79% yield; b. p. 218–219° at 2 mm., m. p. 116.0–117.5° (recrystallized from cyclohexane).

Anal. Calcd. for $C_{17}H_{17}ON_2Cl$: C, 67.9; H, 5.7. Found: C, 67.8; H, 5.7.

2-[2-(4′-Fluorobenzyl)-phenoxymethyl]-imidazoline.—71% yield; b. p. 209–212° at 3 mm., m. p. 104.5–106.5° (recrystallized from cyclohexane).

Anal. Calcd. for $C_{17}H_{17}ON_2F$: C, 71.8; H, 6.0. Found: C, 71.9; H, 6.0.

Two other experiments were carried out on the preparation of II, and gave approximately the same results. In one experiment, the same amounts of ester and ethylenediamine as indicated above were heated for 112 hours on the steam-bath; the imidazoline was obtained in 74% yield. In the second experiment a mixture of 36 g. (0.6 mole) of ethylenediamine and 54 g. (0.2 mole) of ethyl 2-benzylphenoxyacetate was boiled under a short column topped with a total reflux-partial takeoff condenser. After 4.5 hours, the theoretical amount of ethanol had been collected. Distillation of the reaction mixture gave 36.9 g. (69% yield) of II.

Imidazoline Hydrochlorides.—Saturation of cold ethereal solutions of the imidazolines with dry hydrogen chloride caused precipitation of the hydrochlorides, which were collected by filtration and purified by recrystallization from suitable solvents. These hydrochlorides are summarized in Table II.

Acknowledgment.—The authors wish to express their appreciation to Mr. Richard M. Downing and Mrs. Neva Knight, who performed the microanalyses reported herein.

Summary

The synthesis of 2-(2-benzylphenoxymethyl)-imidazoline and certain of its substituted analogs is reported. These imidazolines were prepared by heating the ethyl 2-benzylphenoxyacetates with an excess of anhydrous ethylenediamine.

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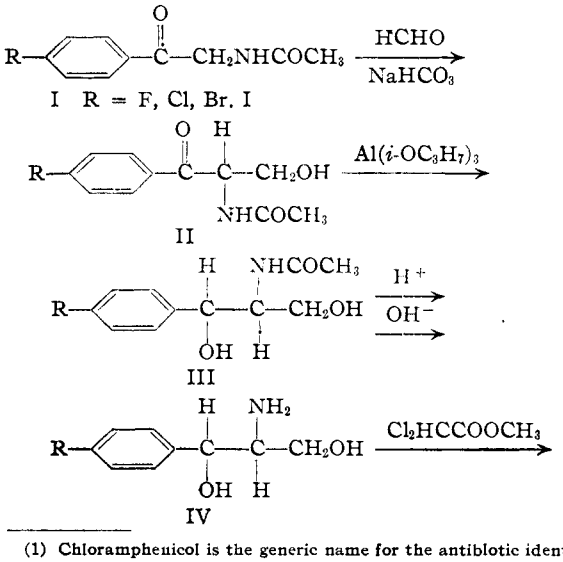
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS & CO.]

Chloramphenicol[1] (Chloromycetin). VIII. The Synthesis of Ring Halogenated Compounds

BY L. L. BAMBAS, H. D. TROUTMAN AND LOREN M. LONG

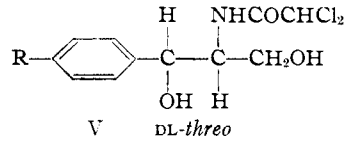
The success of the method described in paper VII[2] of this series for the preparation of essential intermediates in the synthesis of D-(levo)-*threo*-2 - dichloroacetamido - 1 - *p* - nitrophenyl - 1,3 - propanediol (chloramphenicol) has encouraged the authors to extend the procedure to a number of compounds related to the antibiotic. Application of the synthesis to compounds containing a halogen atom rather than a nitro group in the para position has proved entirely feasible. Results of the investigation are reported in this paper.

The principal reactions involved in the preparation are those outlined in the series of reactions.



(1) Chloramphenicol is the generic name for the antiblotic identified as Chloromycetin, a Parke Davis & Co. trademark.

(2) Long and Troutman, THIS JOURNAL, **71**, 2473 (1949).



V DL-*threo*

Intermediate I in the series was obtained in each case by condensing the α-bromoacetophenone derivative with hexamethylenetetramine, hydrolyzing the salt and subsequently acetylating the product with acetic anhydride. Each indicated reaction leads to the desired product in relatively high yields.

The chief product (III) obtained by the aluminum isopropoxide reduction of II is apparently the DL-*threo* derivative. Evidence for this opinion lies in the method of synthesis, which has been shown to yield the *threo* racemate, as well as similarity of the crystalline form of III to the corresponding intermediates obtained in the synthesis of chloramphenicol.[2] Also the final product (V) exhibits a higher degree of activity than the corresponding product prepared from the other racemate which is present in the reduction mixture in minor amounts.

Table I summarizes pertinent data concerning various compounds prepared in the investigation. In each case product V is reported as the *threo* racemate. Results of pharmacological testing will be made available at a later date.

Experimental

α-Bromo-*p*-fluoro, chloro, bromo and iodoacetophenone.—These intermediates were prepared by methods described in the literature. *p*,α-Dibromoacetophenone may be obtained from the Eastman Kodak Co.

Hexamethylenetetramine Salts of α-Bromo-*p*-fluoro, chloro, bromo and iodoacetophenone.—The α-bromoaceto-

TABLE I

Compound	R	M. p., °C.	Yield, %[b]	Formula	Carbon, %[a] Calcd.	Found	Hydrogen, % Calcd.	Found
I	F	152–154	24	$C_{10}H_{10}FNO_2$	61.53	61.62	5.16	5.02
	Cl	174–177	75	$C_{10}H_{10}ClNO_2$	56.74	56.71	4.76	4.84
	Br	175–177	75	$C_{10}H_{10}BrNO_2$	46.89	46.51	3.92	4.04
	I	183–184	80	$C_{10}H_{10}INO_2$	39.62	39.81	3.33	3.39
II	F	125–127	59	$C_{11}H_{12}FNO_3$	58.66	58.52	5.37	5.53
	Cl	125–126	73	$C_{11}H_{12}ClNO_3$	54.66	54.88	5.01	5.11
	Br	145–147	81	$C_{11}H_{12}BrNO_3$	46.17	46.43	4.23	4.14
	I	158–159	78	$C_{11}H_{12}INO_3$	39.66	39.57	3.63	3.64
III	F	144–146	57	$C_{11}H_{14}FNO_4$	58.14	58.15	6.21	6.45
	Cl	166–168	50	$C_{11}H_{14}ClNO_4$	54.21	54.51	5.79	5.58
	Br	176–178	39	$C_{11}H_{14}BrNO_4$	45.85	46.33	4.90	4.99
	I	180–182	45	$C_{11}H_{14}INO_4$	39.42	39.56	4.21	4.25
IV	F	138–140	61	$C_9H_{12}FNO_2$	58.36	58.52	6.53	6.72
	Cl	122–123	98	$C_9H_{12}ClNO_2$	53.60	53.58	6.00	6.22
	Br	104–106	70	$C_9H_{12}BrNO_2$	43.92	44.06	4.92	4.94
	I	188–189	50	$C_9H_{12}INO_2$	36.88	38.10	4.13	4.35
V	F	82–84	52	$C_{11}H_{12}Cl_2FNO_3$	44.61	44.67	4.09	4.30
	Cl	118–120	70	$C_{11}H_{12}Cl_3NO_3$	42.26	42.93	3.87	4.08
	Br	134–135	55	$C_{11}H_{12}BrCl_2NO_3$	37.00	37.00	3.39	3.51
	I	121–122	40	$C_{11}H_{12}Cl_2INO_3$	32.70	33.15	3.00	3.14

[a] The analytical data were determined by Mr. C. E. Childs of this Laboratory. [b] Yields of I are based on the hexamethylenetetramine salt. Yields of II, III, IV and V are based on the preceding intermediate.

phenone derivatives were condensed with hexamethylenetetramine in chloroform as described by Jacobs and Heidelberger.[3] The yields of salts so obtained are usually in excess of 90%.

α-Amino-*p*-fluoro, chloro, bromo and iodoacetophenone.—The procedure employed by Mannich and Hahn[4] for hydrolyzing the hexamethylenetetramine salts was modified somewhat. α-Amino-*p*-bromoacetophenone was prepared as follows.

Six hundred and two grams of the corresponding hexamethylenetetramine salt was mixed with 2450 ml. of concentrated hydrochloric acid and 4900 ml. of 95% ethanol. The mixture was stirred at room temperature for sixteen hours, cooled to 5° and filtered. The solid was stirred with 750 ml. of cold water, filtered and the solid air-dried. The product may be acetylated without further purification. A small sample was recrystallized from dilute hydrochloric acid; m. p. 278–281° (dec.).

Anal. Calcd. for $C_8H_8BrNO_2 \cdot HCl$: N, 5.59. Found: N, 5.67.

α-Acetamido-*p*-bromoacetophenone (I, R = Br).—Since the procedures for the preparation of the intermediates in Table I are similar for each type, the synthesis of each *p*-bromo compound will be described.

Crude α-amino-*p*-bromoacetophenone hydrochloride obtained in the above experiment was suspended in 4500 ml. of cold water containing 100 ml. of acetic anhydride. The cooled mixture was stirred rapidly while a solution of 130 g. of sodium hydroxide in 1500 ml. of water was added. When one half of the sodium hydroxide solution had been added, an additional 40 ml. of acetic anhydride was added. During the addition of the alkali the temperature was maintained at 10° or lower. Fifteen minutes after the addition was complete the mixture was acidified with hydrochloric acid and filtered. The solid was washed with water and dried at 60°. An analytical sample was obtained by recrystallization from ethyl acetate.

α-Acetamido-*p*-bromo-β-hydroxypropiophenone (II, R = Br).—A mixture of 102.4 g. (0.4 mole) of α-acetamido-*p*-bromoacetophenone, 300 ml. of 95% ethanol, 4 g. of sodium bicarbonate and 52 ml. of 36–38% aqueous formaldehyde was stirred and warmed to 42° for two hours. The mixture was cooled to 0° and filtered. The solid was washed with cold water and air-dried. Additional product (*ca.* 5%) may be obtained by allowing the original filtrate to stand for several hours. An analytical sample was obtained by recrystallization from ethyl acetate.

DL-*threo*-2-Acetamido-1-*p*-bromophenyl-1,3-propanediol (III, R = Br).—A mixture of 57.5 g. (0.2 mole) of α-acetamido-*p*-bromo-β-hydroxypropiophenone, 81.6 g. (0.4 mole) of aluminum isopropoxide and 500 ml. of dry isopropyl alcohol was alternately refluxed and slowly distilled until the acetone test was negative. A total of 300 ml. of distillate was collected. The warm residue was mixed with 45 ml. of water and refluxed for fifteen minutes, then filtered through a layer of Super-Cel. Extraction of the filter-cake with 250-ml. portions of hot 80% aqueous isopropyl alcohol was carried out until the extracts were colorless. The combined extracts were concentrated *in vacuo* and the residue mixed with several volumes of hot ethyl acetate, cooled and filtered. This solid product may be recrystallized from hot water.

DL-*threo*-2-Amino-1-bromophenyl-1,3-propanediol (IV, R = Br).—Fourteen and four-tenths grams of the acetylated derivative was mixed with 150 ml. of 5% hydrochloric acid and heated on the steam-bath for three hours. After filtration the filtrate was cooled and made strongly basic with 20% aqueous sodium hydroxide. The product precipitated as a crystalline solid. It was removed by filtration and washed with cold water. A sample was recrystallized from chloroform.

DL-*threo*-*p*-Bromophenyl-2-dichloroacetamido-1,3-propanediol (V, R = Br).—Five grams of the free base was mixed with 25 ml. of methyl dichloroacetate and heated on a steam-bath for twenty minutes. The mixture was concentrated *in vacuo* and the residue recrystallized from 150 ml. of chloroform. Water is a suitable solvent for recrystallization.

DL-*erythro*-1-*p*-Bromophenyl-2-dichloroacetamido-1,3-propanediol.—By allowing the ethyl acetate filtrate obtained in working up the aluminum isopropoxide reduction described above to stand for several hours a small quantity (*ca.* 5%) of DL-*erythro*-2-acetamido-1-*p*-bromophenyl-1,3-propanediol was obtained; m. p. 186–188°; % N calcd., 4.86; found, 4.68. The free base was prepared by removal of the acetyl group with 5% hydrochloric acid and precipitation with alkali; m. p. 109–110°; % N calcd., 5.69; found, 5.64. Treatment of the free base with methyl dichloroacetate gave the desired DL-*erythro* derivative; m. p. 159–160°.

(3) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 459 (1915).

(4) Mannich and Hahn, *Ber.*, **44**, 1542 (1911).

Anal. Calcd. for $C_{11}H_{12}BrCl_2NO_3$: N, 3.92. Found: N, 3.90.

Summary

A method for the synthesis of the antibiotic, chloramphenicol, has been extended to the preparation of compounds containing a halogen atom rather than a nitro group in the para position of the phenyl ring.

DETROIT, MICHIGAN RECEIVED MARCH 9, 1950

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Geometrical Isomerism of 2,4-Dibenzylidene-3-phenyl-5-oxazolidones. Their Rearrangement to 1,4-Diphenyl-2-benzylidene-3,5-pyrrolidiones

BY SVEND LARSEN[1] AND JACK BERNSTEIN

The preparation of 2,4-dibenzylidene-3-phenyl-5-oxazolidone by the condensation of benzaldehyde with N-phenacetyl-N-phenylglycine (I) in the presence of acetic anhydride was reported during the work on the synthesis of penicillin.[2] Additional investigation of this reaction has shown that the product was not homogeneous, but was apparently a mixture of geometrical isomers, II (red, m. p. 189.5–191°) and III (yellow, m. p. 171–173°). The presence of two isomers could be demonstrated by paper chromatography when hexane was used for the development, since III could be separated as a faster-moving yellow band from the slower-moving red band of II. These isomers could be separated by repeated fractional crystallization since II crystallized more rapidly from acetone than did III. A similar isomerism was observed in the oxazolidones obtained by the condensation of *p*-chlorobenzaldehyde with N-phenyl-N-phenacetylglycine in the presence of acetic anhydride. The two isomers were separated by fractional crystallization and existed as a red compound (IIa), corresponding to II, and a yellow compound (IIIa), corresponding to III.

III had the expected empirical formula, $C_{23}H_{17}NO_2$, and showed the usual reactions of a lactone. An amide was obtained when an acetone solution of III was treated with dry ammonia, and a methyl ester was isolated when III was treated with methanolic hydrogen chloride. Hydrolysis of the lactone occurred even upon refluxing in moist benzene or moist chloroform and the acid (V), $C_{23}H_{19}NO_3$, was isolated. This acid is apparently N-phenacetyl-N-phenyl-α-aminocinnamic acid since it readily absorbed one mole of hydrogen to give N-phenacetyl-β,N-diphenyl-α-alanine (VI). Treatment of V with hydriodic acid and red phosphorus gave reduction and hydrolysis to phenylacetic acid and the known β,N-diphenyl-α-alanine (VII). V upon treatment with acetic anhydride was reconverted to III.

Similarly II, isomeric with III, showed the reactions of a lactone and upon hydrolysis formed an acid (IV), isomeric with V. IV was also reduced to form VI, and by treatment with hydriodic acid and red phosphorus formed phenylacetic acid and VII. II was reformed by treatment of IV with acetic anhydride.

In practice, large amounts of the isomeric lactones were synthesized from the corresponding isomeric acids (IV and V). These were prepared by refluxing the original crude mixture of lactones in moist benzene, from which IV crystallized upon cooling, while V remained in solution. The lactones were then resynthesized by treatment of the acids with acetic anhydride.

It was interesting to note that either II or III could be isomerized to a mixture of the two by warming in acetic anhydride containing a trace of bromine, although only one of a pair of geometrical isomers is usually isomerized. Dufraisse[3] had observed a similar example with the isomers of α,β-dibromo-β-benzoylstyrene. The oxazolidones showed some differences in ultraviolet absorption[4] (Fig. 1), but attempts to analyze mixtures of II and III on the basis of the absorption were unsuccessful. Although either of the lactones could be isomerized to a mixture of the two isomers, the corresponding acids, IV and V, did not show this same property. IV was isomerized to V by heating in an inert atmosphere at 135° for eighteen hours. V, however, did not change under these conditions.

An interesting reaction was observed when II or III was treated with alcoholic potassium hydroxide instead of aqueous alkali. From II, IV was obtained as in other hydrolyses, but in addition another acidic compound (IX) was isolated. This acidic compound was obtained as the only reaction product when the lactone was treated with a solution of sodium in an alcohol. Analyses indicated an empirical formula $C_{23}H_{17}NO_2$, corresponding to a compound isomeric with the original lactone. III behaved similarly and gave the acidic compound (X), isomeric with IX.

IX and X were geometrical isomers since reduction of either of the compounds gave the same di-

(1) American-Scandinavian Foundation Honorary Fellow; present address, Nörregade 72, Grindsted, Denmark.

(2) O. S. R. D. Progress Reports on Synthesis of Penicillin, S. **20**, 7, June, 1944.

(3) Dufraisse, *Compt. rend.*, **158**, 1691 (1914).

(4) The coöperation of Dr. N. H. Coy of the Department of Applied Physics, Squibb Research and Development Laboratories, in providing the spectroscopic measurements cited in this paper is gratefully acknowledged.