br	H	69–70	5.78	5.46	185–185.5	11.88	12.25	136.5–137.5	Br, 26.71	26.70
Br	5-Cl	86.5–87	5.06	4.93	[c]			122–122.5	8.40	8.38
Br	7-Cl	107.5–108	5.06	4.82	143–144.5	11.06	10.48	159–159.5	8.40	8.08
I	H	96–97	4.84	4.83	188–189	10.80	11.30	177.5–178	8.09	8.36
I	5-Cl	110–111	4.32	4.18, 4.31	218[d]	10.13	10.04	146–147	7.36	7.37
I	7-Cl	111–112	4.32	4.12	162–162.5	10.13	10.22	172.5–173	7.36	7.03

[a] Turns brown about 220° and gradually becomes black but fails to melt up to 285°. [b] Calculated for two moles of 3,4,-5-trichloroquinoline to one of picric acid; —NO_2 analysis determined by reduction with titanous chloride. [c] Acts similar to the 3,4,5-trichloro derivative but no satisfactory analysis could be obtained. [d] Turns brown at about 175° and gradually shrinks and darkens till it melts at 218°. The melting point varies somewhat with the rate of heating.

solid precipitated which on purification proved to be 4,5-dichloroquinoline in about 15–20% yield.

3-X-Y-4-Anilinoquinoline.—One-half gram of the 4-chloro compound in 1 ml. of aniline was heated in a test-tube at 150–160° for two to ten minutes. After adding 1 ml. of glacial acetic acid to the cooled solution, the reaction mixture was poured into 100 ml. of water. The oil which separated was rubbed until solidification occurred. The yellow product was recrystallized from benzene.

TABLE IV



X	Y	$n^{26}D$	Analyses, % Calculated C	H	N	Found C	H	N
Cl	H	1.5761	67.58	8.19	13.14	67.27	8.36	12.98
Cl	5-Cl	1.5840	61.01	7.12	11.86	60.99	7.04	11.65
Cl	7-Cl	1.5834	61.01	7.12	11.86	60.84	6.90	11.88
Br	H	1.5865	59.34	7.19	11.54	59.00	6.71	11.81
Br	5-Cl	1.5960	54.21	6.32	10.54	54.41	6.30	10.35
Br	7-Cl	1.5921	54.21	6.32	10.54	54.65	6.57	10.93
I[a]	H[b]	1.6410	48.12	5.55	10.53	48.42	5.61	10.43
I[a]	5-Cl[c]	1.6450	44.30	4.88	9.69	44.90	4.80	10.43
I[a]	7-Cl[d]	1.6474	44.30	4.88	9.69	44.44	4.82	9.62

[a] The 3-iodo compounds were condensed with 3-diethylamino-2-hydroxypropylamine. [b] The product was obtained as a pale yellow crystalline powder, m. p., 79.5–80.5°. The diphosphate is a white powder melting at 160–161° (dec.). Calcd. for $C_{16}H_{22}IN_3O \cdot 2H_3PO_4$: H_3PO_4, 32.92; N, 7.06. Found: H_3PO_4, 33.56; N, 6.78. [c] Obtained only as a yellow-orange, viscous oil. The diphosphate was obtained as a white powder melting at 144–146° (dec.) with browning at about 139°. Calcd. for $C_{16}H_{21}ClIN_3O \cdot 2H_3PO_4$: H_3PO_4, 31.12; N, 6.67. Found: H_3PO_4, 31.11; N, 6.56. [d] A pale cream-colored crystalline powder, m. p., 81.5–82.5°. The diphosphate forms white rosets, m. p., 188° (dec.). Calcd. for $C_{16}H_{21}ClIN_3O \cdot 2H_3PO_4$: H_3PO_4, 31.12; N, 6.67. Found: H_3PO_4, 31.08; N, 6.48.

3-X-Y-4-(4-Diethylamino-1-methylbutylamino)-quinoline.—A stirred mixture of one mole of 3-X-Y-4-chloroquinoline and 2 moles of 4-diethylamino-1-methylbutylamine was heated for five to ten hours at 160–170° where X = Cl and Br and Y = H and 7-Cl. Where X = Cl and Br and Y = 5-Cl, heating for one hour at 150° was sufficient. The reaction was assumed to be complete when a sample of the reaction mixture dissolved in acetic acid did not give a precipitate on dilution with water. The reaction mixture was dissolved in 20% acetic acid, filtered with charcoal and the filtrate made alkaline with 35% sodium hydroxide solution. The oil which separated was extracted with ether and the combined ether was washed several times with water and then dried over anhydrous potassium carbonate. After removing the ether by distillation, the residue (80–85% yield) was distilled at about 0.1 micron to give a light-yellow colored viscous oil. No true boiling points were determined. The chloro compounds distilled near 125°, the bromo compounds near 150°. Where X = I and Y = H, the product obtained after distillation was 4-(4-diethylamino-1-methylbutylamino)-quinoline, m. p., 75–77°.[17] Where X = I and Y = 7-Cl, a 40% yield of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline[1] was obtained without distillation.

Condensation of 4-chloro-3-iodoquinoline with 2-diethylamino-2-hydroxypropylamine at 115–145° for two hours likewise resulted in the loss of iodine giving a 42% yield of 4-(3-diethylamino-2-hydroxypropylamino)-quinoline; m. p., 123–123.5°.

Anal. Calcd. for $C_{16}H_{23}N_3O$: C, 70.29; H, 8.48; N, 15.37. Found: C, 70.06; H, 8.76; N, 15.30.

Reduction of 4,7-Dichloro-3-iodoquinoline.—The 4,7-dichloro-3-iodoquinoline (1.61 g.) in alcohol was catalytically reduced with palladium-on-charcoal in the presence of 3 g. of fused sodium acetate at room temperature. The picrate of the resulting oil was identified by direct comparison with the picrate of 7-chloroquinoline prepared below.

7-Chloro-4-quinolinehydrazine.—Ten grams of 4,7-dichloroquinoline and 10 g. of hydrazine hydrate in 50 cc. of absolute alcohol was refluxed on the steam-bath for eight hours. After diluting with water, the solid was filtered off, yield 8 g., m. p., 214–216°, and recrystallized from dilute alcohol; m. p., 220–221°.

Anal. Calcd. for $C_9H_8N_3Cl$: N, 21.7. Found: N, 22.2.

7-Chloroquinoline.—To a stirred suspension of 8 g. of the crude hydrazine in 60 cc. of boiling water was added dropwise, a 10% solution of copper sulfate, until a definite blue-green color remained in the reaction mixture. The copper oxide was filtered off, the filtrate made strongly alkaline with ammonium hydroxide and extracted with ether. After removal of the ether, the residue was steam distilled and the distillate extracted with ether to give 4.4 g. of the monochloroquinoline. The picrate melted at 219–221°.

Anal. Calcd. for $C_{15}H_9ClN_4O$: N, 14.30. Found: N, 14.12.

3-Iodo-Y-4-(3-diethylamino-2-hydroxypropylamino)-quinoline.—A stirred mixture of one mole of 3-iodo-Y-4-chloroquinoline and 2 moles of 3-diethylamino-2-hydroxypropylamine was heated cautiously to about 100°. At this point, an exothermal reaction usually occurred. The reaction temperature was allowed to reach 125° at which time external cooling was applied. The temperature was then maintained at about 115° for about fifteen minutes where Y = 5-Cl and ninety minutes where Y = H and 7-Cl. The reaction mixture was dissolved in 20% acetic acid, made alkaline to litmus with aqueous ammonia and any unreacted 4-chloro compound removed by filtration. Ether was added to the filtrate and the latter treated further with dilute ammonia with good stirring. By careful addition of the dilute ammonium hydroxide, the 3-iodo bases were liberated from the aqueous solution and collected in the ether layer. The iodine-free bases, which also formed during the condensations, remained in the aqueous layer due to their greater basicity. The ether layer was washed with water, dried over anhydrous potassium carbonate, and filtered with charcoal to give a pale yellow solution. Evaporation of the ether gave about 40–55% of the crude bases which were purified by means of their diphosphate salts. The solid bases were recrystallized from a mixture of Skellysolve B and benzene.

Proof of Structures.—The 3-X-Y-4-hydroxyquinaldic acids were oxidized with potassium permanganate followed by acid hydrolysis of the oxanilic acids according to reported procedures[10] to yield either anthranilic acid (Y = H), 4-chloroanthranilic acid (Y = 7-Cl), or *m*-chloroaniline (Y = 5-Cl). However, no pure product was obtained where X = I and Y = H. In this instance a considerable amount of iodine was liberated on acidification of the oxidized product. Hydrolysis yielded an iodinated compound which was not identified.

Acknowledgment.—The authors wish to thank Dr. C. M. Suter for valuable suggestions.

Summary

The halogenation of ethyl 4-hydroxy-, ethyl 5-chloro-4-hydroxy- and ethyl 7-chloro-4-hydroxyquinaldate with sulfuryl chloride, bromine and iodine to yield the 3-halo derivatives is described.

(17) The product was identified by direct comparison with a known sample, m. p., 76–77°, prepared in these laboratories by Dr. L. L. Hallock.

By means of hydrolysis, decarboxylation and treatment with phosphorus oxychloride, the ethyl quinaldates were converted to the corresponding 4-chloro-3-halo derivatives which were condensed with 4-diethylamino-1-methylbutylamine. Reductive dehalogenation which occurred in the attempts to condense the 4-chloro-3-iodoquinolines with 4-diethylamino-1-methylbutylamine is reported. These same iodoquinolines were successfully condensed with 3-diethylamino-2-hydroxypropylamine by using lower temperatures.

RENSSELAER, NEW YORK RECEIVED AUGUST 27, 1946

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF TEMPLE UNIVERSITY]

The Synthesis of Certain Substituted 2,2′-Bipyridyls[1]

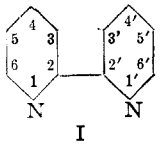
BY FRANCIS H. CASE

The compound 1,10-phenanthroline, in the form of its ferrous complex, has found important use as an indicator in volumetric analysis. Recently Richter and Smith[2] have modified the structure of this compound by the introduction of various substituents in the 5- and 6- positions of the original molecule, and observed corresponding differences in the potentials needed to oxidize the ferrous complexes.

The compound 2,2′-bipyridyl I containing the same grouping, $=N-\overset{\|}{C}-\overset{\|}{C}-N=$ as 1,10-phenanthroline, also forms a deep red-colored complex (ferroin reaction) with ferrous salts and is used extensively as a sensitive qualitative reagent for ferrous iron. As an oxidation–reduction indicator, the ferrous complex has a desirably low oxidation potential but is unfortunately relatively unstable to oxidation.

It was felt that the introduction of various substituent groups in the bipyridyl molecule might provide complexes with higher and lower oxidation potentials than those now available and also possibly increase the stability of the ferrous complex.

Up to the present time practically all substituted 2,2′-bipyridyls have contained the substituent groups either in the 6- or the 6,6′-positions.

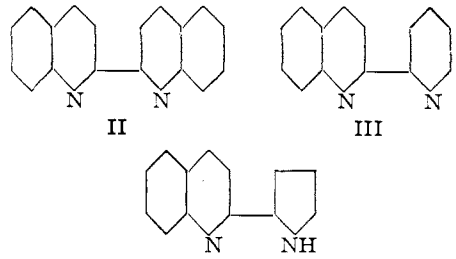


I

These groups include bromo, amino, cyano, carboxyl and methyl. Other bipyridyls substituted in the above positions include such fused ring heterocycles as 2,2′-biquinolyl II, 2-(2′-pyridyl)-quinoline III, and 2-(2′-pyrryl)-quinoline IV.[3]

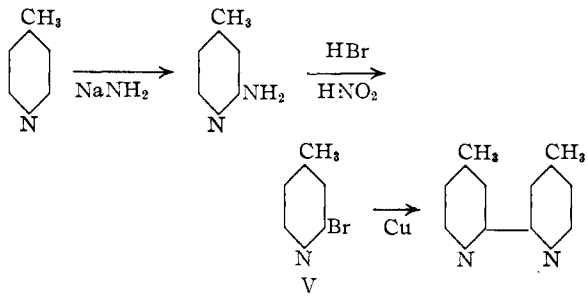
It has been found that in all the above derivatives the power to form colored ferrous complexes is practically lost.

By the bromination of 2,2′-bipyridyl hydrobromide at 250° Burstall[4] obtained mono and dibromobipyridyls which he regarded as 5-bromo and 5,5′-dibromo derivatives, respectively. Proof of structure was lacking. The mono-bromo derivative gave a deep red color with ferrous sulfate, but none was afforded by the di-bromo compound.



In this Laboratory attention has been directed to the synthesis of various substituted 2,2′-bipyridyls other than the 6,6′-derivatives.

When γ-picoline was subjected to the action of anhydrous $FeCl_3$ at 320° (the method used by Hein and Retter[5] to prepare 2,2′-bipyridyl from pyridine) it was converted into 4,4′-dimethyl-2,2′-bipyridyl V. The structure of this product was confirmed by its synthesis according to the scheme



V

β-Picoline, similarly treated with sodamide, yields 2-amino-3-methylpyridine which by a similar process is converted into 3,3′-dimethyl-2,2′-bipyridyl, a high-boiling liquid.

The action of ferric chloride on β-picoline could conceivably lead to the formation of any one of three possible isomers: 3,3′-dimethyl-2,2′-bipyridyl VI, 5,5′-dimethyl-2,2′-bipyridyl VII, or 3,5′-dimethyl-2,2′-bipyridyl VIII.

(1) Presented before the Organic Division at the Atlantic City Meeting of the American Chemical Society, April, 1946.

(2) Richter and Smith, THIS JOURNAL, **66**, 396 (1944).

(3) Smirnoff, *Helv. Chim. Acta*, **4**, 802 (1921).

(4) Burstall, *J. Chem. Soc.*, 1662 (1938).

(5) Hein and Retter, *Ber.*, **61**, 1790 (1928).