ketone with aluminum isopropoxide.[10] To the chilled purple reaction mixture was added 6 ml. of water followed by 6 ml. of concd. hydrochloric acid. After stirring for 30 min. the reddish brown solid was collected, washed thoroughly with water and recrystallized from a large volume of ethanol to give 0.7 g. (73%) of tan needles, m.p. 188°.

Anal. Calcd. for $C_{12}H_{13}BrClNO_2$: C, 45.23; H, 4.11; N, 4.39. Found: C, 44.98; H, 4.02; N, 4.51.

α-Bis(β-hydroxyethyl)aminomethyl-6-methoxy-4-quinolinemethanol dihydrochloride. A mixture of 0.6 g. of the above bromohydrin and 2.8 g. of iminodiethanol was stirred at 50° for 29 hr. After pouring into 15 ml. of water the mixture was extracted with chloroform. To the solid remaining after removal of the chloroform 2.5 ml. of 2*N* hydrochloric acid was added. Removal of the water in a vacuum desiccator left 0.45 g. of residue which was recrystallized from methanol-ether.

α-Bis(β-chloroethyl)aminomethyl-6-methoxy-4-quinolinemethanol hydrochloride. (IV). This was prepared by the general method from the above dihydrochloride. The air-dried product after recrystallization from methanol-ether formed clusters of tiny orange needles. This was a solvated dihydrochloride which lost solvent and one molecule of hydrogen chloride on drying under vacuum at 50°.

α-Bis(β-hydroxyethyl)aminomethyl-8-chloro-2-phenyl-4-quinolinemethanol. A mixture of 4.8 g. of α-bromomethyl-8-chloro-2-phenyl-4-quinoline methanol[8] and 16.0 g. of iminodiethanol was stirred and heated at 75° for 22 hr. and then allowed to stand at room temperature for 4 days. It was then poured into 100 ml. of cold water with stirring. The tan solid was collected and taken up in 100 ml. of hot benzene. After treatment with decolorizing carbon, petroleum ether (b.p. 60–75°) was added to turbidity. On scratching, the substance crystallized.

α-Bis(β-chloroethyl)aminomethyl-8-chloro-2-phenylquinolinemethanol. (V). Prepared by the standard procedure, this formed clusters of small yellow needles from methanol-ether.

α-Bis(β-hydroxyethyl)aminomethyl-2-(4'-chlorophenyl)-4-quinolinemethanol. A mixture of 1.5 g. of α-bromomethyl-2-(4'-chlorophenyl)-4-quinolinemethanol[8] and 5.6 g. of iminodiethanol was stirred and heated at 62° for 23 hr. On pouring into water, the product separated and was recrystallized from absolute ethanol.

α-Bis(β-chloroethyl)aminomethyl-2-(4'-chlorophenyl)-4-quinolinemethanol (VII). Prepared by the standard method this formed a hemihydrate from absolute methanol-ether. It could not be dried without decomposition.

α-Bromomethyl-6,8-dichloro-2-phenyl-4-quinolinemethanol. This was prepared by aluminum isopropoxide reduction of the bromo ketone.[8] A reaction time of 5 hr. was necessary for completion. The substance melted at 145° dec. after recrystallization from a 2:1 mixture of ligroin and dioxane. Reported[8] m.p. 130–131° dec.

Anal. Calcd. for $C_{17}H_{12}BrClNO$: C, 51.41; H, 3.04; N, 3.53. Found: C, 51.65; H, 3.08; N, 3.64.

α-Bis(β-hydroxyethyl)aminomethyl-6,8-dichloro-2-phenyl-4-quinolinemethanol. The above bromohydrin was stirred with a 10-fold excess of iminodiethanol at 100° for 4 days. After pouring into ice water, the crude compound was recrystallized from acetonitrile.

α-Bis(β-chloroethyl(aminomethyl-6,8-dichloro-2-phenyl-4-quinolinemethanol. (VI). This was prepared by the standard procedure. The crude product became slightly gummy on filtration and was dried immediately in a vacuum desiccator before recrystallization from absolute methanol.

2-Hydroxy-4-(2-hydroxyethyl-2-(2-phenyl-4-quinolyl)-morpholine (XIII). To a solution of 48 g. of iminodiethanol in 750 ml. of acetone was added with stirring, 40.8 g. of crude α-bromomethyl-2-phenyl-4-quinolyl ketone hydrobromide. A second liquid phase appeared as the ketone hydrobromide dissolved. After stirring for 30 min. 400 ml. of water was added and the mixture became homogeneous. After refrigeration, the solid was collected and washed successively with aqueous acetone, water and acetone. Recrystallization from 2 l. of acetone gave 17 g. (48%) of short square prisms, m.p. 160–164°. An additional 5.1 g. was obtained from the mother liquor.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 71.98; H, 6.33; N, 8.00. Found: C, 71.95; H, 6.27; N, 8.07.

Hydrochloride of XIII. When XIII was dissolved in 2*N* hydrochloric acid the dihydrochloride separated as colorless crystals with no well-defined melting point. After drying in a desiccator the substance still retained two waters of crystallization.

Anal. Calcd. for $C_{21}H_{24}Cl_2N_2O_3 \cdot 2H_2O$: C, 54.91; H, 6.14; N, 15.44. Found: C, 55.12; H, 6.22; N, 15.31.

When XIII was treated with thionyl chloride in chloroform according to the standard procedure, only the hydrochloride was obtained. Identity was established on the basis of infrared spectra.

Acknowledgment. We wish to acknowledge the valuable assistance of Mr. James Hudson in the preparation of many of the intermediates.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, SETON HALL UNIVERSITY]

Carcinogenic Activity of Analogs of *p*-Dimethylaminoazobenzene. III. The Quinoline Series

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Received December 28, 1960

All of the isomeric *p*-dimethylaminophenylazoquinolines have been prepared as well as the isomeric *p*-dimethylaminophenylazoquinoline *N*-oxides in order to compare their carcinogenic activity. In the latter syntheses it was necessary to prepare the isomeric acetamidoquinoline *N*-oxides and the corresponding aminoquinoline *N*-oxides.

As part of a general project on the relationship of chemical structure to carcinogenic activity, Brown and co-workers[2] have shown that there is a wide range of activity in the three possible isomers of the monopyridine analogs of *p*-dimethylaminoazo-

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(2) E. V. Brown *et al.*, *Cancer Research*, **14**, 22 (1954); **14**, 715 (1954).

TABLE I

THE *p*-DIMETHYLAMINOPHENYLAZOQUINOLINES

Isomers Position	Method Used	Yield, %	M.P.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
2	—	7	151–152	73.89	5.84	73.50	5.92[7]
3	A	68	155.5–156.5	73.89	5.84	73.75	5.85[7]
4	B	50	197.5–199	73.89	5.84	73.98	5.89[7]
5	A	69	156–158	73.89	5.84	74.29	6.00[7]
6	B	71	167–168	73.89	5.84	73.78	5.79[8]
7	A	69	182–184	73.89	5.84	74.10	5.92[8]
8	A	45	122–123	73.89	5.84	73.74	5.72[8]

TABLE II

THE (*p*-DIMETHYLAMINOPHENYLAZO)QUINOLINE *N*-OXIDES

Isomer Position	Method Used	Yield, %	M.P.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
2	B	45	191	69.84	5.52	69.73	5.43[8]
3	A	69	193–194	69.84	5.52	69.77	5.54[7]
4	A	41.3	199–200	69.84	5.52	69.89	5.75[7]
5	A	72.4	197–198	69.84	5.52	69.71	5.60[7]
6	A	73	224	69.84	5.52	69.74	5.47[8]
7	A	71	217–218	69.84	5.52	69.80	5.63[8]
8	B	55	171	69.84	5.52	69.72	5.48[8]

benzene—that is, the *p*-dimethylaminophenylazopyridines. Further variation in activity was observed when the pyridine nitrogen was converted to the *N*-oxide. The interesting results observed in the pyridine series led us to attempt the syntheses of the isomeric *p*-dimethylaminophenylazoquinolines as well as their corresponding *N*-oxides. In this new series we have the interesting possibility of attaching the azo linkage to either pyridine or the benzene rings of the quinoline nucleus and thereby preparing compounds which can be considered pyrido analogs of Butter yellow or benzo analogs of the previously prepared pyridine azo dyes.[2]

In general, the new quinoline azo compounds were prepared by diazotization of the proper aminoquinoline and coupling of the diazonium salt with *N*,*N*-dimethylaniline. However, as 2-aminoquinoline does not diazotize and couple normally, 2-(*p*-dimethylaminophenylazo)quinoline was prepared by the method of Brown and Faessinger.[3] This method involves the reaction of the sodium derivative of the amine with *p*-nitrosodimethylaniline.

The quinoline *N*-oxide azo compounds were also prepared from the available aminoquinolines by acetylation, oxidation of the acetyl compounds with peracetic acid followed by hydrolysis to the aminoquinoline *N*-oxides. These were diazotized and coupled with dimethylaniline. The only exception was 4-aminoquinoline *N*-oxide which was readily prepared by the low pressure hydrogenation of 4-nitroquinoline *N*-oxide.[4]

The azo compounds are listed in Tables I and II and the aminoquinoline *N*-oxides in Table III.

All the compounds listed in the three tables are new. 6-(*p*-Dimethylaminophenylazo)quinoline was reported by Kneuppel,[5] but from his description it is very doubtful that he had this compound.

The results of the biological studies are reported in another place.[6]

EXPERIMENTAL

2-Aminoquinoline was prepared from commercially available 2-chloroquinoline thru 2-hydrazinoquinoline and reduction[9] in an overall yield of 70%.

3-Aminquinoline was obtained from Eastman Kodak. 4-Aminoquinoline was prepared by high pressure hydrogenation of 4-nitroquinoline *N*-oxide.[4]

(3) E. V. Brown and R. W. Faessinger, *J. Am. Chem. Soc.*, **73**, 4606 (1951).

(4) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1953).

(5) C. Kneuppel, *Ann.*, **310**, 87 (1899).

(6) *J. National Cancer Institute*, **26**, 1461 (1961).

(7) These analyses courtesy of the Warner-Chilcott Laboratories, Morris Plains, N. J.

(8) These analyses by Drs. Weiler and Strauss, Analytical Laboratory, Oxford, England.

(9) W. Marckwald and E. Meyer, *Ber.*, **33**, 1894 (1900).

TABLE III

QUINOLINE *N*-OXIDES

Isomer	M.P.	Yield, %	Calcd.		Found		Isomer	M.P.	Yield, %	Calcd.		Found	
			% C	% H	% C	% H				% C	% H	% C	% H
2-Acetamido	199–200	72	65.33	4.98	65.56	5.00[a]	2-Amino	168–169	73	67.48	5.03	67.18	5.10[f]
3-Acetamido	285–286.5	85	65.33	4.98	65.16	5.16[a]	3-Amino	189–190	82	67.48	5.03	67.32	5.07[g]
5-Acetamido	231–232.5	72	65.33	4.98	65.28	5.10[f]	5-Amino	201–202.5	79	67.48	5.03	68.00	5.22[f]
6-Acetamido	203–205	80	65.33	4.98	65.40	5.03[f]	6-Amino	125–127	74	67.48	5.03	67.52	5.17[f]
7-Acetamido	261	79	65.33	4.98	65.28	5.11[f]	7-Amino	240–242	67	67.48	5.03	67.61	5.07[g]
8-Acetamido	191	90	65.33	4.98	65.42	5.00[f]	8-Amino	112	70	67.48	5.03	67.59	5.00[g]

5-, 6-, and 8-Aminoquinolines were prepared by low pressure hydrogenation (palladium-carbon) of the commercially available nitroquinolines.

7-Aminoquinoline was prepared by lower pressure hydrogenation of 7-nitroquinoline prepared by the method of Kneuppel.[10]

2-(p-Dimethylaminophenylazo)quinoline. 2-Aminoquinoline (7.2 g.) and 6.4 g. of naphthalene were dissolved in 75 ml. of dry toluene and to this mixture was added 1.15 g. of clean sodium with stirring under a nitrogen atmosphere. The reaction mixture was refluxed with vigorous stirring until no free sodium was apparent (1.5 hr.). Then 7.5 g. of *p*-nitrosodimethylaniline was added and the mixture refluxed 1 hr. The solvent was removed under vacuum, the residue dissolved in 400 ml. of 25% acetic acid, and filtered. The purple solution was diluted with 1 l. of water and filtered. The filtrate was neutralized with sodium hydroxide solution to precipitate the crude azo compound. This was chromatographed on an alumina column using benzene as the solvent. The low bright orange band after elution was recrystallized from ethyl alcohol to give orange plates which melted at 151–152°. The yield of purified material was 7%.

Diazotization and coupling. Method A. 3-Aminoquinoline (14.4 g.) was dissolved in 100 ml. of water and 50 g. of concd. hydrochloric acid. Seven grams of sodium nitrite was added over a 1-hr. period at −5–0°. Then a mixture of 12 g. of dimethylaniline in 60 ml. of water, 125 ml. of ethanol, and 36 g. of sodium acetate was added keeping the temperature around 0°. After stirring 1 hr. neutralization was completed with dilute ammonium hydroxide, the crude dye was filtered and washed with water.

Method B. 6-Aminoquinoline (11.6 g.) was dissolved by stirring in an ice cold mixture of 20 ml. of concd. nitric acid and 40 ml. of phosphoric acid. Sodium nitrite (5.6 g.) was added keeping the temperature below 0°. Over a period of 1 hr. a solution of 9.6 g. of dimethylaniline, 30 ml. of water, 13.6 g. of sodium acetate, and 70 ml. of ethanol was added keeping the temperature below 0°. After stirring for an additional hour, dilute ammonium hydroxide was added to precipitate the crude dye.

In all cases the dry crude dye was dissolved in benzene and chromatographed on alumina. The eluted azo compound was recrystallized from ethanol to constant melting point.

Oxidation of acetamidoquinoline. In a typical run, 40 g. of 6-acetamidoquinoline was dissolved in 40 ml. of glacial acetic acid and 40 ml. of 40% peracetic acid.[11] The temperature was never allowed to rise above 70°. When the reaction had subsided, another 30 ml. of 40% peracetic acid was added and then the temperature was maintained at 70% for 3 hr. The solvent was removed *in vacuo*, the residue dissolved in ice water and the crude *N*-oxide was precipitated with ammonium hydroxide. The dried crude was recrystallized from ethanol.

Hydrolysis of acetamidoquinoline N-oxide. Twenty grams of acetamidoquinoline *N*-oxide and 120 ml. of 30% sodium hydroxide was refluxed for 5 hr. The reaction mixture was cooled and the crude *N*-oxide was collected and recrystallized from ethanol.

Acknowledgment. This investigation was supported in part by research grant C-2219 from the National Cancer Institute, U. S. Public Health Service.

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(10) C. Kneuppel, *Ber.*, 29, 706 (1896).

(11) We are indebted to Becco Chemical Division, Food Machinery and Chemical Corporation for a generous supply of this material.