showed practically no purine absorption in the ultraviolet and were discarded. Evaporation of pooled identical fractions *in vacuo* yielded 27.2 mg. of III, m.p. 180–182° and 61 mg. of XIII, m.p. 189–191°. A sample of XIII obtained in a similar partition chromatogram and recrystallized from hot ethyl acetate with just enough methanol to effect solution had a m.p. 200–201° after drying *in vacuo* for 3 hours at 110°; $[\alpha]^{24.5}D$ −85.5° (*c* 0.415 in 60% ethanol). In the ultraviolet the compound showed the following maxima: $\lambda_{max}^{ethanol}$ 291 mμ (ε 22400 at *p*H 1), 298 mμ (ε 17720 at *p*H 7), 298 mμ (ε 17480 at *p*H 14).

Anal. Calcd. for $C_{12}H_{17}N_5O_4$: C, 48.80; H, 5.80; N, 23.72. Found: C, 49.17; H, 6.05; N, 23.74.

The compound was somewhat hygroscopic and a sample which had not been dried as well as the one just described, analyzed for a semihydrate, m.p. 199–200°.

Anal. Calcd. for $C_{12}H_{17}N_5O_4{}^1/_2H_2O$: C, 47.36; H, 5.96; N, 23.02. Found: C, 47.67; H, 6.07; N, 23.28.

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

Compounds Related to Chloromycetin.[1] 1-Biphenylyl and Ring-substituted 1-Biphenylyl-2-dichloroacetamido-1,3-propanediols

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The preparations of 4′-bromo- and 4′-methyl-1-biphenylyl-2-dichloroacetamido-1,3-propanediol are described. DL-*threo*-1-Biphenylyl-2-amino-1,3-propanediol was resolved by the fractional crystallization of a salt of dextrorotatory phenylethylsuccinic acid to obtain the D-*threo* intermediate base for use in preparing the biologically active dichloroacetamide.

An extensive group of compounds related to Chloromycetin in which the nitro group in the *para* position is replaced by various types of organic radicals, has now been described in the literature. The substituents include the halogens: iodine,[2-4] bromine,[2,3] chlorine[2,3,5] and fluorine.[2,3] Compounds have also been prepared with methoxy and phenoxy,[6] methyl,[7] cyano,[8] acylamido and aroylamido,[9] alkylmercapto and arylmercapto,[10] alkylsulfonyl[10] and trifluoromethyl[11] groups in the *para* position.

Although Colonna and Runti prepared 1-biphenylyl-2-acetamido-1,3-propanediol,[12] conversion to the dichloroacetamide was not reported by these workers. Bambas in a patent[13] has described the synthesis of the latter compound. Further details in the preparation of D- and DL-*threo*-1-biphenylyl-2-dichloroacetamido-1,3-propanediol as well as the 4′-methyl and 4′-bromo related compounds are reported in this paper. The procedure developed by Long and Troutman[14] as a method for the preparation of Chloromycetin, or a slight modification of this approach first described in the literature by Sorm and co-workers,[5] proved useful in synthesizing these compounds. According to the first method α-acetamido-β-hydroxymethylacetophenones are reduced to the corresponding phenylacetamidopropanediols. The amino group is then liberated by hydrolysis, the free base is resolved, and the D-threo isomer converted to the dichloroacetamide. If dichloroacetamidoacetophenones are used instead of acetamides, reduction leads directly to the racemic substituted 1-phenyl-2-dichloroacetamido-1,3-propanediols. A disadvantage in the latter approach may lie in the fact that the presence of labile halogens limits the reducing agents which can be used. Meerwein-Ponndorf-Verley conditions have been found useful in the reduction of such dichloroacetamides but these conditions usually lead to the formation of one diastereoisomer in much greater quantity than the other. In some cases only one of the two possible racemates has been isolated. Fortunately when both isomers were obtained, the compound which predominated had some antibacterial activity, while the isomer formed in lower yield always proved to be virtually inactive under the conditions of our testing program.[15]

On the other hand, it was advantageous to have the α-dichloroacetamido-β-hydroxymethylacetophenone intermediates for investigation as possible antifungal agents. These compounds are related to α-dichloroacetamido-β-hydroxymethyl-*p*-nitroacetophenone, a compound prepared by Long and Troutman and found by Hillegas to be very effective in inhibiting the growth of certain fungi.[16]

The reduction of α-dichloroacetamido-β-hydroxymethyl-4′-methylphenylacetophenone using Meer-

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

(2) L. L. Bambas, H. D. Troutman and L. M. Long, THIS JOURNAL, **72**, 445 (1950).

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(11) W. T. Caldwell and G. C. Schweiker, *ibid.*, **75**, 5884 (1953).

(12) M. Colonna and C. Runti, *Boll. sci. fac. chim. ind. Bologna*, **9**, 531 (1951) [*C. A.*, **46**, 3023 (1952)]; *Ann. Chim.*, **41**, 739 (1951) [*C. A.*, **47**, 2147 (1953)].

(13) L. L. Bambas, U. S. Patent 2,543,267 (1951).

(14) L. M. Long and H. D. Troutman, THIS JOURNAL, **71**, 2469 (1949).

(15) We are indebted to Drs. J. Ehrlich and A. S. Schlingman, Mrs. M. Galbraith, Mrs. Della Fox, Miss Mary Manning and co-workers for detailed antibacterial studies of these compounds.

(16) L. M. Long and H. D. Troutman, THIS JOURNAL, **73**, 481 (1951).

TABLE I

1-BIPHENYLYL AND 4'-SUBSTITUTED BIPHENYLYL-2-DICHLOROACETAMIDO-1,3-PROPANEDIOLS AND INTERMEDIATES USED IN THE PREPARATION OF THESE COMPOUNDS

Structure R	R'	Formula	M.p., °C.[19]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
4'-R-C_6H_4-C_6H_4-$COCH_2NH_2HCl$ (I)									
Br		$C_{14}H_{13}NOClBr$	249–250 d.	51.48	51.27	4.01	3.96		
CH_3		$C_{15}H_{16}NOCl$	246–248 d.	68.83	68.85	6.16	6.21	5.35	5.38
4'-R-C_6H_4-C_6H_4-CO-CH_2NHR' (II)									
H	$-COCH_3$	$C_{16}H_{15}NO_2$	154–155[12,13]						
H	$-COCHCl_2$[18]	$C_{16}H_{14}NO_2Cl_2$	175–176	59.61	59.90	4.07	4.09	4.35	4.40
Br	$-COCHCl_2$	$C_{16}H_{12}NO_2Cl_2Br$	186.5–187	47.91	48.18	3.02	3.32	3.49	3.31
CH_3	$-COCHCl_2$	$C_{17}H_{15}NO_2Cl_2$	196–197	60.73	60.73	4.50	4.56	4.17	4.11
4'-R-C_6H_4-C_6H_4-CO-$CHNHR'$-CH_2OH (III)									
H	$-COCH_3$	$C_{17}H_{17}NO_3$	166–167[12,13]						
H	$-COCHCl_2$[18]	$C_{17}H_{15}NO_3Cl_2$	166–167	57.97	58.19	4.29	4.55	3.98	4.16
Br	$-COCHCl_2$	$C_{17}H_{14}NO_3Cl_2Br$	166.5–167	47.36	47.64	3.27	3.30	3.25	3.29
CH_3	$-COCHCl_2$	$C_{18}H_{17}NO_3Cl_2$	172–173	59.03	59.22	4.68	4.93	3.83	3.82
4'-R-C_6H_4-C_6H_4CHOH-$CHNHR'$-CH_2OH (IV)									
H	$COCH_3$	$C_{17}H_{19}NO_3$	227[12]						
H	$COCHCl_2$	$C_{17}H_{17}NO_3Cl_2$	149–150	57.64	57.97	4.84	5.19	3.95	3.91
Br	$COCHCl_2$	$C_{17}H_{16}NO_3Cl_2Br$	143.5–144	47.14	46.95	3.72	3.88	3.23	3.28
CH_3	$COCHCl_2$[20]	$C_{18}H_{19}NO_3Cl_2$	211–212	58.70	58.52	5.20	5.42	3.80	3.65
CH_3	$COCHCl_2$[20]	$C_{18}H_{19}NO_3Cl_2$	137–138	58.70	58.88	5.20	5.37	3.80	4.05

wein–Ponndorf–Verley conditions gave the two possible diastereoisomeric racemates as pure crystalline entities. The biologically active compound was formed predominately. From similar reductions of α-dichloroacetamido-β-hydroxymethyl-4'-bromophenyl or phenylacetophenones only a single crystalline racemate was isolated. Each of these compounds had biological activity comparable to that of the biologically active isomer of the methyl compound. It is believed that the racemates isolated in the case of the biphenyl and bromobiphenyl compounds are analogous in configuration to the biologically active *p*-4'-methylphenyl compound.

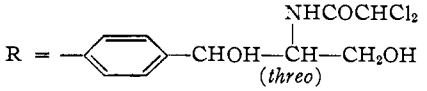
In view of the antibacterial activity of these compounds, it was desirable to study the resolved forms of 1-biphenylyl-2-dichloroacetamido-1,3-propanediol further. This compound was chosen since it was slightly more active *in vitro* than the bromo and methyl analogs. A convenient resolution of the base, 1-biphenylyl-2-amino-1,3-propanediol was accomplished by forming a salt with dextro- or levorotatory phenylethylsuccinic acid[17] and recrystallizing the product to a constant melting point and optical rotation. When the levorotatory form of the resolving acid was used, the salt of the L-*threo* or biologically inactive base was less soluble and was consequently obtained pure upon further recrystallization. Similarly with the dextrorotatory acid, the salt of the D-base separated. By reconverting base residues isolated from the mother liquors of such resolution mixtures to the salt of the acid of opposite configuration, an excellent yield of the other base isomer salt was obtained.

Since many of the reactions used in the preparation of the above biphenyl analogs have been described adequately in several publications, only variations necessarily due to the unique character of certain of these compounds or representing improvements in technique are reported in the Experimental section. Table I summarizes the physical characteristics of the compounds described in this paper, while Table II shows *in vitro* antibiotic activity of the products against a limited group of bacteria.

TABLE II

In vitro ANTIBACTERIAL ACTIVITY OF 1-BIPHENYLYL-2-DICHLOROACETAMIDO-1,3-PROPANEDIOL AND 4'-RING-SUBSTITUTED DERIVATIVES,[21] (DISC-PLATE STUDIES)

Concn. of compound in γ/0.1 ml. causing inhibition equivalent to that of Chloromycetin

R = 

Organism	D-C_6H_5-R	DL-4'-BrC_6H_4-R	DL-4'-$CH_3C_6H_4$-R	Chloromycetin
Aerobacter aerogenes 0126	2.5–5	5	>10	1.0
Escherichia coli 04420	>25	>25	>25	10.0
Neisseria catarrhalis 03447	1.0	2.5	5	1.0
Streptococcus hemolyticus 04664	5.0	5–10	10	5.0
Brucella suis 1772	1.0	2.5	5	1.0
Sarcina lutea 04813	1.0	5	10	2.5
Shigella sonnei 04630	>10	>10	>10	5.0

Experimental

Phenylphenacyl Bromide and *p*-Substituted Phenylphenacyl Bromides.—These compounds were formed directly by condensing biphenyl, *p*-methylbiphenyl or *p*-bromobiphenyl with bromoacetyl bromide under the conditions of

(17) The resolved phenylethylsuccinic acids were provided by Dr. L. M. Long of these laboratories.

(18) We are indebted to Miss Elizabeth L. Pfeiffer for the preparation of these compounds.

(19) Melting points were taken on a calibrated Fisher–Johns block.

(20) The inactive or *erythro*-racemate melted at 211–212° while the biologically active product melted at 137–138°.

(21) We are indebted to Dr. A. S. Schlingman, Mrs. Della Fox and Miss Mary Manning for these data.

the Friedel–Crafts synthesis. The properties of the products were in agreement with those reported in the literature.

Phenylphenacylamine Hydrochloride and *p*-Substituted Phenylphenacylamine Hydrochlorides.—Hexamethylenetetramine salts of the phenylphenacyl and *p*-substituted phenylphenacyl bromides were prepared in chloroform solution as described previously.[2,14] The salts were then hydrolyzed with ethanol–concd. HCl mixtures, and the crude amine hydrochlorides obtained in this manner were converted directly to the dichloroacetamides. Analytical data and melting points for samples of purified, *p*-methylphenyl and *p*-bromophenyl-α-aminoacetophenone hydrochlorides are given in Table I.

α-Dichloroacetamido-4′-methyl- or 4′-Bromophenylacetophenone (II).—Good yields of the amides were obtained by carrying out the acylation reaction in dimethylformamide solution. A sample of 15.8 g. of *p*-methylphenylphenacylamine hydrochloride was suspended in 110 ml. of dry dimethylformamide. To the stirred solution was added 9.8 g. of dichloroacetyl chloride (10% excess) dropwise during 10 min. The temperature of the reaction mixture rose to 43° and the solid gradually went into solution. The reaction mixture was stirred at room temperature for 4 hours longer and then diluted with an equal volume of ice-cold water. The crystalline dichloroacetamide which separated was removed by filtration. A yield of 15.25 g. of product melting at 195–197° was obtained. The material was substantially pure, a sample recrystallized for analysis from ethylene dichloride melting at 196–197°.

α-Dichloroacetamido-β-hydroxymethyl-4′-methyl- or 4′-Bromophenylacetophenones (III).—The problem of hydroxymethylation of the α-dichloroacetamidophenylacetophenones was one of solubility. The hydroxymethylation of α-dichloroacetamido-*p*-bromophenylacetophenone, the least soluble of this group of compounds in ethanol, is described. Ten grams of α-dichloroacetamido-*p*-bromophenylacetophenone was suspended in 750 ml. of 95% ethanol. The mixture was heated with stirring to 60° to dissolve a large part of the material, and then cooled to 37°. Eight milliliters of formalin (36–38%) and 0.75 g. of sodium bicarbonate were added. The mixture was stirred for 5 hours at 37° and finally for 18 hours at room temperature. A solid which proved to be mainly starting material amounting to 3.48 g. (m.p. 185–188°) was filtered off. The filtrate was evaporated to a small volume under reduced pressure at 40° and then diluted with 200 ml. of water and extracted twice with ethyl acetate. The combined extracts were washed with dilute sulfuric acid, saturated sodium bicarbonate solution and water. The ethyl acetate was then dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The crude product amounting to 5.8 g. which melted at 158–159°, was recrystallized from 160 ml. of benzene. Upon chilling 3.18 g. of the α-dichloroacetamido-β-hydroxymethyl-*p*-bromophenylacetophenone which melted at 164–167° was obtained. A sample recrystallized for analysis from ethylene dichloride melted at 166.5–167°. The compound appeared to be hygroscopic as the melting point dropped after the material had stood for a few minutes. Small amounts of an insoluble material totaling 1.02 g. were isolated from both the recovered starting material and the hydroxymethylation product. From the ultraviolet absorption and the extreme insolubility of this compound in most organic solvents, it is likely that the by-product has the bis structure ($[p\text{-}BrC_6H_4\text{–}C_6H_4\text{–}C(=O)\text{–}CH(NHCOCHCl_2)\text{–}]_2CH_2$). Compounds of this kind have been obtained repeatedly in the synthesis of Chloromycetin and Chloromycetin related compounds during hydroxymethylation.[14] By controlling the conditions of the formylation such by-products usually can be eliminated.

α-Dichloroacetamido-β-acetoxy-4′-methylphenylpropiophenone.—As further evidence that the hydroxymethylation product of α-dichloroacetamido-4′-methylphenylacetophenone was the desired monoformylation derivative, a 1-g. sample was acetylated with acetic anhydride in pyridine solution in the usual manner. The product was recrystallized from ethanol several times for analysis (m.p. 160–161°).

Anal. Calcd. for $C_{20}H_{19}NO_4Cl_2$: C, 58.85; H, 4.69; N, 3.43. Found: C, 59.10; H, 4.51; N, 3.51.

Meerwein–Ponndorf–Verley Reduction of α-Dichloroacetamide-β-hydroxymethyl-4′-bromo- or 4′-Methylphenylacetophenones.—The reductions were carried out in dry isopropylalcohol in the presence of aluminum isopropylate and the products isolated as usual. In the case of the 4′-methyl compound a chloroform-insoluble product melting at 211–212° after two recrystallizations from ethanol proved to be the biologically inactive isomer. The major portion of the reduction product was isolated from the chloroform mother liquors. Three recrystallizations from smaller quantities of chloroform yielded the biologically active racemate which melted at 137–139°.

The yield of crude crystalline mixture from the reduction of 3.66 g. of α-dichloroacetamido-β-hydroxymethyl-*p*-methylphenylacetophenone was 2.24 g. The yield of purified *erythro* (inactive) isomer was 160 mg.; 1.3 g. of purified *threo* isomer was obtained. The structure assigned to the *erythro* isomer was supported by ultraviolet and infrared absorption curves.

1-Biphenylyl-2-dichloroacetamido-1,3-propanediol.—The preparation of this compound has been described in detail by Bambas in a patent.[13]

The Resolution of DL-*threo*-1-Biphenylyl-2-amino-1,3-propanediol.—Samples of 6.89 g. of DL-*threo*-1-biphenylyl-2-amino-1,3-propanediol[13] and 6.29 g. of levo phenylethylsuccinic acid were dissolved in 35 ml. of hot *n*-butyl alcohol. The mixture was allowed to stand at room temperature overnight, a yield of 9.1 g. of crystalline salt (m.p. 159–163°) being obtained. Recrystallization from 91 ml. of absolute ethanol yielded 4.36 g. of product (m.p. 176–179°) after 72 hours at room temperature. Two further recrystallizations from ethanol using 15 ml. of solvent per gram yielded 2.4 g. of optically pure salt (m.p. 183–184°). The last crystallization did not change the melting point or rotation of the material, $[\alpha]^{25}D$ +50.0° (*c* 5% in dimethylacetamide). The 2.4 g. of salt was converted to the free base by suspending in 70 ml. of water, making the solution strongly alkaline with ammonium hydroxide and stirring for one hour. The solid base was then removed by filtration and recrystallized from absolute ethanol to yield 1.0 g. of product melting at 179–180°, $[\alpha]^{25}D$ +28° (*c* 5% in dimethylacetamide). When converted to the dichloroacetamide in the usual manner the product had no antibacterial activity.[15] This product melted at 158–159°, $[\alpha]^{25}D$ −20.0° (*c* 5% in absolute ethanol).

To obtain the levorotatory base, the mother liquors from the butanol and ethanol crystallizations of the above salt were combined and evaporated. The base which was now rich in the D-*threo* isomer was liberated and treated with 4.55 g. of *d*-phenylethylsuccinic acid. The mixture was heated on the steam-bath until all of the solid had dissolved, then was kept at room temperature overnight. The 4.85 g. of product (m.p. 175–177°) was crystallized from 75 ml. of absolute ethanol to give 3.2 g. of optically pure salt (m.p. 182–183°), $[\alpha]^{25}D$ −50.0° (*c* 5% in dimethylacetamide).

Anal. Calcd. for $C_{27}H_{31}NO_6$: C, 69.66; H, 6.71; N, 3.01. Found: C, 70.01; H, 6.61; N, 3.24.

The D base was liberated and recrystallized from 60 ml. of absolute ethanol (m.p. 179–180°), $[\alpha]^{25}D$ −28° (*c* 5% in dimethylacetamide).

Conversions of the D base to the dichloroacetamide gave a product melting at 158–159° after recrystallization from aqueous ethanol and finally ethylene dichloride, $[\alpha]^{25}D$ +20.6° (*c* 5% in absolute ethanol).

Anal. Calcd. for $C_{17}H_{17}NO_3Cl_2$: C, 57.64; H, 4.84; N, 3.95. Found: C, 57.95; H, 4.91; N, 4.19.

The antibacterial activity of this compound was twice that found for the DL-racemate.[15]

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