under reduced pressure. One hundred fifty cc. of diamyl ether was added and the temperature was brought to 100°, at which time 40 cc. of acetic anhydride was added. After sixty-five minutes the mixture was cooled, filtered and washed with ethanol. The product was steeped in ethanol overnight, filtered and air-dried. The moisture content was 4.53%.

Anal. Calcd. for $C_6H_9O_5(C_2H_3O)$: acetyl, 21.08. Found: acetyl, 21.1.

STARCH AND DEXTROSE DIVISION
NORTHERN REGIONAL RESEARCH LABORATORY[5]
PEORIA, ILL.
RECEIVED MARCH 13, 1950

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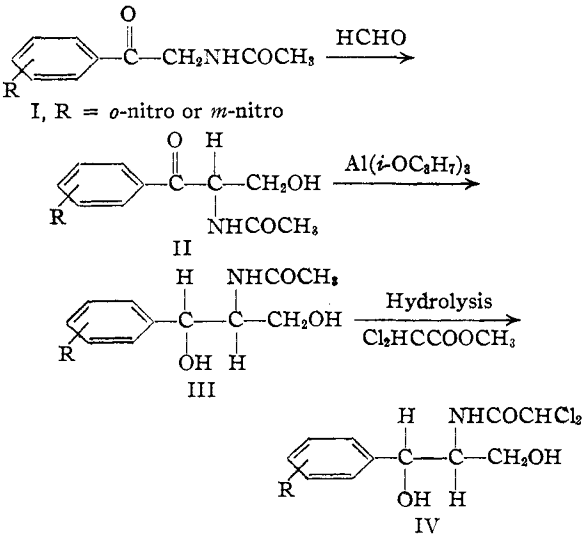
[5] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

Chloramphenicol[1] (Chloromycetin). Related Compounds

BY LOREN M. LONG AND N. JENESEL

Chloramphenicol has been shown to be D-(*levo*)-*threo*-2-dichloroacetamido-1-*p*-nitrophenyl-1,3-propanediol.[2] The recent publication by Buu-Hoï and Khôi[3] of the synthesis of the related compound, DL-*threo*-2-dichloroacetamido-1-*m*-nitrophenyl-1,3-propanediol, prompts the present authors to report the results of their investigation of this compound and also the corresponding *o*-nitro derivative.

The procedure for the synthesis of chloramphenicol originally developed by Long and Troutman[4,5] has proved to be of value in the preparation of many compounds related to the antibiotic and was applied with success to the derivatives reported herein. Important steps involved in the synthesis are illustrated in the series of reactions.



I, R = *o*-nitro or *m*-nitro

II

III

IV

The intermediate α-acetamidoketones (I) may be prepared from the corresponding nitroacetophenones[6] by bromination and subsequent conversion to the aminoketone by use of hexamethylenetetramine.[7]

Condensation of I with formaldehyde proceeds satisfactorily. As in the previous publication,[5] reduction of the propiophenone derivative (II) is accomplished with aluminum isopropoxide. The principal product so obtained is the desired *threo* racemate.

In the authors' first attempt to prepare the *m*-nitro compound a product melting at 157° was obtained. This melting point corresponds fairly well to that reported by Buu-Hoï and Khôi.[3] However, the substance did not analyze correctly despite repeated recrystallization. Unfortunately, analyses are not given in the earlier publication.[3] The preparation was repeated, using a shorter period of hydrolysis of compound III. A compound melting at 135–136° was then obtained which gives the correct analysis. The ultraviolet absorption spectrum of the higher melting material shown in Fig. 1 except that the absorption maximum is at 266.5 mμ.

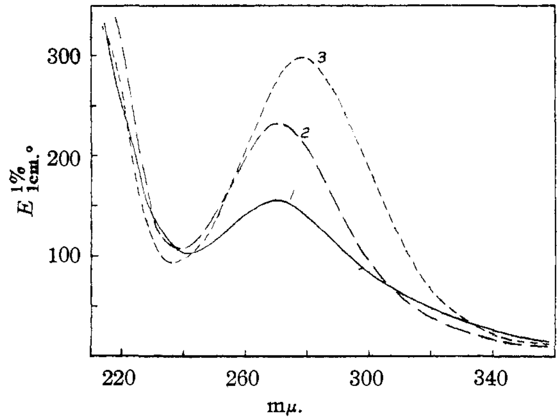


Fig. 1.—Ultraviolet absorption spectra of: 1, 2-dichloroacetamido-1-*o*-nitrophenyl-1,3-propanediol; 2, 2-dichloroacetamido-1-*m*-nitrophenyl-1,3-propanediol; 3, chloramphenicol. The solvent in each case was water.

Table I summarizes data concerning the intermediates illustrated in the series of reactions. Compound IV is assumed to be the *threo* racemate. This assumption is based on comparisons with derivatives reported previously.[4,5] Figure 1 gives the ultraviolet absorption spectra of the three related nitro compounds.[8]

Experimental

α-Acetamido-β-hydroxy-*o*-nitropropiophenone.—A mixture of 29.4 g. (0.132 mole) of α-acetamido-*o*-nitroacetophenone, 10 ml. of methanol and 12 ml. of 36–38% aqueous formaldehyde was placed in a flask and heated to 35°.

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[1] Chloramphenicol is the generic name for the antibiotic identified as Chloromycetin, a Parke, Davis & Co. trademark.

[2] Rebstock, Crooks, Controulis and Bartz, THIS JOURNAL, **71**, 2458 (1949).

[3] Buu-Hoï and Khôi, *Compt. rend.*, **229**, 1343 (1949).

[4] Long and Troutman, THIS JOURNAL, **71**, 2469 (1949).

[5] Long and Troutman, *ibid.*, **71**, 2473 (1949).

[6] Walker and Hauser, *ibid.*, **68**, 1386 (1946).

[7] Mannich and Hahn, *Ber.*, **44**, 1542 (1911).

[8] The ultraviolet absorption spectra were determined under the direction of Dr. J. M. Vandenbelt of this Laboratory.

TABLE I

Compound	R	M. p., °C.	Yield, %[b]	Formula	Carbon, %[a] Calcd.	Carbon, %[a] Found	Hydrogen, % Calcd.	Hydrogen, % Found
I	*o*-NO$_2$	131–132	71	$C_{10}H_{10}N_2O_4$	54.05	54.22	4.54	4.62
	m-NO$_2$	142–143	72	$C_{10}H_{10}N_2O_4$	54.05	54.19	4.54	4.67
II	*o*-NO$_2$	126–127	81	$C_{11}H_{12}N_2O_5$	52.38	52.30	4.80	4.95
	m-NO$_2$	160–162	78	$C_{11}H_{12}N_2O_5$	52.38	52.48	4.80	5.03
III	*o*-NO$_2$	187–188	19	$C_{11}H_{14}N_2O_5$	51.96	51.98	5.55	5.69
	m-NO$_2$	172–173	28	$C_{11}H_{14}N_2O_5$	51.96	51.82	5.55	5.64
IV	*o*-NO$_2$	125–126	52	$C_{11}H_{12}Cl_2N_2O_5$	40.88	41.10	3.75	3.88
	m-NO$_2$	135–136	61	$C_{11}H_{12}Cl_2N_2O_5$	40.88	41.25	3.75	3.95

[a] Analytical data were determined by Mr. C. E. Childs of this Laboratory. [b] Yield of I is based on hexamethylenetetramine salt while yields of II, III and IV are based on the preceding intermediate.

The mixture was stirred and a solution of 1.2 g. of sodium bicarbonate and 0.4 g. of sodium carbonate in 20 ml. of water was added. After twenty minutes a clear solution was formed and within an additional twenty minutes a granular solid began to precipitate. The mixture was stirred for forty-five minutes and then cooled to 5°. The solid product was filtered off, washed thoroughly with water and dried. A sample was recrystallized from a mixture of benzene and isoöctane.

DL-*threo*-2-Acetamido-1-*o*-nitrophenyl-1,3-propanediol.—To a hot solution of 13.1 g. (0.064 mole) of aluminum isopropoxide in 110 ml. of anhydrous isopropyl alcohol was added 13.5 g. (0.053 mole) of α-acetamido-β-hydroxy-*o*-nitropropiophenone. The mixture was stirred and acetone was removed by means of a Hahn condenser over a period of two hours. A total of 70 ml. of isopropyl alcohol was removed by distillation. The residue was allowed to cool somewhat and 25 ml. of water was added. The mixture was refluxed for fifteen minutes and then filtered through a layer of Super-cel. The filter-cake was extracted twice with hot 50-ml. portions of 80% isopropyl alcohol. The extracts were combined and concentrated *in vacuo*. The residue was dissolved in a small quantity of ethyl acetate. On cooling the solution a crystalline product was obtained.

DL-*threo*-2-Dichloroacetamido-1-*o*-nitrophenyl-1,3-propanediol.—A mixture of 2.5 g. (0.01 mole) of DL-*threo*-2-acetamido-1-*o*-nitrophenyl-1,3-propanediol and 25 ml. of 5% hydrochloric acid was heated on a steam-bath with occasional swirling for one hour. The hot solution was charcoaled and filtered. The filtrate was cooled and made strongly basic with 20% aqueous sodium hydroxide. The resulting solution was extracted several times with small portions of ethyl acetate. The extracts were combined, dried over anhydrous magnesium sulfate and then concentrated *in vacuo*. The residue was mixed with 1.5 g. of methyl dichloroacetate in 7.5 ml. of methanol and refluxed for one hour. The solution was diluted with 25 ml. of ethylene dichloride and concentrated *in vacuo*. The residue, a colorless solid, was recrystallized from water.

THE RESEARCH LABORATORIES
PARKE, DAVIS & COMPANY
DETROIT, MICHIGAN

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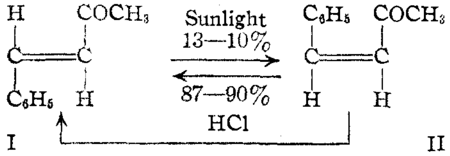
Spectroscopic Evidence for the Sunlight Conversion of *trans* to *cis*-Benzalacetone

BY ROBERT E. LUTZ, CARL R. BAUER[1] AND ROBERT H. JORDAN[2]

In an investigation stemming from the recent isolation of *cis*-benzalacetophenone[3] it has been possible to demonstrate the formation of a *cis*-isomer (II) upon exposure to bright sunlight of an isoöctane solution of ordinary (*trans*) benzalacetone (I). The optical density of the solution decreased rapidly to a quasi-equilibrium point without apparent change in λ_{max}, but beyond this point upon further exposure there occurred a continuing slow decrease in optical density which was evidence of other (permanent) transformations. The contribution to the optical density by the *cis* isomer and secondary transformation products, and the concentration of the *trans* isomer, were determined by measuring the optical density of the same solution after freezing out the bulk of the *trans* isomer to reduce concentration to a small and known value. It followed from the data obtained that the concentration of the *trans* isomer in the original solution after exposure to sunlight was 77% of the original, and that 23% had been converted into the *cis* isomer and other transformation products. The actuality of the presence of *cis*-benzalacetone in the solution after exposure to sunlight was demonstrated by the increase in optical density of this solution after treatment with hydrochloric acid according to the scheme used for converting *cis*- to *trans*-benzalacetophenone,[3] and, in the case of the solution from which the bulk of the *trans* isomer had been frozen out, by similar treatment with hydrochloric acid followed by freezing out and identification of the *trans* compound regenerated. These facts are consistent with the postulated *cis–trans* relationships but not with polymerization–depolymerization.



The best estimate of the actual ratio of *cis*-benzalacetone at photoequilibrium is 13% and the lowest 10%, and of the *trans* isomer 87–90%.

The absorption spectrum of the solution after exposure and removal of the bulk of the *trans*-benzalacetone showed only one measurable peak at 278 mμ, and a part of the absorption at this point is attributed to *cis*-benzalacetone. It appears that λ_{max} for the *cis* isomer is approximately the same as that of the *trans*. The molar extinc-

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(1) du Pont Co. Fellow, 1949–1950.

(2) Medical School, University of Virginia.

(3) Lutz and Jordan, THIS JOURNAL, 72, 4090 (1950).