TABLE I

Derivative	M. p., °C. (cor.)	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Other Calcd.	Other Found
p-Toluide	123	$C_{12}H_{15}ON$	76.15	75.46	7.99	7.87	7.40	7.62		
Hydrazide	156.0–156.5	$C_{11}H_{14}ON_2$	69.44	70.20	7.42	7.32	14.73	14.03		
p-Bromophenacyl ester	81.5–82.0	$C_{18}H_{13}O_3Br$	52.54	52.77	4.41	4.59			(Br) 26.89	27.07
p-Phenyl phenacyl ester	91.5	$C_{19}H_{18}O_3$	77.53	77.45	6.16	6.31				
Benzylisothiouronium salt	160–161	$C_{18}H_{18}O_2N_2S$	58.62	58.65	6.81	6.72	10.52	10.34	(S) 12.04	12.04

in this Laboratory by standard methods[2] and are listed in Table I. The anilide, m.p. 111°, has been reported previously.[3]

(2) Shriner and Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N.Y., 1944, pp. 154–159.

(3) Freund and Gudeman, *Ber.*, **21**, 2692 (1888).

DEPARTMENT OF CHEMISTRY
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO 16, ILLINOIS RECEIVED AUGUST 4, 1950

Non-reduction of the Acetal Group by Lithium Aluminum Hydride

BY C. S. MARVEL AND H. W. HILL, JR.[1]

We have recently had occasion to prepare the glycol acetal (II) and it occurred to us that the reduction of the corresponding malonic ester derivative (I) would produce this substance if the acetal group were not affected by the action of lithium aluminum hydride.

$$(C_2H_5O)_2CHCH_2CH_2CH(CO_2C_2H_5)_2 \longrightarrow$$
I

$$(C_2H_5O)_2CHCH_2CH_2CH(CH_2OH)_2$$
II

Preliminary tests of the action of lithium aluminum hydride on acetal, $CH_3CH(OC_2H_5)_2$, indicated no reaction. Hence the ester was prepared by the condensation of the diethylacetal of β-chloropropionaldehyde with sodium malonic ester[2] and the reduction of the acetal ester accomplished with lithium aluminum hydride. The glycol acetal (II) was isolated from the alkaline medium in 33% yield.

Preparation of 5-Hydroxy-4-hydroxymethylpentanal Diethyl Acetal.—When 83.3 g. (0.286 mole) of 3,3-diethoxy-1-propylmalonic acid diethyl ester was added dropwise over a period of 2.5 hours to a solution of 14.6 g. (0.385 mole) of lithium aluminum hydride in 300 ml. of absolute ether and the excess hydride decomposed by the cautious addition of water, a product which boiled at 140–144° at 1.2 mm.; $n^{20}D$ 1.4540; d^{20}_4 1.0178 was obtained upon distillation of the ethereal solution. The yield was 19.5 g. (33.2%).

Anal. Calcd. for $C_{10}H_{22}O_4$: C, 58.22; H, 10.75; *MR*, 54.72. Found: C, 58.33; H, 10.99; *MR*, 54.89.

(1) Allied Chemical and Dye Corporation Fellow, 1949–1950. Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.

(2) D. T. Warner and O. A. Moe, THIS JOURNAL, **70**, 3470 (1948).

NOYES CHEMICAL LABORATORY
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URBANA, ILLINOIS RECEIVED JULY 31, 1950

Polyalkylene Sulfides. VII. The Polymer from Tetramethylenedithiol and Biallyl

BY C. S. MARVEL AND ALEX KOTCH

Marvel and Chambers[1] added tetramethylenedithiol to biallyl under the influence of ultraviolet light to obtain a low-molecular weight polymer. This addition reaction carried out in emulsion according to the method recently described[2] gives a polymer with an inherent viscosity of 0.52 which melts at 64–67°. The polymer can be cold drawn to give a fiber. Surprisingly enough we have also been able to form this polymer with an inherent viscosity of 0.63 and m.p. 65–68° from tetramethylene bromide and the disodium salt of hexamethylenedithiol in a benzene–alcohol mixture.

This condensation polymerization reaction was carried out by dissolving 0.46 g. of sodium in 15 ml. of absolute alcohol (distilled from magnesium ethoxide[3]) and then adding 1.5 g. of hexamethylenedithiol. The sodium salt of the dithiol precipitated and then redissolved when the mixture was heated. To this boiling solution were added 25 ml. of dry thiophene-free benzene and then 2.15 g. of tetramethylene bromide. Immediately a vigorous reaction set in, and vigorous refluxing of the solvent mixture occurred. When the spontaneous reaction subsided, the mixture was diluted with an additional 25 ml. of benzene and then heated under refluxing conditions overnight. The cold, filtered solution was poured into methanol, and the polymer was collected on a filter. The yield was 1.08 g. of polymer, m.p. 63–65° with an inherent viscosity of 0.36. The benzene insoluble material was treated with water and an additional 0.26 g. of polymer, m.p. 65–68°, with an inherent viscosity of 0.63 was obtained.

(1) C. S. Marvel and R. R. Chambers, THIS JOURNAL, **70**, 993 (1948).

(2) C. S. Marvel and P. H. Aldrich, *ibid.*, **72**, 1978 (1950).

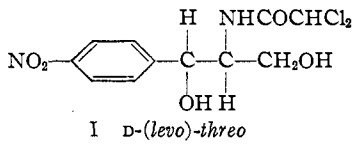
(3) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, New York, N. Y., 1941, p. 359.

NOYES CHEMICAL LABORATORY
URBANA, ILLINOIS RECEIVED JULY 31, 1950

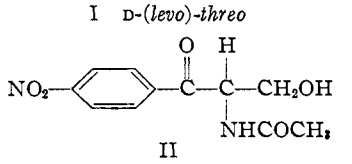
Chloromycetin.[1] Synthesis of α-Dichloroacetamido-β-hydroxy-*p*-nitropropiophenone

BY LOREN M. LONG AND H. D. TROUTMAN

In an earlier paper[2] the authors describe a method for the preparation of D-(*levo*)-*threo*-2-dichloroacetamido - 1 - *p* - nitrophenyl - 1,3 - propanediol (Chloromycetin, I) in which a necessary intermediate is *p*-nitroacetophenone. One of the latter steps in the synthesis involves the preparation of α-acetamido-β-hydroxy-*p*-nitropropiophenone (II). A comparison of the structure of II with that of I suggests that the substitution of a dichloroacetyl



I D-(*levo*)-*threo*



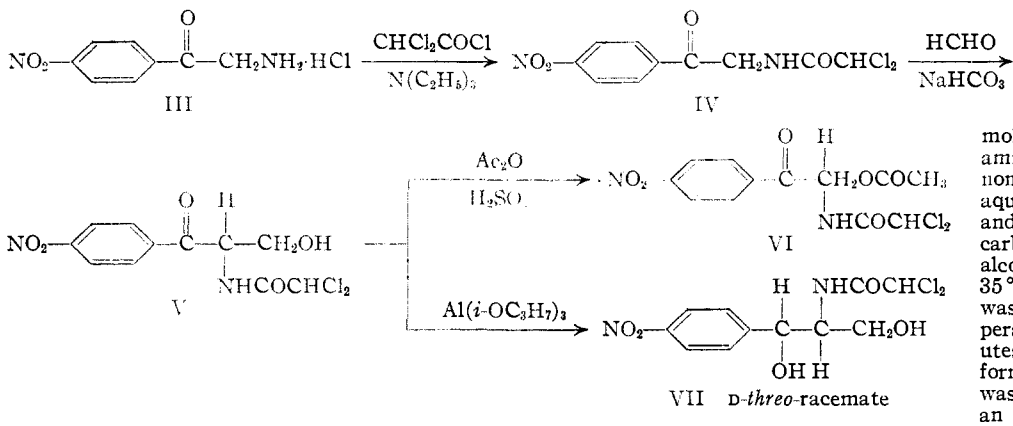
II

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

(2) L. M. Long and H. D. Troutman, THIS JOURNAL, **71**, 2473 (1949).

group for the acetyl group in II would produce a compound (V) which may be considered the racemate of a dehydro derivative of Chloromycetin. The possibility that such a compound would possess worthwhile therapeutic activity was interesting enough to justify the investigation. In addition, the aluminum alkoxide reduction of V would constitute a synthesis of racemic Chloromycetin (VII).

The procedure employed for the synthesis of V is illustrated in the series of reactions.



Some difficulty was encountered in the preparation of α-dichloroacetamido-*p*-nitroacetophenone (IV). Various alkaline reagents were used for the purpose of neutralizing the hydrogen chloride formed during the reaction. Best results were obtained when triethylamine was added to a mixture of α-amino-*p*-nitroacetophenone hydrochloride (III) and dichloroacetyl chloride in an inert solvent.

Monohydroxymethylation of IV proceeds under the same conditions described[2] for the preparation of II. However, the product usually precipitates as an oil which solidifies slowly. Purification is somewhat difficult, but acetylation yields a derivative (VI) which is easily purified and analyzed.

Further proof of the structure of V is obtained through reduction with aluminum isopropoxide. The principal product of the reaction is the racemic form of Chloromycetin (VII).

A brief examination of V as to pharmacological activity has been made. The compound exhibits a surprising degree of fungicidal potency, *e.g.*, a dilution of 1:487,805 (2.05 γ/ml.) causes 50% inhibition in growth of *Candida albicans*.[3] Compounds II, III and IV show little fungicidal activity.

Experimental[4]

α-Dichloroacetamido-*p*-nitroacetophenone (IV).—One-hundred and eight grams (0.5 mole) of α-amino-*p*-nitroacetophenone hydrochloride (III)[2] and 88.5 g. (0.6 mole) of dichloroacetyl chloride were mixed together with 1 l. of dry benzene in a 2-l. flask equipped with a reflux condenser, a mechanical stirrer and a dropping funnel. The mixture was cooled and stirred while 111 g. (1.1 moles) of triethylamine was added over a period of 1 hour. Toward the end of the addition the mixture thickened and the cooling bath was removed. Stirring was continued for a total of 2 hours.

The mixture was then heated to reflux and filtered hot. As the filtrate cooled a quantity of solid product separated which was filtered off. The filtrate was concentrated *in vacuo*. The residue was washed with ligroin then water. It was dissolved in hot alcohol and the resulting solution diluted to cloudiness with water. The mixture was cooled and filtered. The solid was combined with the material obtained originally and recrystallized from benzene; yield 72.7 g. or 50%; m.p. 144–146°. An analytical sample was obtained by repeated recrystallization from benzene; m.p. 148–149°.

Anal. Calcd. for $C_{10}H_8Cl_2N_2O_4$: C, 41.26; H, 2.77; Cl, 24.36. Found: C, 41.62; H, 2.80; Cl, 24.08.

α-Dichloroacetamido-β-hydroxy-*p*-nitropropiophenone (V).—A mixture containing 2.91 g. (0.01 mole) of α-dichloroacetamido-*p*-nitroacetophenone, 3.5 ml. of 36–38% aqueous formaldehyde and 0.2 g. of sodium bicarbonate in 10 ml. of alcohol was warmed to 35°. After the mixture was shaken at this temperature for a few minutes, a clear solution was formed. The solution was allowed to stand for an hour before being cooled in an ice-bath. There was no precipitation. Addition of water to the solution produced an oil which solidified slowly. The solid material was refluxed with a little chloroform and cooled. The mixture was filtered and the product dried *in vacuo;* m.p. 105–115°. It was recrystallized repeatedly by solution in hot chloroform and cooling and finally by solution in hot isopropyl alcohol; yield 1.3 g. or 40%; m.p. 124–125°.

Anal. Calcd. for $C_{11}H_{10}Cl_2N_2O_5$: C, 41.14; H, 3.14; Cl, 22.08; N, 8.73. Found: C, 41.58; H, 3.26; Cl, 22.21; N, 8.96.

β-Acetoxy-α-dichloroacetamido-*p*-nitropropiophenone (VI).—To a mixture of 3.21 g. (0.01 mole) of α-dichloroacetamido-β-hydroxy-*p*-nitropropiophenone in 9 ml. of acetic anhydride was added two drops of sulfuric acid. The mixture became warm and a clear solution was formed. After 30 minutes the solution was diluted with several volumes of water and stirred until the excess anhydride was hydrolyzed. The solid material was filtered off and dried; m.p. 120–123°. The product was recrystallized from benzene; yield 3.3 g. or 90%; m.p. 124°. The melting point of a mixture of this product and starting material was 105–110°.

Anal. Calcd. for $C_{13}H_{12}Cl_2N_2O_6$: C, 42.99; H, 3.33. Found: C, 43.13; H, 3.49.

Racemic Chloromycetin (VII).—To a hot solution of 6.12 g. (0.03 mole) of aluminum isopropoxide in 100 ml. of isopropyl alcohol was added 6.42 g. (0.02 mole) of α-dichloroacetamido-β-hydroxy-*p*-nitropropiophenone. The mixture was stirred while slow distillation was continued for 3 hours. Initially the mixture was light yellow in color but gradually darkened to a deep red. The solution was cooled somewhat and 20 ml. of water was added. The resulting mixture was refluxed for 15 minutes and then filtered hot through Super-Cel. The filter-cake was extracted with 100 ml. of hot 80% aqueous isopropyl alcohol. The combined extracts were concentrated *in vacuo*. The gummy residue was refluxed with 30 ml. of ethyl acetate and cooled. The solid was filtered off and recrystallized from 30 ml. of ethyl acetate; yield 2.4 g. or 37%; m.p. 152°. The melting point of a mixture with authentic racemic Chloromycetin was 152°.

Anal. Calcd. for $C_{11}H_{12}Cl_2N_2O_5$: C, 40.88; H, 3.75. Found: C, 41.24; H, 3.87.

(3) Unpublished data by Dr. A. B. Hillegas of this Laboratory.

(4) The analytical data were determined by Mr. C. E. Childs and Miss Geraldine Saladonis of this Laboratory.

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