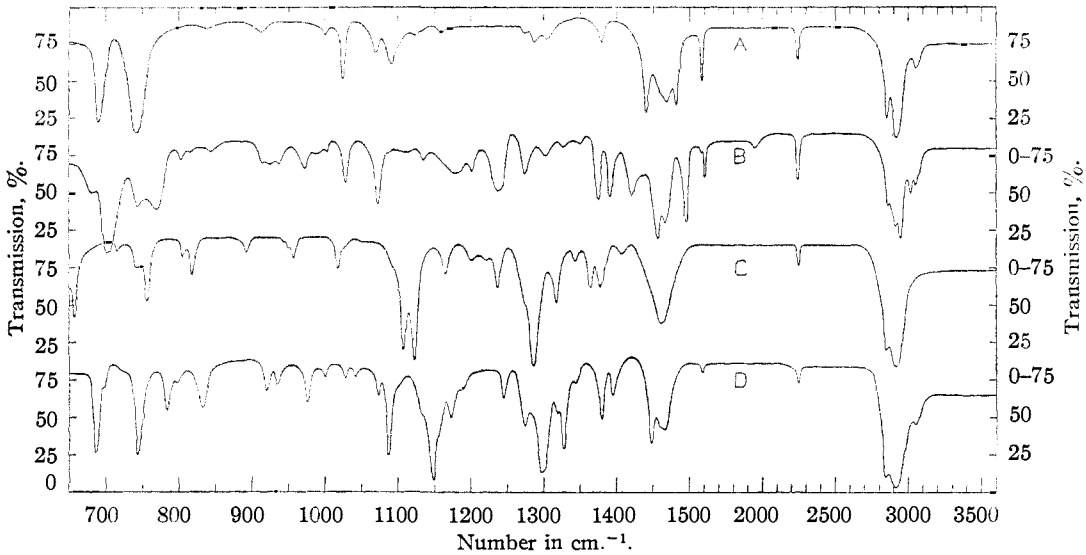


Fig. 1.—Infrared absorption spectra: A, β-phenylmercapto α-*n*-amylpropionitrile; B, β-benzylmercapto α-isopropylpropionitrile; C, β-*t*-butylsulfonyl α-ethylpropionitrile; D, β-phenylsulfonyl α-isopropylpropionitrile (the liquids A and B were examined in a cell of 0.025 mm. thickness; the solids C and D were examined in Nujol).

ever, in the samples of α-isopropylacrylonitrile[4] used; these may have prevented smooth reaction from taking place.

All the adducts were converted to the corresponding sulfonyl derivatives. Characterization of the thio ethers and the sulfones was aided by infrared analysis,[5] and representative examples of several absorption curves are illustrated in Fig. 1.

(4) Our preparation of α-isopropylacrylonitrile followed that which was described by C. S. Marvel and W. R. Miller, THIS JOURNAL, **72**, 5408 (1950). The latter authors have pointed out that the product they obtained was unstable and therefore impure. In attempting to purify the nitrile, even careful fractionation failed, and a satisfactory analytical sample has not been prepared as yet.

(5) We are indebted to Miss Elizabeth M. Petersen for the infrared analyses, their interpretation, and the tracing of the absorption curves.

Experimental[6,7]

Nitriles.—α-Methylacrylonitrile was purchased from Shell Chemical Corporation. All other nitriles were prepared according to the method of Marvel and Miller (see citation 4).

Cyanoalkylations.—A detailed procedure for similar cyanoalkylations has been described in an earlier communication.[1] Quantities of reactants and other pertinent data are listed in Tables I and II.

All additions were carried out over a reflux period of 48 hours; *t*-butyl alcohol was used as the solvent.

(6) All melting points are corrected and were determined on a brass micro melting point apparatus. Reported boiling points are not corrected.

(7) Microanalyses were carried out by Miss Emily Davis, Miss Rachel Kopel and Mr. Maurice Dare to whom we are indebted.

URBANA, ILL. RECEIVED AUGUST 7, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Chloromycetin.[1] Synthesis of DL-*threo*-2-Dichloroacetamido-1-(4-nitro-1-naphthyl)-1,3-propanediol

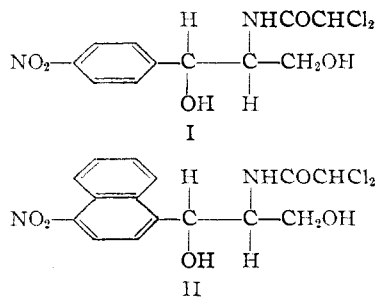
BY LOREN M. LONG AND H. D. TROUTMAN

Two compounds related to the antibiotic, Chloromycetin, have been prepared, These derivatives contain a 4-nitro-1-naphthyl or a 2-naphthyl group in place of the *p*-nitrophenyl group present in the antibiotic.

During the course of our investigation of the chemistry of D-(*levo*)-*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol (Chloromycetin) it became desirable to prepare certain compounds related to the antibiotic. One of these, DL-*threo*-2-dichloroacetamido-1-(4-nitro-1-naphthyl)-1,3-propanediol, is the subject of this paper. Structure I, established by Rebstock, *et al.*,[2] represents Chloromycetin while structure II is that of the 4-nitro-1-naphthyl derivative. In addition the 2-naphthyl derivative was prepared.

(1) Parke, Davis & Co. registered trademark for chloramphenicol.

(2) M. C. Rebstock, H. M. Crooks, Jr., J. Controulis and Q. R. Bartz, THIS JOURNAL, **71**, 2458 (1949).



I

II

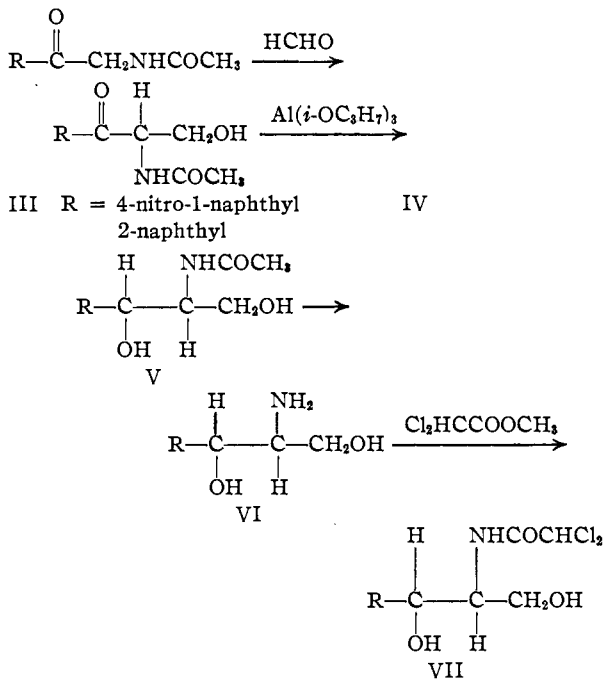
The principal steps involved in the synthesis are illustrated in the series of reactions. This

TABLE I

Compound	R	M. p., °C.	Yield, %[b]	Formula	Carbon, %[a] Calcd.	Carbon, %[a] Found	Hydrogen, % Calcd.	Hydrogen, % Found
III	2-Naphthyl	134–136	91	$C_{14}H_{13}NO_2$	73.99	74.07	5.76	5.67
	4-Nitro-1-naphthyl	179–182	70	$C_{14}H_{12}N_2O_4$	61.76	61.83	4.44	4.54
IV	2-Naphthyl	164–166	78	$C_{15}H_{15}NO_3$	70.02	69.73	5.88	5.77
	4-Nitro-1-naphthyl	150–152	56	$C_{15}H_{14}N_2O_5$	59.60	59.70	4.67	5.03
V	2-Naphthyl	169–171	59	$C_{15}H_{17}NO_3$	69.48	69.29	6.61	6.73
	4-Nitro-1-naphthyl	218–221	18	$C_{15}H_{16}N_2O_5$	59.20	59.10	5.30	5.64
VI	2-Naphthyl	118–119	86	$C_{13}H_{15}NO_2$	71.86	71.67	6.96	6.92
	4-Nitro-1-naphthyl	170–171	85	$C_{13}H_{14}N_2O_4$	59.53	59.16	5.38	5.64
VII	2-Naphthyl	153–155	79	$C_{15}H_{15}Cl_2NO_3$	54.89	55.18	4.61	4.78
	4-Nitro-1-naphthyl	181–182	53	$C_{15}H_{14}Cl_2N_2O_5$	48.27	48.69	3.78	4.24

[a] Analytical data were determined by Mr. C. E. Childs of this Laboratory. [b] Yields are based on the preceding intermediate.

general procedure has been discussed in earlier publications.[3,4] The reactions proceed as indicated to yield the desired products. Although the aluminum isopropoxide reduction of α-acetamido-β-



hydroxy-2-propionaphthone gives good yields of the propanediol (V), the reduction of the corresponding 4-nitro-1-naphthyl derivative gave a much lower yield. Apparently there was some further decomposition occurring since ammonia was evolved during hydrolysis following reduction. Although the configuration of V has not been completely established, it is assumed to be the *threo* configuration on the basis of the preparative method and a comparison of properties with compounds of known structure.

Table I summarizes data concerning the various compounds prepared in the investigation.

Experimental

Acetonaphthones.—2-Acetonaphthone was purchased from the Eastman Kodak Co. 4-Nitro-1-acetonaphthone was prepared from 4-nitro-1-naphthoyl chloride[5] by a previously described variation[4] of the method of Walker and Hauser.[6] The yield of ketone was 82%; m.p. 88–89°.

Anal. Calcd. for $C_{12}H_9NO_3$: C, 66.97; H, 4.21; N, 6.51. Found: C, 66.73; H, 4.20; N, 6.61.

β-Bromoacetonaphthones.—α-Bromo-2-acetonaphthone has been described.[7] α-Bromo-4-nitro-1-acetonaphthone was prepared by the following method.

To 118.3 g. (0.55 mole) of 4-nitro-1-acetonaphthone in 1200 ml. of glacial acetic acid containing 1 ml. of concentrated hydrochloric acid was added 88 g. (0.55 mole) of bromine in 100 ml. of glacial acetic acid. The temperature was maintained at 25° and stirring was continued for 30 minutes after the addition was complete. The solution was then poured into 8 l. of water. The solid was removed and washed twice with water. After drying, the product was recrystallized from glacial acetic acid. The yield was 145 g. or 89%; m.p. 100–101°.

Anal. Calcd. for $C_{12}H_8BrNO_3$: C, 49.00; H, 2.74; N, 4.76. Found: C, 48.70; H, 2.92; N, 4.63.

α-Acetamidoacetonaphthones (III).—Since α-acetamido-2-acetonaphthone is described in the literature,[8] the preparation of α-acetamido-4-nitro-1-acetonaphthone will be given. The conversion of this derivative to the final product (VII) will be described. Corresponding reactions with α-acetamido-2-acetonaphthone are similar.

The hexamethylenetetramine salt was prepared from α-bromo-4-nitro-1-acetonaphthone in 90% yield; m.p. 143–147°. The salt (30.5 g.) was hydrolyzed at 25° over a period of 20 hours in a mixture of 90 ml. of concentrated hydrochloric acid and 180 ml. of 95% ethanol. The α-amino-4-nitro-1-acetonaphthone hydrochloride was filtered off, washed with cold water and suspended in 200 ml. of 50% acetic acid. The mixture was cooled to 5° and stirred while 17 ml. of acetic anhydride followed by a solution of 19 g. of sodium acetate trihydrate in 120 ml. of water was added. During the addition the temperature was maintained below 10°. The mixture was stirred and allowed to warm up to 20° over a period of 30 minutes. The mixture was diluted with 350 ml. of 60% acetic acid and heated to 95°. The hot solution was filtered. On cooling, a crystalline product was obtained. It was recrystallized from 50% acetic acid and then 95% ethanol.

α-Acetamido-β-hydroxy-4-nitro-1-propionaphthone (IV).—A mixture of 59.4 g. (0.218 mole) of α-acetamido-4-nitro-1-acetonaphthone, 20 ml. of 36–38% aqueous formaldehyde, 175 ml. of methanol and 2 g. of anhydrous sodium carbonate was stirred at 35–38° for about 1 hour. The mixture was acidified with 3 ml. of glacial acetic acid, cooled and filtered. The product was filtered off and washed with 15 ml. of cold methanol then with water. The product was dried and recrystallized from ethyl acetate.

α-Acetamido-β-acetoxy-4-nitro-propionaphthone.—A derivative of the preceding compound was prepared by acetylating the β-hydroxy group. One gram of α-acetamido-β-hydroxy-4-nitro-1-propionaphthone was heated with 7 ml. of acetic anhydride and one drop of concentrated sulfuric acid at 75° for 10 minutes. The mixture was cooled and

(3) L. M. Long and H. D. Troutman, THIS JOURNAL, **71**, 2469 (1949).
(4) L. M. Long and H. D. Troutman, *ibid.*, **71**, 2473 (1949).
(5) F. F. Blicke and H. C. Parke, *ibid.*, **61**, 1200 (1939).
(6) H. G. Walker and C. R. Hauser, *ibid.*, **68**, 1386 (1946).
(7) T. Immediata and A. R. Day, *J. Org. Chem.*, **5**, 517 (1940); C. B. Radcliffe, I. R. Sherwood and W. F. Short, *J. Chem. Soc.*, 2293 (1931).
(8) B. B. Dey and S. Rajagopalan, *Arch. Pharm.*, **277**, 386 (1939).

diluted with water. The acid was filtered off, washed with water and dried; yield 0.94 g. It was recrystallized from ethyl acetate; m.p. 123–126°.

Anal. Calcd. for $C_{17}H_{16}N_2O_6$: N, 8.14. Found: N, 7.98.

DL-*threo*-**2-Acetamido-1-(4-nitro-1-naphthyl)-1,3-propanediol (V).**—A mixture of 24.2 g. (0.08 mole) of α-acetamido-β-hydroxy-4-nitro-1-propionaphthone, 32.6 g. (0.16 mole) of aluminum isopropoxide and 250 ml. of anhydrous isopropyl alcohol was distilled slowly until the acetone test was negative. During the distillation a total of 180 ml. of distillate was collected. To the warm residue was added 120 ml. of isopropyl alcohol and 45 ml. of water. The mixture was refluxed for several minutes. Apparently ammonia was formed. The hot mixture was filtered through a layer of Super-cel. The filter-cake was extracted three times with hot 250-ml. portions of 80% isopropyl alcohol. The extracts were combined and concentrated thoroughly at 20 mm. and 80° (water-bath). The residue, a thick oil, partially solidified after standing several hours. It was mixed with 50 ml. of ethyl acetate, cooled and filtered to yield 2.1 g. of solid. Additional material was obtained by concentration of the ethyl acetate. The solids were combined and recrystallized from water.

DL-*threo*-**2-Amino-1-(4-nitro-1-naphthyl)-1,3-propanediol (VI).**—A mixture of 1.75 g. of the acetamido derivative and 80 ml. of 5% hydrochloric acid was heated on a steam-bath for 3 hours, then mixed with 2 g. of Darco and filtered. An excess of 20% aqueous sodium hydroxide was added to the cooled filtrate. The cold mixture was filtered and the solid washed with water and dried. The product was recrystallized from dilute methanol.

DL-*threo*-**2-Dichloroacetamido-1-(4-nitro-1-naphthyl)-1,3-propanediol (VII).**—A solution of 1.05 g. (0.004 mole) of the free base in 25 ml. of methyl dichloroacetate was warmed on the steam-bath for 25 minutes. The solution was concentrated at 20 mm. and 90° (water-bath). The solid residue was washed with chloroform and then recrystallized from water.

DETROIT, MICHIGAN RECEIVED SEPTEMBER 13, 1950

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MARYLAND]

Quinolinequinones.[1] I. Quinones and Hydroquinones Related to Pentaquine[1a]

BY NATHAN L. DRAKE AND YOLANDA T. PRATT

Certain quinones and hydroquinones related to pentaquine (I) have been prepared by the reactions indicated in Fig. 1. The high *in vitro* antimalarial activities of compounds IIIb and Vb, in contrast to the inactivity of I, lend support to Schönhöfer's theory that the *in vivo* action of the 8-aminoquinolinesupon the erythrocytic forms of malaria plasmodia is due to the quinonoid products to which these drugs are converted by the host.

On the basis of certain correlations of chemical structure with activity against the erythrocytic forms of avian plasmodia, Schönhöfer postulated that the action of 6-methoxy-8-aminoquinolines (*e.g.*, I) is due to the quinonoid products (*e.g.*, IV) to which they are converted by the host organism.[2,3,4]

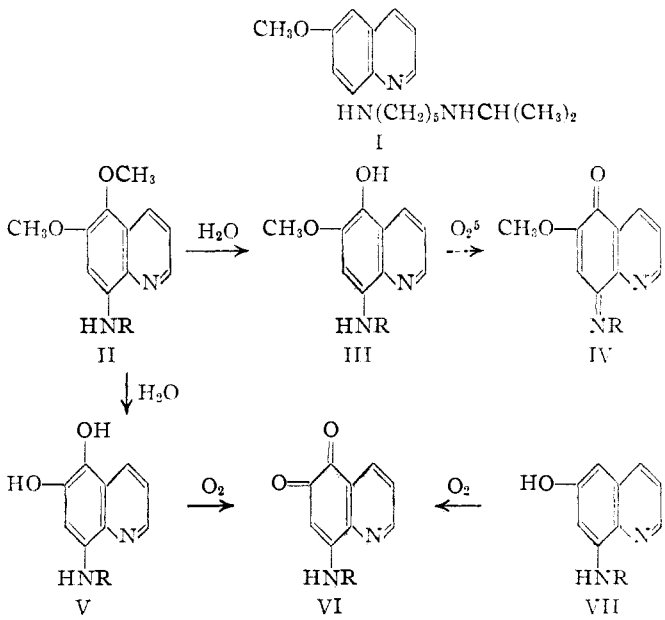


Fig. 1.—In the a series R = H; in the b series R = $-(CH_2)_5NHCH(CH_3)_2$.

It has also been suggested that the methemoglobinemia resulting from administration of these drugs might be caused by such quinonimines.[3] In view of these theories and the fact that certain naphthoquinones display antimalarial activity, the quinones and quinonimines of quinoline and its derivatives are of considerable interest.

With the ultimate objective of preparing potential drugs based on quinonimines such as IV or on quinones such as VI as well as on the quinolinequinone (dihydroquinolinedione) analogs of the naphthoquinone antimalarials, a general study of the quinolinequinones has been initiated in these laboratories. In this paper are considered certain quinones and hydroquinones related to pentaquine (I) as shown in Fig. 1.

The hydroxy compounds (IIIa, IIIb, Va and Vb) were prepared as hydrobromides by hydrolysis of the related 5,6-dimethoxy-8-aminoquinolines, IIa and IIb, with constant-boiling hydrobromic acid under nitrogen. The salts were isolated directly from the reaction mixture without liberation of the highly unstable free bases.

The possibility of obtaining 5-hydroxy-6-methoxy-8-aminoquinolines (III) by selective hydrolysis of the 5,6-dimethoxy compounds (II) was suggested by the observation that the 5-methoxyl group in 5,6-dimethoxy-8-nitroquinoline

(1) Dihydroquinolinediones.

(1a) This work was supported by Contract RG 191 and continuation grants from the National Institutes of Health.

(2) F. Schönhöfer, *Z. physiol. Chem.*, **274**, 1 (1942).

(3) K. C. Blanchard, in Wiselogle, "A Survey of Antimalarial Drugs 1941-1945," J. W. Edwards, Ann Arbor, Mich., 1946, Vol. I, p. 129 ff.

(4) The isolation of 5,6-quinolinequinone from the urine of rabbits and humans after the administration of quinoline has been claimed [H. Fühner, *Arch. exp. Path. Pharm.*, **55**, 27 (1906); B. Schuenemann, *ibid.*, **100**, 51 (1923)].

(5) The broken arrow signifies that the reaction products have not been isolated and characterized.