A Quinoline N-Oxide Analog of Chloramphenicol[1]

JOHN R. E. HOOVER AND BENJAMIN BLANK

Research and Development Division, Smith Kline and French Laboratories, Philadelphia, Pa.

Received May 7, 1963

The preparation of a quinoline and quinoline N-oxide analog of chloramphenicol in which the 2-dichloroacetamido-1,3-propanediol side chain is attached to the 6-position of the quinoline ring system is described. The DL-*threo* configuration of the side chain on the analogs studied was established by the preparation and comparison of both DL-*threo* and DL-*erythro* derivatives, the assignment of configuration being based on analogy with previously studied systems. The results of *in vitro* and *in vivo* antibacterial and antifungal screening are also presented.

The chemical stability of chloramphenicol,[2] as well as the relative ease with which the 2-amino-1,3-propanediol side chain can be attached to various aromatic systems, has made this antibiotic a popular candidate for modification studies. Although a large number of analogs of chloramphenicol have been prepared and studied in biological systems, specific structural requirements for maximum antibacterial activity have not been fully determined. Comparison of the relative activities of various analogs suggests that optimum microbiological activity may be dependent on the presence of a flat surface (phenyl moiety) with an electron-rich substituent in the *para* position. This substituent may enhance the activity of the molecule by serving as a point of attachment to an enzyme surface or similar biological system.[3,4]

On the basis of this premise, we have examined analogs with substituents of high electron density in the *para* position. This paper reports the preparation of 2-dichloroacetamido-1-(6-quinolyl N-oxide)-1,3-propanediol (XI), a structure with the electron-rich N-oxide moiety in the quinoline nucleus.

Quinoline-6-carboxylic acid (I) served as starting material for the reaction sequence. It was converted to the ethyl ester *via* a Fischer esterification,[5] and the resulting ester was condensed with ethyl acetate in the presence of alkoxide to give ethyl β-oxo-β-(6-quinolyl)-propionate. An unsuccessful attempt was made to convert this keto ester to the desired 2-amino-1,3-propanediol *via* the isonitroso ester.[6a,b] The α-isonitroso-β-oxo-β-(6-quinolyl)-propionic acid was readily obtained on treatment of the acetoacetic ester derivative with nitrous acid. Treatment of the isonitroso intermediate with lithium aluminum hydride furnished a complex ninhydrin-positive mixture which could not be resolved into characterizable components. Viscontini[6b] reported a similar occurrence when he reduced ethyl α-isonitrosobenzoylacetate with lithium aluminum hydride. Hydrogenation of the isonitroso intermediate in the presence of platinum resulted in concomitant reduction of the heterocyclic ring giving (1,2,3,4-tetrahydro-6-quinolyl)-serine ethyl ester.

Consequently, a route similar to the sequence used by Long and Troutman[7] for the preparation of chloramphenicol was followed. Acid hydrolysis and decarboxylation of ethyl β-oxo-β-(6-quinolyl)-propionate using a modification of a reaction described by Jones and co-workers[8] gave 6-acetylquinoline (II). This ketone was brominated in the α-position. Treatment of the bromomethyl ketone III with hexamethylenetetramine followed by decomposition of the quaternary salt with concentrated hydrochloric acid at room temperature produced aminomethyl 6-quinolyl ketone. The use of dilute acid and or elevated temperatures for the hydrolysis resulted in extensive decomposition of the amino ketone, which was isolated as the hydrochloride. Acylation in cold aqueous solution using sodium acetate and acetic anhydride gave acetamidomethyl 6-quinolyl ketone (IV).

Hydroxymethylation of IV was accomplished in methanol solution using paraformaldehyde and potassium carbonate. None of the bishydroxymethylated material which is frequently encountered in this reaction[7] was isolated. Conversion of the resulting 2-acetamido-3-hydroxy-1-(6-quinolyl)-1-propanone (V) to the 1,3-propanediol (VI) was carried out using the Meerwein Ponndorf–Verley reduction. This reduction generates a second asymmetric carbon atom in the molecule and thus can potentially give a racemic mixture having either the desired *threo* or the undesired *erythro* configuration, or a mixture of both. A single product was obtained from this reduction. It was assigned the DL-*threo* configuration. Studies carried out to determine the configuration of this compound are described below.

Acid hydrolysis of VI and subsequent treatment of the resulting 2-amino-1-(6-quinolyl)-1,3-propanediol (VII) with methyl dichloroacetate in methanol gave the corresponding dichloroacetamide VIII.

Initially, the oxidation of the quinoline nitrogen atom was carried out on N_2O^1,O^3-triacetyl-2-amino-1-(6-quinolyl)-1,3-propanediol, obtained by the peracetylation of VI. The oxidation was accomplished using monoperphthalic acid. The excess monoperphthalic acid and the phthalic acid which formed during the oxidation were removed by passing the reaction mixture, dissolved in methanol, through an Amberlite IRA-400 (OH) column. In this process, transesteri-

(1) This work was presented in part at the Third Delaware Valley Regional Meeting of the American Chemical Society on February 25, 1956, at Philadelphia, Pa.

(2) M. C. Rebstock, H. M. Crooks, Jr., J. Controulis, and Q. R. Bartz, *J. Am. Chem. Soc.*, **71**, 2458 (1949), and succeeding papers.

(3) R. J. Collins, B. Ellis, S. B. Hansen, H. S. Mackenzie, R. J. Monaldo, V. Petrow, O. Stephenson, and B. Sturgeon, *J. Pharm. Pharmacol.*, **4**, 693 (1952).

(4) M. M. Shemyakin, M. N. Kolosov, M. M. Levitov, K. I. Germanova, M. G. Karapetyan, Yu. B. Shvetsov, and E. M. Bamdas, *J. Gen. Chem. USSR*, **26**, 885 (1956).

(5) A. Einhorn, *Ber.*, **42**, 4854 (1909).

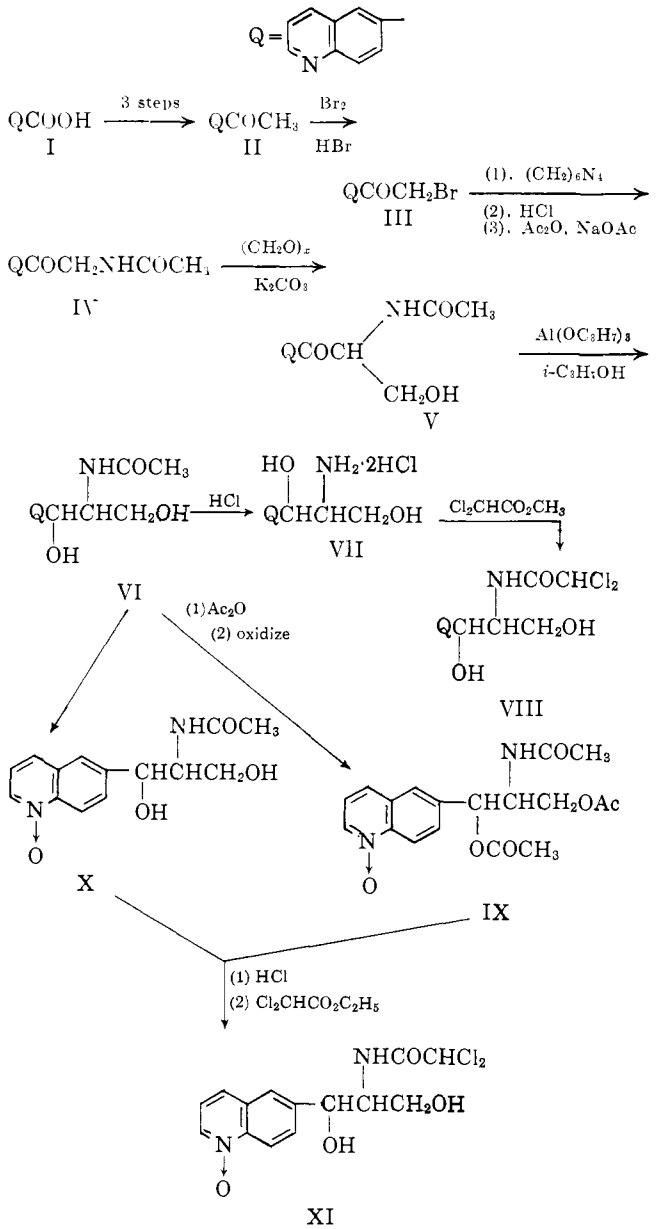
(6) (a) M. C. Rebstock, G. W. Moersch, A. C. Moore, and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **73**, 3666 (1951); (b) M. Viscontini, *Helv. Chim. Acta*, **35**, 1803 (1952).

(7) L. M. Long and H. D. Troutman, *J. Am. Chem. Soc.*, **71**, 2469, 2473 (1949).

(8) R. G. Jones, Q. F. Soper, O. K. Behrens, and J. W. Corse, *ibid.*, **70**, 2843 (1948).

fication occurred, resulting in a mixture of the mono- and triacetyl derivatives X, IX. This oxidation was later carried out directly on the diol VI, using monoperphthalic acid in absolute ethanol.

IX and X were hydrolyzed to the amine and this was converted to 2-dichloroacetamido-1-(6-quinolyl N-oxide)-1,3-propanediol (XI) as in the preparation of VIII.



The 1,3-propanediol preparations described above have the DL-*threo* configuration. One method for establishing the configuration of such a structure was originally described by Fodor, Kiss, and Sallay.[9] It utilizes the difference in the ease with which *erythro* and *threo* amino alcohols undergo N to O migration of an appropriate acyl group under the influence of hydrogen chloride in an inert solvent. With 2-amino-1-phenyl-1,3-propanediols, migration of the N-acyl group to the oxygen atom of the secondary alcohol occurs when the primary hydroxyl group is protected. This migration occurs readily in the *threo* series but at an unappreciable rate with the *erythro* isomers. Unoxidized VII was studied in this manner. O^1,O^3-

(9) G. Fodor, J. Kiss, and I. Sallay, *J. Chem. Soc.*, 1858 (1951).

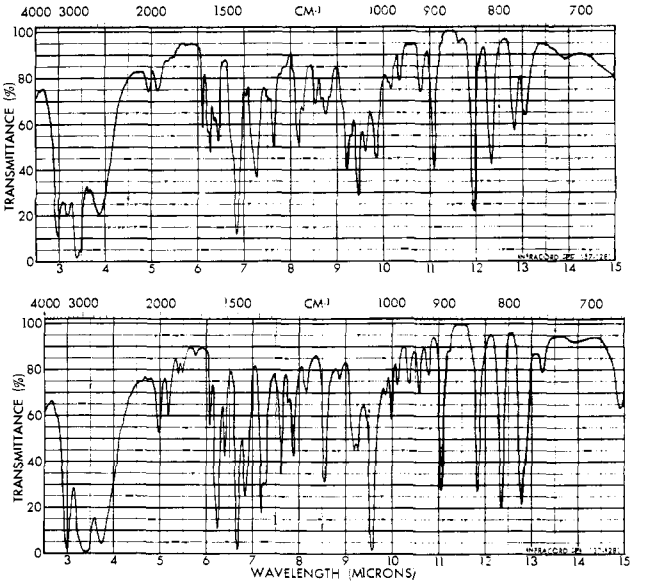


Fig. 1.—Infrared spectra of 2-amino-1-(6-quinolyl)-1,3-propanediol dihydrochloride in Nujol: top, DL-*threo* derivative (VII); bottom, DL-*erythro* derivative (XIV).

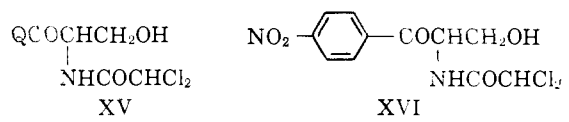
Diacetyl-2-amino-1-(6-quinolyl)-1,3-propanediol dihydrochloride was prepared by treating VII with acetyl chloride in glacial acetic acid containing dry hydrogen chloride. The O^1,O^3-diacetyl derivative was converted to N,O^3-diacetyl-2-amino-1-(6-quinolyl)-1,3-propanediol by brief treatment with aqueous sodium carbonate solution. However, attempts to determine the configuration by acyl migration studies on this N, O^3-diacetyl derivative were unsuccessful. In contrast to the neutral phenyl derivatives which remained in solution until acyl migration occurred, addition of hydrogen chloride to a solution of the N,O^3-diacetyl derivative in nonpolar solvents resulted in immediate precipitation of the hydrochloride because of the quinoline nitrogen. When polar solvents were used to prevent this precipitation, loss of the O^3-acetyl group occurred, and VI was recovered in nearly quantitative yield from the reaction mixture after careful neutralization, isolation, and purification. The identity of this product as VI was established by means of its melting point and infrared spectrum.

Because of this, the problem was attacked by observing the differences in reduction of V with and without the presence of bulky substituents on the hydroxyl group. N,O-Diacetyl-2-amino-3-hydroxy-1-(6-quinolyl)-1-propanone (XII) was prepared by treating V with acetic anhydride at 100°. When acetylation was attempted using acetic anhydride in pyridine at room temperature, cyclodehydration occurred to give (2-methyl-4-oxazolinyl) 6-quinolyl ketone. With the hydroxyl group free, the Meerwein–Ponndorf–Verley reduction of V gave the DL-*threo* compound VI which could be hydrolyzed to the DL-*threo* aminodiol VII as already indicated. On the other hand, the diacetylpropanone XII, when reduced with aluminum isopropoxide, underwent simultaneous loss of the O-acetyl group to give DL-*erythro*-2-acetamido-1-(6-quinolyl)-1,3-propanediol (XIII) which displayed a different infrared spectrum than the DL-*threo* compound and, while melting at a temperature close to the melting point of the DL-*threo*-acetamidodiol, depressed the melting point of the latter material (DL-*threo* m.p. 194–196°; DL-*erythro* m.p.

189–190°; m.m.p. 168°). The DL-*erythro*-aminodiol dihydrochloride XIV obtained by acid hydrolysis of XIII displayed a different melting point (DL-*threo* m.p. 259–260°; DL-*erythro* m.p. 228–229°) and infrared spectrum (Fig. 1) from those of the DL-*threo* derivative VII.

Finally, 2-acetamido-1-(6-quinolyl)-3-trityloxy-1-propanone was prepared by treating V with triphenylmethyl chloride in pyridine. Meerwein–Ponndorf–Verley reduction of this material gave 2-acetamido-1-(6-quinolyl)-3-trityl-1,3-propanediol. Hydrolysis of this compound with acid gave 2-amino-1-(6-quinolyl)-1,3-propanediol dihydrochloride (XIV) which was identical with the DL-*erythro* material obtained by reduction of the N,O-diacetyl derivative XII. By analogy with previously described reactions[10a,b] of this type, the *threo* and *erythro* configurations were assigned.

In the course of this work the quinoline analog XV of 2-dichloroacetamido-3-hydroxy-1-(*p*-nitrophenyl)-1-propanone (XVI) was prepared. This analog was obtained by dichloracetylating aminomethyl 6-quinolyl ketone and then hydroxymethylating with formaldehyde to give 2-dichloroacetamido-3-hydroxy-1-(6-quinolyl)-1-propanone (XV). Compound XVI had been previously reported to have a surprising degree of fungicidal activity *in vitro*.[11]



Microbiological Studies.—*In vitro* bacterial inhibition studies were carried out on the quinoline and the quinoline N-oxide analogs of chloramphenicol (VIII and XI) using the following organisms: *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus vulgaris*, *Micrococcus pyogenes* var. *aureus*, *Diplococcus pneumoniae* Type 1, and *Klebsiella pneumoniae* Type A. The test consisted of applying the compounds to agar plates seeded with the previously mentioned organisms using 13-mm. filter paper disks wet with solutions of the test compounds at concentrations of 20,000, 2000, 400, and 80 γ/ml. and measuring the diameters of the zones of inhibition. The N-oxide XI was inactive at all test levels. The quinoline VIII gave zones of inhibition only at 20,000 γ/ml. against *D. pneumoniae* and *Klebsiella pneumoniae* (17 and 20 mm., respectively). The lowest concentrations of chloramphenicol (in γ/ml.) that produced a zone of inhibition were as follows (the zone sizes in mm. at the given concentrations are shown in parentheses): *Pseudomonas*, 20,000 (21); *E. coli*, 2000 (24); *Proteus*, 400 (15); *S. aureus*, 2000 (22); *D. pneumoniae*, 400 (23); and *Klebsiella*, 80 (16).

In spite of their low *in vitro* activities, these derivatives were also studied in a mouse infection-protection test using the Finland 400 strain of *Staphylococcus aureus* as the infecting agent. The infection was induced intravenously and the treatment consisted of three oral doses at 1, 24, and 48 hr. *post* infection. Neither XI nor VIII protected the mice as seen by the following 7-day survival figures for the dose levels indicated. VIII: control, 0/10; 100 and 800 mg./kg. dose, 0/5 and 1/5, respectively. XI: control, 2/10; 50 mg./kg. 1/5; 100 and 500 mg./kg., 0/5. Chloramphenicol: control, 0/10; 50 mg./kg. 1/10; 100 and 300 mg./kg., 8/10.

A very slight protective effect was obtained with VIII in a mouse infection-protection test using a *K. pneumoniae* infection (intravenous) with oral treatment at 1 and 24 hr. *post* infection. Here 7-day survival rates were as follows: control, 1/10. VIII: 100 mg./kg., 0/5; 800 mg./kg., 1/5. Chloramphenicol: 150 mg./kg., 8/10.

The *in vitro* antifungal activities of XV and XVI were compared using an agar diffusion technique similar to that described for the *in vitro* antibacterial studies. These results are summarized in Table I.

TABLE I

In Vitro ANTIFUNGAL ACTIVITY

Organism	Compound	Diameter of zone of inhibition (mm.): Concentration of compd., γ/ml. 2000	400	80	Polyethylene glycol 200 diluent control
Candida albicans	XV	16	11	11	0
	XVI	23	13	0	0
Trichophyton mentagrophytes	XV	32	20	11	0
	XVI	11	28	11	0

The *in vivo* antifungal activities of XV and XVI were compared by infecting mice with *Candida albicans* intravenously and then administering the test compounds orally once daily for 5 days. The mice were sacrificed; the kidneys were removed, cultured, and studied for the presence of infection. From groups of 10 animals, the numbers having kidneys which cultured positively for *Candida albicans*, based on the number of animals surviving, were as follows: none (control), 9/10; XV at 300 mg./kg., 8/10; XVI at 50 mg./kg., 5/9; amphotericin B at 6.4 mg./kg., 0/10.

Experimental[12]

6-Acetylquinoline (IX).—In order to prepare suitable quantities of this compound for further investigation, it was necessary to modify the published procedures of Jones, *et al.*[8] It was found more feasible to eliminate the isolation of ethyl β-oxo-(6-quinolyl)-propionate and to convert this crude material directly to 6-acetylquinoline. For reproducible results, it was necessary to dry thoroughly all equipment and reagents used in the ester condensation.

The 6-quinolyl acetoacetic ester was converted to 6-acetylquinoline without isolation by adding 25% sulfuric acid to the reaction mixture of the ester and distilling the lower boiling organic components. When the temperature of the distillate reached 100°, the distilling head was replaced by a reflux condenser, and the mixture was refluxed for 5 hr. The reaction mixture was cooled and adjusted to pH 9 with 10% sodium hydroxide. It was extracted with ether, and the ethereal solution was dried over magnesium sulfate and evaporated to dryness *in vacuo*. The solid residue was recrystallized from petroleum ether (b.p. 115–140°); yields averaged 59%, m.p. 69–71°.

Ethyl α-Isonitroso-β-oxo-β-(6-quinolyl)-propionate.—To a solution of 8.0 g. (0.033 mole) of ethyl 6-quinolyl acetoacetate in 50 ml. of 95% alcohol was added 10 ml. of glacial acetic acid. The yellow solution was cooled while 90 ml. of a 10% aqueous solution of sodium nitrite was added. After stirring and cooling, the mixture was diluted with water to precipitate a white solid which was recrystallized from ethanol, yielding 6.0 g. (67%), m.p. 203–204° dec.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 62.00; H, 4.74; N, 10.01.

(1,2,3,4-Tetrahydro-6-quinolyl)-serine Ethyl Ester Dihydrochloride.—To a suspension of 0.4 g. of platinum oxide (previously hydrogenated) in 200 ml. of *N* hydrochloric acid was added 5.44 g. (0.02 mole) of the isonitroso compound. The mixture was hydrogenated for 7 hr. in a Parr shaker under an initial pressure of 50 p.s.i. (3.5 kg./cm.²) of hydrogen. The catalyst was removed and the filtrate was evaporated at reduced pressure. The white residue was suspended in a little absolute alcohol, filtered, washed with ether, and dried; yield 5.0 g. (78%); m.p. 224° dec. Further purification was effected by recrystallization from methanol–ether. The material was dried at 100° to constant weight for analysis.

Anal. Calcd. for $C_{14}H_{22}Cl_2N_2O_4$: C, 49.86; H, 6.58; N, 8.31. Found: C, 49.68; H, 6.82; N, 8.20.

(10) (a) J. Sicher, M. Svoboda, M. Hrdá, J. Rudinger, and F. Sorm, *Collection Czech. Chem. Commun.*, **18**, 487 (1953); (b) A. Hajós and J. Kollonitsch, *Acta Chim. Acad. Sci. Hung.*, **16**, 461 (1958); *Chem. Abstr.*, **53**, 6206*e* (1959).

(11) L. M. Long and H. D. Troutman, *J. Am. Chem. Soc.*, **73**, 481 (1951); J. W. MacIntosh, Jr., J. D. Gray, and C. M. Jones, *Can. Med. Assoc. J.*, **72**, 903 (1955).

(12) Melting points were taken in a Thomas–Hoover capillary melting point apparatus and are corrected. The microanalyses were performed by Mrs. Doris Rolston and co-workers, Analytical and Physical Chemical Section, Smith Kline and French Laboratories.

Bromomethyl 6-Quinolyl Ketone (III).—The acetyl compound II (67.0 g., 0.39 mole) was suspended in 180 ml. of 48% hydrobromic acid. The material dissolved and then reprecipitated as the hydrobromide salt. The mixture was heated on a steam bath while 24 ml. of bromine was added dropwise. After all of the bromine had been added, stirring was continued for 30 additional min. The mixture was cooled and filtered, and the solid was washed with acetone. The crude product weighed 118 g. (91%), m.p approximately 225° dec. Recrystallization from methanol–ether yielded an analytical sample, m.p. 236–237° dec.

Anal. Calcd. for $C_{11}H_8Br_2NO$: C, 39.91; H, 2.74; N, 4.23. Found: C, 40.00; H, 2.98; N, 4.56.

For use in subsequent reactions, it was necessary to convert the hydrobromide to the free base. This unstable base was best prepared by neutralization of the hydrobromide salt in aqueous solution at 0° with sodium bicarbonate. The product was filtered, washed with water, and extracted into chloroform. These operations were all performed below 5°. The chloroform solution of the free base was dried over magnesium sulfate and was used directly in the following reaction.

It was possible to prepare an analytical sample by drying the crude base from the neutralization in a vacuum desiccator over sodium hydroxide and then recrystallizing it from warm ether, m.p. approximately 115° dec.

Anal. Calcd. for $C_{11}H_8BrNO$: C, 52.82; H, 3.22; N, 5.60. Found: C, 52.42; H, 3.41; N, 5.61.

Acetamidomethyl 6-Quinolyl Ketone (IV).—A chloroform solution of III obtained from 30.0 g. (0.09 mole) of the hydrobromide salt was filtered into a stirred solution of 62.0 g. (0.45 mole) of hexamethylenetetramine in 400 ml. of chloroform. This was stirred at room temperature for 1 hr., cooled, and filtered. The resulting solid was washed with chloroform; yield 28–33.0 g. (80–94%), m.p. 159–161° dec. The material decomposed when attempts were made to recrystallize it.

To 40 ml. of concentrated hydrochloric acid was added 19.0 g. (0.049 mole) of the hexamine salt. The mixture was stirred for 1 hr. at room temperature, diluted with two volumes of absolute alcohol, cooled, and filtered. After washing with alcohol and ether, the amino ketone hydrochloride was contaminated with paraformaldehyde and ammonium chloride. It weighed 13.7 g. (theoretical yield, 12.7 g.) and melted at 229–230° dec. It was used in this form for subsequent operations.

Crude aminomethyl 6-quinolyl ketone dihydrochloride (50.0 g., 0.19 mole) was dissolved in 350 ml. of water and cooled, while 40 ml. of acetic anhydride and enough solid sodium acetate to maintain the mixture at pH 5–6 were added with vigorous stirring. The mixture was stirred for 2 hr. at 0° and for 1 hr. at room temperature. The solid was filtered, washed with water, and dried to yield 24.3 g. of IV, m.p. around 95°. After recrystallization from ethyl acetate it was necessary to dry the product at 60° *in vacuo* to obtain a sharp melting point, 120–122°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.37; H, 5.37; N, 12.02.

2-Acetamido-3-hydroxy-1-(6-quinolyl)-1-propanone (V).—To 22.8 g. (0.1 mole) of IV and 6.0 g. of paraformaldehyde in 200 ml. of methanol was added 0.6 g. of solid potassium carbonate. After stirring for 2 hr. at room temperature the reaction mixture was cooled and filtered. The product was washed with water, dried, and recrystallized from alcohol; yield 19.0 g. (74%), m.p. 185–187°.

Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.10; H, 5.46; N, 10.85. Found: C, 65.08; H, 5.75; N, 10.81.

DL-*threo*-2-Acetamido-1-(6-quinolyl)-1,3-propanediol (VI).—In a 250-ml. three-necked flask fitted with a stirrer and a short distilling column packed with glass helices were placed 16.0 g. (0.08 mole) of redistilled aluminum isopropoxide and 100 ml. of anhydrous 2-propanol. The solution was heated and stirred while 15.6 g. (0.06 mole) of V was added. Refluxing and slow distillation were continued until the distillate no longer gave a positive test for acetone with 2,4-dinitrophenylhydrazine reagent (about 6 hr.). Celite and 25 ml. of water were added, and the gelatinous mixture was stirred and heated for 15 min. and filtered. (Difficulty was often encountered in the filtration and extraction of the inorganic mixture. Therefore, it was often more feasible to extract the inorganic mixture overnight with absolute alcohol in a Soxhlet apparatus.) The filter cake was washed with hot absolute ethanol, the combined filtrates were evaporated, and the residue was triturated with ethyl acetate. The resulting solid was recrystallized from alcohol–ethyl acetate to give 9.65 g. (45%) of VI, m.p. 194–196°.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.30; H, 6.50; N, 10.50.

DL-*threo*-2-Amino-1-(6-quinolyl)-1,3-propanediol Dihydrochloride (VII).—A suspension of 10.4 g. (0.04 mole) of VI in 80 ml. of *N* hydrochloric acid was heated on a steam bath for 2 hr. The resulting solution was concentrated almost to dryness under reduced pressure (bath temperature kept below 50°). After evaporating twice with absolute alcohol, the solid was purified by recrystallization from methanol–ether; yield 9.4 g. (81%), m.p. 259–260° dec.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_2O_2$: C, 49.50; H, 5.54; N, 9.62. Found: C, 49.96; H, 5.72; N, 9.88.

DL-*threo*-2-Dichloroacetamido-1-(6-quinolyl)-1,3-propanediol (VIII).—The dihydrochloride VII (7.7 g., 0.026 mole) was dissolved in methanol and passed through an IRA-400 (OH) column. The column was washed with methanol and the eluates were reduced to 150 ml. This solution was refluxed for 1 hr. with 20 ml. of methyl dichloroacetate and then allowed to stand at room temperature overnight. The solvent was removed under reduced pressure, and the white residue was recrystallized from absolute ethanol and dried at 100° *in vacuo;* yield 4.4 g. (51%), m.p. 190–192°.

Anal. Calcd. for $C_{14}H_{14}Cl_2N_2O_3$: C, 51.08; H, 4.29; N, 8.51. Found: C, 51.17; H, 4.48; N, 8.59.

DL-*threo*-N,O^1,O^3-Triacetyl-2-amino-1-(6-quinolyl)-1,3-propanediol. Acetic Anhydride Method.—To 140 ml. of acetic anhydride was added 9.1 g. (0.035 mole) of VI. The mixture was refluxed for 15 to 20 min., cooled, and concentrated *in vacuo* to a sirup. The sirup was dissolved in ice–water, made alkaline with solid sodium carbonate, and extracted with ethyl acetate. The organic extract was dried over sodium sulfate and concentrated at reduced pressure. The sirup (usually representing about 80% yield) was triturated with ether until crystallization occurred: yield 7.0 g. (58%), m.p. 105°. An analytical sample was obtained after several recrystallizations from ethyl acetate–petroleum ether (40–60°), m.p. 106–108°.

Anal. Calcd. for $C_{18}H_{20}N_2O_5$: C, 62.78; H, 5.85; N, 8.14. Found: C, 62.59; H, 5.93; N, 8.34.

Acetic Anhydride and Pyridine Method.—A solution of 6.0 g. (0.023 mole) of VI in 25 ml. of acetic anhydride and 25 ml. of pyridine was permitted to stand at room temperature for 24 hr. The reaction mixture was concentrated under reduced pressure, and the residue was evaporated twice with toluene. The residue when triturated with ether did not crystallize. The sirup, weighing 6.5 g. (81%), was used without further purification.

DL-*threo*-2-Acetamido-1-(6-quinolyl N-oxide)-1,3-propanediol (X). A. From 2-Acetamido-1-(6-quinolyl)-1,3-propanediol and Monoperphthalic Acid.—A solution of 2.6 g. (0.01 mole) of VI in 200 ml. of absolute ethanol was treated with 29 ml. of a solution of monoperphthalic acid in ether containing 0.38 mole equiv. of acid per ml. After standing overnight the solution was concentrated *in vacuo*. The residue was dissolved in methanol and passed through an IRA-400 (OH) ion-exchange column. The phthalic acid-free eluates were evaporated *in vacuo;* yield 2.23 g. (81%), m.p. 185–190°. Recrystallization from absolute alcohol gave a material which melted at 223–226°.

B. From N,O^1,O^3-Triacetyl-2-amino-1-(6-quinolyl)-1,3-propanediol.—A solution of 14.4 g. (0.04 mole) of N,O^1,O^3-triacetyl-2-amino-1-(6-quinolyl)-1,3-propanediol in 350 ml. of an ethereal solution of monoperphthalic acid containing 0.35 mol. equiv. of peracid per ml. of solution was kept at room temperature for 2.5 hr. It was then concentrated to one-half its volume, diluted with about two volumes of methanol, and passed through an IRA-400 (OH) ion-exchange column. The eluates were taken to dryness *in vacuo*, and the resulting solid was suspended in hot absolute ethanol, cooled, and filtered to give 6.35 g. of X melting at 226°. Concentration of the alcoholic filtrate yielded a mixture of mono- and triacetyl derivatives which were converted to the monoacetyl derivative by allowing the mixture, dissolved in methanol, to stand at room temperature with an equal volume of methanol saturated with ammonia at 0°. This gave an additional 1.3 g. of material which melted at 222–226°. The total yield of acetanide was 7.65 g. (69%).

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: N, 10.14. Found: N, 10.43.

DL-*threo*-N,O^1,O^3-Triacetyl-2-amino-1-(6-quinolyl N-oxide)-1,3-propanediol (IX).—This could be obtained in 41% yield by extracting the residue from the IRA-400 (OH) column eluate with warm absolute alcohol and cooling. This material after recrystallization from absolute alcohol melted at 220–222°.

Anal. Calcd. for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.99; H, 5.64; N, 7.92.

DL-*threo*-**2-Amino-1-(6-quinolyl N-oxide)-1,3-propanediol Dihydrochloride.**—The N-oxide X (4.1 g., 0.015 mole) in 40 ml. of 1.5 *N* hydrochloric acid was heated on a steam bath for 2 hr. and then concentrated to dryness *in vacuo*. The residue was evaporated twice *in vacuo* with absolute alcohol; yield 4.3 g. (93%), m.p. 224–226° dec. This material after recrystallization from methanol–ether and drying *in vacuo* overnight at 100° melted at 234–235° dec.

Anal. Calcd. for $C_{12}H_{16}Cl_2N_2O_3$: C, 46.92; H, 5.25; N, 9.12. Found: C, 47.11; H, 5.48; N, 9.27.

DL-*threo*-**2-Dichloroacetamido-1-(6-quinolyl N-oxide)-1,3-propanediol (XI).**—2-Amino-1-(6-quinolyl N-oxide)-1,3-propanediol dihydrochloride (2.05 g., 0.0067 mole) was converted to the free base and reacted with methyl dichloroacetate as was VII, yielding 1.4 g. (61%), m.p. 198–199° dec. Recrystallization from water followed by drying *in vacuo* at 100° yielded 0.8 g. of white needles, m.p. 205° dec.

Anal. Calcd. for $C_{14}H_{14}Cl_2N_2O_4$: C, 48.71; H, 4.09; N, 8.12. Found: C, 48.76; H, 4.20; N, 8.12.

DL-*threo*-**2-Amino-1-(6-quinolyl)-1,3-propanediol-O^1,O^3-diacetate Dihydrochloride.**—A mixture of 3.0 g. of VII and 15 ml. of acetyl chloride in 80 ml. of glacial acetic acid saturated with dry hydrogen chloride was allowed to stand at room temperature overnight. The white needles which separated were washed with acetic acid, then with ether, and dried *in vacuo* over sodium hydroxide yielding 3.45 g. (89%), m.p. 176–178° dec. Recrystallization from 95% alcohol did not alter the decomposition point. The analytical sample was dried at 100° *in vacuo*.

Anal. Calcd. for $C_{16}H_{20}Cl_2N_2O_4$: C, 51.21; H, 5.37; N, 7.47. Found: C, 51.06; H, 5.61; N, 7.66.

Picrate.—The amine hydrochloride was added to a saturated solution of picric acid in water. A gum separated which crystallized on standing, m.p. 126–128° dec.

DL-*threo*-**N,O^3-Diacetyl-2-amino-1-(6-quinolyl)-1,3-propanediol.**—A solution of 3.0 g. of 2-amino-1-(6-quinolyl)-1,3-propanediol-O^1,O^3-diacetate dihydrochloride was dissolved in 20 ml. of water, and the pH was adjusted to 8. After 20 min. the white solid was removed and dried *in vacuo*, yielding 1.2 g. (50%), m.p. 153–155°. Recrystallization from chloroform–petroleum ether gave 1.04 g. of solid, m.p. 159–160°.

Anal. Calcd. for $C_{16}H_{18}N_2O_4$: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.28; H, 6.19; N, 9.13.

N,O-Diacetyl-2-amino-3-hydroxy-1-(6-quinolyl)-1-propanone (XII).—A mixture of 2.6 g. (0.01 mole) of V and 20 ml. of acetic anhydride was stirred at 100° for 1 hr. The acetic anhydride was removed *in vacuo* and the residue was treated with a little ice, made alkaline with solid sodium carbonate, and extracted into ethyl acetate. The ethyl acetate solution was dried over sodium sulfate and concentrated. The sirup was triturated with ether. The resulting solid was extracted with ethyl acetate, and the solution was filtered from 0.26 g. of unreacted starting material. The solid, which formed on addition of petroleum ether to the ethyl acetate solution, was recrystallized from chloroform–petroleum ether; yield 1.6 g. (60%), m.p. 109–110°.

Anal. Calcd. for $C_{16}H_{16}N_2O_4$: C, 63.99; H, 5.37; N, 9.33. Found: C, 63.97; H, 5.78; N, 9.06.

(2-Methyl-4-oxazolinyl) 6-Quinolyl Ketone.—A solution of 4.0 g. (0.015 mole) of V in 30 ml. of acetic anhydride and 15 ml. of pyridine was allowed to stand at room temperature overnight. The excess pyridine and acetic anhydride were removed by distillation under diminished pressure. The residue was evaporated *in vacuo* several times with toluene. The sirup remaining was triturated with ether; yield 4.2 g. (93%), m.p. 95–122°. This was recrystallized from water to give a product melting at 136–138°. The infrared spectrum and elemental analysis indicated that the oxazoline had been produced.

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.98; H, 5.04; N, 11.66. Found: C, 69.79; H, 5.08; N, 11.67.

DL-*erythro*-**2-Acetamido-1-(6-quinolyl)-1,3-propanediol (XIII).**—N,O-Diacetyl-2-amino-3-hydroxy-1-(6-quinolyl)-1-propanone (9.0 g., 0.03 mole) was reduced with 9.6 g. (0.045 mole) of aluminum isopropoxide and 90 ml. of dry 2-propanol in a manner analogous to the reduction of V; yield 4.6 g. (66%), m.p. 175–180°. The yield after two recrystallizations from absolute alcohol was 1.2 g., m.p. 189–190°.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.83; H, 6.33; N, 10.84.

2-Acetamido-1-(6-quinolyl)-3-trityloxy-1-propanone.—A suspension of V (10.0 g., 0.039 mole) and trityl chloride (24.0 g., 0.086 mole) in 25 ml. of pyridine was allowed to stand at room temperature for 5 days. The heterogeneous mixture was then poured into ice water and allowed to stand until crystallization occurred. The solid was filtered, suspended in a small amount of alcohol, and filtered again to give 17.1 g. (88%) of product, m.p. 119–120°. After standing at room temperature for 1 week, the melting point had changed to 154–155°. The material, when recrystallized from methanol, displayed the higher melting point. Infrared spectra of samples having both melting points were identical. For analysis, the sample was recrystallized from ethanol, and then from chloroform–petroleum ether.

Anal. Calcd. for $C_{33}H_{28}N_2O_3$: C, 79.18; H, 5.64. Found: C, 78.97; H, 5.88.

DL-*erythro*-**2-Acetamido-1-(6-quinolyl)-3-trityloxy-1-propanol.**—The tritylated ketone (5.0 g., 0.01 mole) was reduced with 5.0 g. (0.025 mole) of aluminum isopropoxide and 80 ml. of dry 2-propanol as previously described. Recrystallization from ethyl acetate–petroleum ether gave 4.2 g. (84%) of the reduction product, m.p. 173–175°. The analytical sample melted at 183–185°.

Anal. Calcd. for $C_{33}H_{30}N_2O_3$: C, 78.86; H, 6.02; N, 5.57. Found: C, 78.74; H, 6.38; N, 5.75.

DL-*erythro*-**2-Amino-1-(6-quinolyl)-1,3-propanediol Dihydrochloride (XIV). From** DL-*erythro*-**2-Acetamido-1-(6-quinolyl)-1,3-propanediol.**—A mixture of 0.65 g. (0.0025 mole) of *erythro*-acetamidopropanediol, prepared by the reduction of N,O-diacetyl-2-amino-3-hydroxy-1-(6-quinolyl)-1-propanone, and 50 ml. of *N* hydrochloric acid was heated at 100° for 2 hr. The resulting solution was evaporated to a sirup *in vacuo*, and the sirup was evaporated twice with absolute alcohol. Recrystallization of the residue from methanol gave 0.52 g. (71%) of white crystalline dihydrochloride, m.p. 228° dec.

From DL-*erythro*-**2-Acetamido-1-(6-quinolyl)-3-trityloxy-1-propanol.**—A solution of 1.5 g. (0.003 mole) of tritylated *erythro*-propanediol [prepared by the Meerwein reduction of 2-acetamido-1-(6-quinolyl)-3-trityloxy-1-propanone] in 25 ml. of 2 *N* hydrochloric acid was heated under reflux for 2 hr. Filtration of the reaction mixture gave 0.8 g. of triphenylcarbinol, m.p. 160–162°. The aqueous filtrate was extracted with ether and then evaporated to a sirup under reduced pressure. The isolation and purification of the amine dihydrochloride were carried out as described previously, yielding 0.4 g. (46%), m.p. 228° dec. The infrared spectrum of this material was identical with the spectrum of the preceding preparation. A mixture of these preparations did not result in depression of the decomposition point.

Anal. Calcd. for $C_{12}H_{18}Cl_2N_2O_2$: C, 49.50; H, 5.54; N, 9.62. Found: C, 49.85; H, 5.62; N, 9.90.

Dichloroacetamidomethyl 6-Quinolyl Ketone.—A suspension of 2.6 g. (0.01 mole) of crude aminomethyl 6-quinolyl ketone dihydrochloride and 10 ml. of α,α-dichloroacetyl chloride was heated and stirred at 80° for 30 min. The mixture was cooled and poured into 50 ml. of ice–water. The resulting aqueous solution was stirred for 1 hr. at room temperature and was then made slightly alkaline by the addition of solid sodium carbonate. The mixture was extracted three times with ethyl acetate. The ethyl acetate extracts were dried over sodium sulfate and the solvent was removed *in vacuo*. The residue was suspended in ether and filtered to give 1.7 g. (57%) of solid, m.p. 137–144° dec. Recrystallization from absolute alcohol gave pure material, m.p. 156–157° dec.

Anal. Calcd. for $C_{13}H_{10}Cl_2N_2O_2$: C, 52.54; H, 3.39; N, 9.43. Found: C, 52.64; H, 3.69; N, 9.27.

2-Dichloroacetamido-3-hydroxy-1-(6-quinolyl)-1-propanone (XV).—A suspension of 1.6 g. (0.057 mole) of the dichloroacetamido ketone in 5 ml. of 37% aqueous formaldehyde and 75 ml. of 95% alcohol containing a small amount of sodium bicarbonate was stirred at room temperature for 2 hr. The mixture was cooled, and the solid was filtered, washed with water, and dried to give 1.8 g. (75%) of white crystals, m.p. 185°. Recrystallization from methanol gave pure material, m.p. 190–191°.

Anal. Calcd. for $C_{14}H_{12}Cl_2N_2O_3$: C, 51.39; H, 3.70; N, 8.56. Found: C, 51.49; H, 3.82; N, 8.84.