Synthesis of *p*-Acyl Analogs of Chloramphenicol and Their Antimicrobial Properties

MAXIMILIAN VON STRANDTMANN, GEORGE BOBOWSKI, AND JOHN SHAVEL, JR.

Department of Organic Chemistry, Warner-Lambert Research Institute, Morris Plains, New Jersey

Received February 16, 1967

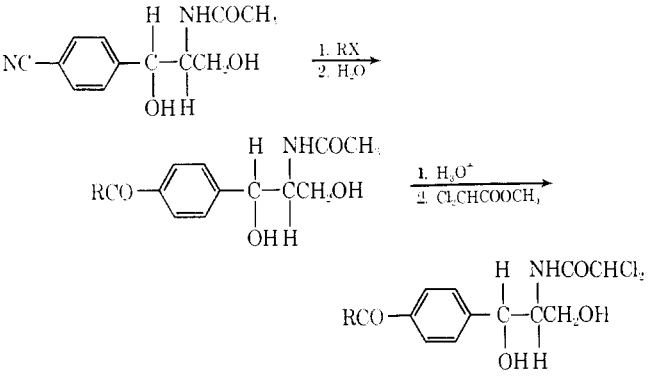
Analogs of chloramphenicol having an acyl group in place of the nitro group have been prepared. The most active of the series, D-*threo*-1-(*p*-acetylphenyl)-2-(2,2-dichloroacetamido)-1,3-propanediol (cetophenicol), was found to be a potent antimicrobial agent, active against gram-positive and gram-negative organisms.

This communication is concerned with *p*-acyl analogs of chloramphenicol, which were synthesized as a part of our program to introduce an acyl group into the aromatic moiety of suitable natural products.[1] The preparation of these compounds appeared attractive in view of the possibility that the replacement of the nitro group of the chloramphenicol molecule by an acyl function might result in antimicrobial agents that are free of some of the undesirable effects of chloramphenicol.[2] Hahn, *et al.*,[3] suggested a correlation between the degree of antimicrobial activity of chloramphenicol analogs and the electronegativity of their *para* substituents. It thus appeared likely that the *p*-acyl analogs could possess considerable antimicrobial activity due to the electron-withdrawing properties of the acyl groups.

The synthetic path chosen involved addition of organolithium compounds or the corresponding Grignard reagents to 2-acetamido-1-(*p*-cyanophenyl)-1,3-propanediol[4] with subsequent hydrolysis and dichloroacetylation as shown in Scheme I. Compounds prepared by this method are listed in Table I, which also includes some of the intermediates and derivatives prepared.

The most active of the series, D-*threo*-N-[*p*-acetyl-β-hydroxy-α-(hydroxymethyl)phenethyl]-2,2-dichloroacetamide (cetophenicol), was found to be a potent antimicrobial agent, active against gram-positive and gram-negative organisms. The minimum inhibitory concentrations by a twofold serial dilution test in broth are as follows (μg/ml): *Staphylococcus aureus* (WLRI-16), 4; *S. aureus* (WLRI-25), 31; *Streptococcus pyogenes*, 62; *Streptococcus faecalis*, 16; *Diplococcus pneumoniae*, 31; *Klebsiella pneumoniae*, 4; *Escherichia coli*, 4; *Aerobacter aerogenes*, 2; *Proteus vulgaris*, 16; *Pseudomonas aeruginosa*, 250. The *in vivo* activity was determined by inoculating Manor Farms (MF-1) female albino mice, weighing 20 g, with a lethal dose of the test organism and administering the test compound orally twice daily for 3 days starting 0.5 hr after inoculation. The objective of this assay was to determine the effective dose (ED_{50}), which would protect 50% of animals. The following are the ED_{50}'s (in mg/kg): *S. aureus*, 70; *S. pyogenes*, 53; *D. pneumoniae*, 38; *E. coli*, 66; *K. pneumoniae*, 40; *P. vulgaris*, 27; *Ps. aeruginosa*, 190.

SCHEME I



The water solubility of cetophenicol at 25° was determined to be 2%, eight times greater than that of chloramphenicol. A comparative evaluation of acute toxicities in mice showed cetophenicol (LD_{50} = 5200 mg/kg *po* and >400 mg/kg iv) to be one-half or less as toxic as chloramphenicol (LD_{50} = 2600 mg/kg *po* and 190 mg/kg iv). Similarly to chloramphenicol, cetophenicol has been reported to be an inhibitor of induced protein synthesis in mammalian cell-free systems.[5]

Cetophenicol is currently undergoing clinical evaluation.

The antimicrobial efficacy of the *p*-acyl analogs of chloramphenicol appears to decrease with the increasing molecular weight of the *p*-acyl group. Thus, while the isobutyryl derivative II showed only a moderately decreased activity, the benzoyl compound III and the cyclohexanecarbonyl analog IV were found to be considerably less active than cetophenicol. As with chloramphenicol,[3] replacement of the dichloroacetyl group by the acetyl group (Ib and IIa) results in a strong decrease in antibacterial properties. The *in vitro* mini-

(1) M. von Strandtmann, C. Puchalski, and J. Shavel, Jr., *J. Med. Chem.*, **7**, 141 (1964).

(2) (a) L. S. Goodman and A. Gilman, "The Pharmacological Basis of Therapeutics," 3rd ed, The Macmillan Co., New York, N. Y., 1965, p 1262; C. N. Lewis, L. E. Putnam, F. D. Hendricks, I. Kerlan, and H. Welch, *Antibiot. Chemotherapy*, **2**, 601 (1952); E. L. Loyd, *ibid.*, **2**, 1 (1952); R. G. Shaw and J. A. McLean, *Med. J. Australia*, **1**, 352 (1957). (b) The implication that the undesirable effects of chloramphenicol can be remedied by the replacement of the nitrobenzene moiety with another which does not have the nitro group may be questionable since D. Rubin, A. S. Weisberger, and D. R. Clark [*J. Lab. Clin. Med.*, **56**, 453 (1960)] and L. G. Suhrland and A. S. Weisberger [*ibid.*, **58**, 962 (1961)] have shown that the *p*-CH_3S and the *p*-CH_3SO_2 analogs cause a dose-related reversible depression of hematopoiesis which is stronger than that produced by chloramphenicol. It has to be borne in mind, however, that these studies did not cover the more important, irreversible aspects of bone marrow toxicity.

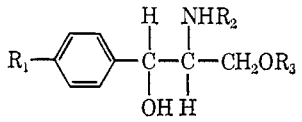
(3) F. E. Hahn, J. E. Hayes, C. L. Weissman, Jr., H. E. Hopps, and J. E. Smadel, *Antibiot. Chemotherapy*, **6**, 531 (1956). M. M. Shemyakin, M. N. Kolosov, M. M. Levitov, K. I. Germanova, M. G. Karapetyan, Yu. B. Shvetsov, and E. M. Bamdas [*Dokl. Akad. Nauk SSSR*, **102**, 953 (1955)] arrived at the same conclusion with the statement that "Activity declines in the series of *para* groups from NO_2 to CN, $COOCH_3$, Cl, SO_2CH_3, and SO_2NH_2." Due to a scant and erroneous abstract [*Chem. Abstr.*, **49**, 16049f (1955)] this contribution remained largely unnoticed.

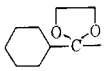
(4) (a) D. S. Morris and S. D. Smith, *J. Chem. Soc.*, 1680 (1954); (b) S. van der Meer, H. Kofman, and H. Veldstra, *Rec. Trav. Chim.*, **72**, 236 (1953); (c) M. Krukziener, Thesis, Leiden, 1953.

(5) (a) A. S. Weisberger and S. Wolfe, *Federation Proc.*, **23**, 978 (1964); (b) A. S. Weisberger, T. M. Daniel, and A. Hoffman, *J. Exptl. Med.*, **120**, 179 (1964).

Table I

D-*threo*-1-(*p*-Acylphenyl)-2,3-propanediols and Derivatives



Compd	R_1	R_2	R_3	Mp, °C	$[\alpha]^{25}D$, deg (c)[a]	Formula	Calcd, % C	H	N	Cl	Found, % C	H	N	Cl
I	CH_3CO	$CHCl_2CO$	H	125–127	+13.4 (1.25)	$C_{13}H_{16}Cl_2NO_4$	48.76	4.72	4.38	22.15	48.48	4.86	4.25	22.35
II	$(CH_3)_2CHCO$	$CHCl_2CO$	H	97–99	+14 (0.8)	$C_{15}H_{19}Cl_2NO_4$	51.73	5.50	4.02	20.36	51.73	5.50	4.26	20.38
III	C_6H_5CO	$CHCl_2CO$	H	160–161	+7.8 (0.9)	$C_{18}H_{17}Cl_2NO_4$	56.55	4.48	3.66	18.55	56.84	4.55	3.81	18.74
IV		$CHCl_2CO$	H	163–164	+10.5 (1.05)	$C_{18}H_{23}Cl_2NO_4$	55.68	5.97	3.61	18.26	55.71	5.86	3.66	18.40
Ia[b]	CH_3CO	$CHCl_2CO$	H	130		$C_{13}H_{16}Cl_2NO_4$	48.76	4.72	4.38	22.15	48.70	4.82	4.48	22.04
Ib	CH_3CO	ClH_2CO	H	166–167	+7 (0.5)	$C_{13}H_{17}NO_4$	62.13	6.82	5.57		61.85	6.95	5.55	
Ic	CH_3CO	H	H	139–140	−24.5 (1.55)	$C_{11}H_{15}NO_3$	63.14	7.23	6.69		63.03	7.45	6.46	
Id	$CH_3C(=NNHCSNH_2)$	$CHCl_2CO$	H	176[c]		$C_{14}H_{18}Cl_2N_4O_3S$	42.75	4.62	14.25	18.03	42.74	4.83	14.46	17.89
Ie	CH_3CO	$CHCl_2CO$	$CO(CH_2)_2CO_2H$	123–124		$C_{17}H_{19}Cl_2NO_7$	48.59	4.56	3.33	16.87	48.55	4.60	3.35	16.91
If	CH_3CO	$CHCl_2CO$	$CH_3(CH_2)_{14}CO$	81–82		$C_{29}H_{45}Cl_2NO_5$	62.36	8.12	2.50	12.69	62.10	8.17	2.64	12.77
Ig	p-$C_6H_4COCH_3$	$CHCl_2CO$	H	187–189	+9.5 (0.45)	$C_{22}H_{21}Cl_2NO_5$	58.68	4.70		15.75	58.89	4.93		15.62
	$CH=CHCO$													
Ih	$C_6H_5CH=CHCO$	$CHCl_2CO$	H	155–156	+5.5 (0.65)	$C_{20}H_{19}Cl_2NO_4$	58.84	4.69		17.37	58.71	4.80		17.22
IIa	$(CH_3)_2CHCO$	CH_3CO	H	138–139	+2 (1.15)	$C_{15}H_{21}NO_4$	64.49	7.58	5.01		64.20	7.58	5.01	
IIb	$(CH_3)_2CHCO$	H	H	108–109	−22 (1.05)	$C_{13}H_{19}NO_3$	65.80	8.07	5.90		66.01	7.96	5.66	
IIIa	$C_6H_5C(=NH)$	CH_3CO	H	186–187	+3.2 (0.95)	$C_{18}H_{20}N_2O_3$	69.21	6.45	8.97		68.93	6.31	8.74	
IIIb	C_6H_5CO	CH_3CO	H	139–140	+5.6 (0.95)	$C_{18}H_{19}NO_4$	68.99	6.11	4.47		69.16	5.98	4.53	
IIIc	C_6H_5CHOH	$CHCl_2CO$	H	129–130	+5.5 (1.1)	$C_{18}H_{19}Cl_2NO_4$	56.26	4.98		18.46	56.17	5.12		18.25
IVa		CH_3CO	H	184–185	+3 (1)	$C_{18}H_{25}NO_4$	67.68	7.89	4.38		67.88	8.01	4.60	
IVb		$CHCl_2CO$	H	112–113		$C_{20}H_{27}Cl_2NO_5$	55.56	6.29		16.40	55.59	6.52		16.43

[a] Concentration in methanol. [b] DL form. [c] At 176° there is a sharp change in color to orange followed by gradual darkening and softening but no definite melting up to 320°.

mum inhibitory concentrations are as follows (in μg/ml): II, *S. aureus* (WLRI-25), 31; *E. coli*, 62; *P. vulgaris*, 125; III, IV, Ib, and IIa, *S. aureus* (WLRI-25), >125; *E. coli*, >125.

Experimental Section

Physical constants and analytical values are reported in Table I. Melting points were determined using the Thomas–Hoover capillary melting point apparatus which was calibrated against known standards. The ultraviolet and infrared spectra were obtained, respectively, with a Beckman DK-1 spectrophotometer and a Baird Model 455 double-beam instrument. Unless otherwise stated, the former were determined as solutions in 95% ethanol and the latter as Nujol mulls.

Tetrahydrofuran (THF) used was purified and dried by distillation from $LiAlH_4$. Prior to evaporation or concentration, the nonaqueous organic solutions were dried over Na_2SO_4. The evaporations and concentrations were carried out *in vacuo* with a rotary flash evaporator at temperatures not exceeding 30°.

D-*threo*-**2-Acetamido-1-(*p*-cyanophenyl)-1,3-propanediol** was prepared as described[4] for the corresponding DL compound: mp 122.5; $[\alpha]^{25}D$ +4.1° (*c* 3, CH_3OH); ν_{max} (cm^{-1}) 2300 (C≡N), 1645 (amide C=O).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.65; H, 6.17; N, 11.82.

D-*threo*-**1-(*p*-Acetylphenyl)-2-(2,2-dichloroacetamido)-1,3-propanediol (I).**—Ethereal CH_3Li (300 ml, 0.8 *N*) was added at 40° over a period of 4 hr to a stirred solution of 8 g of D-*threo*-1-(*p*-cyanophenyl)-2-acetamido-1,3-propanediol in 600 ml of THF. After 2 hr of additional stirring, a solution of 100 g of $(NH_4)_2SO_4$ in 100 ml of water was added over a period of 1 hr. The organic layer was separated; the aqueous phase was extracted four times with 200-ml portions of ethyl acetate–THF (1:1). The extracts were combined with the organic layer, dried (Na_2SO_4), and evaporated. The residue was heated on a steam bath with 300 ml of 10% H_2SO_4 for 3 hr. The solution was cooled, washed twice with 25-ml portions of ethyl acetate, made basic with 20% KOH at 0–5°, and extracted eight times with 400-ml portions of ethyl acetate. The combined extracts were dried and evaporated. The residue was refluxed for 4 hr with 13 ml of methyl dichloroacetate in 50 ml of methanol. After evaporation, the oily residue was passed through 100 g of an activated magnesium silicate column (Florisil) which was eluted with ethyl acetate. The crystalline fractions were combined and recrystallized from ethyl acetate–hexane (1:1) to give 2.8 g of product: λ_{max} [mμ (ε)] 252.5 (15,750); ν_{max} (cm^{-1}) 1672 (amide C=O), 1693 (ketone C=O); $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1688 (ketone C=O), 1708 (amide C=O).[6]

In an alternate procedure, the solution of 1.5 g of D-*threo*-1-(*p*-cyanophenyl)-2-acetamido-1,3-propanediol in THF (400 ml) was treated with 150 ml of 1 *N* ethereal CH_3MgI over a period of 23 hr at reflux temperature. The reaction mixture was worked up as above to give 0.46 g of product.

DL-*threo*-**1-(*p*-Acetylphenyl)-2-(2,2-dichloroacetamido)-1,3-propanediol (Ia)** was prepared from DL-*threo*-1-(*p*-cyanophenyl)-2-acetamido-1,3-propanediol by the above procedure.

D-*threo*-**1-(*p*-Acetylphenyl)-2-acetamido-1,3-propanediol (Ib)** was prepared by the above procedure omitting the hydrolysis and dichloroacetylation steps; ν_{max} (cm^{-1}) 1634 (amide C=O) and 1676 (ketone C=O).

D-*threo*-**1-(*p*-Acetylphenyl)-2-amino-1,3-propanediol (Ic).**—A suspension of 2.5 g of I in 25 ml of 10% H_2SO_4 was heated on a steam bath for 3 hr. After cooling, the solution was washed with 50 ml of ethyl acetate, made basic with NH_4OH at 0–5°, and extracted five times with 150-ml portions of ethyl acetate. The combined extracts were dried and concentrated to *ca.* 25 ml to give on cooling 1.05 g of off-white crystals which were recrystallized from ethyl acetate; ν_{max} (cm^{-1}) 1678 (ketone C=O), $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1682 (ketone C=O).

D-*threo*-**1-(*p*-Acetylphenyl)-2-(2,2-dichloroacetamido)-1,3-propanediol Thiosemicarbazone (Id).**—A solution of 0.132 g of I and 0.037 g of thiosemicarbazide in 25 ml methanol was refluxed for

(6) The dichloroacetamido carbonyl band undergoes a 25–35-cm^{-1} shift to higher frequency on passage from mull to solution (see example IIIc). The band of the ketone function shifts only slightly or remains at the same position (see examples Ic and IIb). As a result, the absorption frequency of the dichloroacetyl carbonyl is believed to be below that of the ketone carbonyl when determined as a mull and above it when determined in solution.

1 hr, treated with 10 ml of 2-propanol, and concentrated to give 0.11 g of product, ν_{max} (cm^{-1}) 1677 (amide C=O).

D-*threo*-1-(*p*-**Acetylphenyl**)-2-(**2,2-dichloroacetamido**)-1,3-**propanediol 3-Hemisuccinate** (**Ie**). A solution of 2 g of I and 0.66 g of succinic anhydride in 20 ml of anhydrous pyridine was heated for 3 hr at 80°. The solvent was evaporated and the gummy residue was dissolved in a solution of 0.6 g of $NaHCO_3$ in 10 ml of water. The solution was washed twice with 25 ml of ethyl acetate and acidified with dilute HCl to give 1.9 g of product which was recrystallized from ethyl acetate: ν_{max} (cm^{-1}) 1658 (amide C=O), 1682 (ketone C=O), 1722 (carboxyl C=O), 1738 (ester C=O).

D-*threo*-1-(*p*-**Acetylphenyl**)-2-(**2,2-dichloroacetamido**)-1,3-**propanediol 3-Palmitate** (**If**).—Palmitoyl chloride (7.85 g) was added dropwise over a period of 10 min to a stirred solution of 8 g of I in 25 ml of dry pyridine. After 3 hr at room temperature, 100 ml of ethyl acetate was added and the resulting precipitate was removed by filtration. The filtrate was washed with saturated aqueous NaCl solution, dried, and evaporated. Crystallization of the residue from ether–hexane (1:1) gave 10.5 g of white crystals: $\nu_{max}^{CHCl_3}$ (cm^{-1}) 1690 broad (ketone and amide C=O), and 1730 (ester C=O).

D-*threo*-1-[*p*-(*p*-**Acetylcinnamoyl**)**phenyl**]-2-(**2,2-dichloroacetamido**)-1,3-**propanediol** (**Ig**).—A solution of 1.5 g of Ie, 3.2 g of *p*-(2-methyl-1,3-dioxolan-2-yl)benzaldehyde,[7] and 1 g of NaOH in 30 ml of 70% aqueous methanol was allowed to stand for 10 hr at room temperature. After evaporation of the solvent, the residue was acidified with cold dilute HCl, washed with 150 ml of ether, made basic with NH_4OH, and extracted three times with 75-ml portions of ethyl acetate. The combined extracts were dried and evaporated. The residue was refluxed with 3 ml of methyl dichloroacetate in 2-propanol for 5 hr. After evaporation of the solvent, the gummy residue was passed over a 50-g Florisil column using ethyl acetate as an eluent. Recrystallization of the combined crystalline fractions from ethyl acetate yielded 0.35 g of off-white crystals: ν_{max} (cm^{-1}) 1608 (aromatic), 1615, 1663 (–CH=CHCO), 1673 (CONH), 1698 (CH_3CO); λ_{max} [mμ (ε)] 314 (33,950), 226 (42,600).

D-*threo*-1-(*p*-**Cinnamoylphenyl**)-2-(**2,2-dichloroacetamido**)-1,3-**propanediol** (**Ih**).—A solution of 1.5 g of Ie, 3 g of benzaldehyde, and 5 ml of 10% aqueous NaOH in 40 ml of methanol was stirred at room temperature for 4 hr. The reaction mixture was worked up as in the preparation of Ig and recrystallized from ethyl acetate–cyclohexane (2:1) to give 0.05 g of white crystals: $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1668 (ketone C=O), 1692 (amide C=O); λ_{max} [mμ (ε)] 310 (25,800), 221 (13,800).

D-*threo*-1-(*p*-**Isobutyrylphenyl**)-2-**amino**-1,3-**propanediol** (**IIb**).—A solution of 8 g of D-*threo*-1-(*p*-cyanophenyl)-2-acetamido-1,3-propanediol in 100 ml of THF was added over a period of 15 min to a stirred solution of isopropylmagnesium bromide (prepared from 0.4 mole of isopropyl bromide and 0.4 g-atom of Mg in 400 ml of ether; 300 ml of ether was then evaporated and replaced by 300 ml of THF). After heating at 50° for 3 hr, 40 g of NH_4Cl in 80 ml of water was added dropwise at 0–5°. The organic layer was separated and the aqueous phase was extracted four times with 150-ml portions of ethyl acetate. The extracts were combined with the organic layer, dried, and evaporated. The residue was heated with 100 ml of 10% H_2SO_4 on a steam bath for 3 hr. After cooling, the solution was washed with 100 ml of ether, made basic with 20% NaOH at 0–5°, and extracted five times with 125-ml portions of ethyl acetate. The combined extracts were dried and evaporated to give 7.2 g of product, which was recrystallized from ethyl acetate: ν_{max} (cm^{-1}) 1680 (ketone C=O); $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1680 (ketone C=O); λ_{max} [mμ (ε)] 251 (14,350).

D-*threo*-1-(*p*-**Isobutyrylphenyl**)-2-**acetamido**-1,3-**propanediol** (**IIa**) was prepared by the above procedure omitting the hydrolysis step; yield 7 g; ν_{max} (cm^{-1}) 1637 (amide C=O), 1672 (ketone C=O).

D-*threo*-1-(*p*-**Isobutyrylphenyl**)-2-(**2,2-dichloroacetamido**)-1,3-**propanediol** (**II**) was prepared by refluxing 4.4 g of IIb with 7 g of methyl dichloroacetate in 50 ml of methanol, followed by evaporation and chromatography of the residue on a 100-g Florisil column with ethyl acetate as eluent; yield 3.8 g; ν_{max} (cm^{-1}) 1679 (ketone and amide C=O); $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1680 (ketone C=O), 1703 (amide C=O).

D-*threo*-1-[*p*-(α-**Iminobenzoylphenyl**)]-2-**acetamido**-1,3-**propanediol** (**IIIa**).—Ethereal phenyllithium (50 ml, 0.9 *N*) was added dropwise over a period of 2 hr at 35° to a stirred solution of 1.5 g of D-*threo*-1-(*p*-cyanophenyl)-2-acetamido-1,3-propanediol in 120 ml of THF. Working up the reaction mixture analogously to the preparation of I, omitting the hydrolysis and dichloroacetylation steps, gave 0.9 g of product which was recrystallized from 2-propanol–acetone (1:1): $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1673 (C=N and C=O); λ_{max} [mμ (ε)] 247 (15,150).

D-*threo*-1-(*p*-**Benzoylphenyl**)-2-**acetamido**-1,3-**propanediol** (**IIIb**) was prepared by heating 0.25 g of IIIa with 25 ml of water for 2 hr, extracting with ethyl acetate, and recrystallizing from ethyl acetate–ether (2:1): yield 0.15 g; $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1660 (amide C=O), 1673 (ketone C=O); λ_{max} [mμ (ε)] 260 (17,350).

D-*threo*-1-(*p*-**Benzoylphenyl**)-2-(**2,2-dichloroacetamido**)-1,3-**propanediol** (**III**) was prepared by heating 0.8 g of IIIa with 50 ml of 10% H_2SO_4 for 2.5 hr, dichloroacetylating and purifying as in the preparation of I; yield 0.55 g. The analytical sample was prepared by recrystallization from ethyl acetate–cyclohexane (1:1): ν_{max} (cm^{-1}) 1638 (ketone C=O), 1678 (amide C=O); $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1660 (ketone C=O), 1709 (amide C=O); λ_{max} [mμ (ε)] 260 (18,100).

1-[*p*-(α-**Hydroxybenzyl**)**phenyl**]-D-*threo*-2-(**2,2-dichloroacetamido**)-1,3-**propanediols** (**IIIc**).—A mixture of 0.5 g of III and 0.3 g of KBH_4 in 10 ml of methanol was stirred for 3 hr. After evaporation of the solvent, the residue was dissolved in 25 ml of water and extracted three times with 25-ml portions of ethyl acetate. The combined extracts were dried and evaporated. The residue was passed through a 10-g Florisil column with ethyl acetate as eluent. The combined crystalline fractions were recrystallized from 30 ml of ether–cyclohexane (2:1) to give 0.32 g of white granules: ν_{max} (cm^{-1}) 1680 (amide C=O); $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1709 (amide C=O); λ_{max} [mμ (ε)] 221 (15,750), 255 (500).

D-*threo*-1-(*p*-**Cyclohexylcarbonylphenyl**)-2-(**2,2-dichloroacetamido**)-1,3-**propanediol** (**IV**).—A solution of 8 g of D-*threo*-1-(*p*-cyanophenyl)-2-acetamido-1,3-propanediol in THF (50 ml) was added dropwise over a period of 10 min to a stirred solution of cyclohexylmagnesium bromide (prepared from 0.4 mole of cyclohexyl bromide and 0.4 g-atom of Mg in 350 ml of ether; 250 ml of ether was then evaporated and replaced by 250 ml of THF). The reaction mixture was heated for 4 hr at 45° and processed analogously to procedure I to give 5.15 g of product which was recrystallized from ethyl acetate: $\nu_{max}^{CH_3CN}$ (cm^{-1}) 1679 (ketone C=O), 1709 (amide C=O); λ_{max} [mμ (ε)] 252 (13,750).

D-*threo*-1-(*p*-**Cyclohexylcarbonylphenyl**)-2-**acetamido**-1,3-**propanediol** (**IVa**) was prepared from 0.5 g of D-*threo*-1-(*p*-cyanophenyl)-2-acetamido-1,3-propanediol according to the procedure for IV. The reaction mixture was worked up analogously to the preparation of I omitting the hydrolysis and dichloroacetylation steps: yield 0.45 g; ν_{max} (cm^{-1}) 1642 (amide C=O), 1672 (ketone C=O); λ_{max} [mμ (ε)] 253 (14,750).

D-*threo*-1-[*p*-(2-**Cyclohexyl**-1,3-**dioxalan**-2-**yl**)**phenyl**]-2-(**2,2-dichloroacetamido**)-1,3-**propanediol** (**IVb**).—A solution of 0.75 g of IV, 4 ml of ethylene glycol, and 0.1 g of *p*-toluenesulfonic acid in 80 ml of benzene was refluxed for 12 hr with azeotropic water entrainment (Dean–Stark trap). After cooling, the solution was made basic with NH_4OH, the organic layer was separated, and the aqueous phase was extracted with 50 ml of ethyl acetate. The extract was combined with the organic layer, dried, and evaporated. The residue was refluxed with 3 ml of methyl dichloroacetate in 50 ml of ethanol for 4 hr. The solvents were evaporated and the residue was triturated with ether to give 0.55 g of a white crystalline product which was crystallized from ether: ν_{max} (cm^{-1}) 1686 (amide C=O); λ_{max} [mμ (ε)] 118 (11,400).

Acknowledgment.—The authors are indebted to the Microbiology Department under the supervision of Mr. B. S. Schwartz, the Analytical and Physical Chemistry Department under Mr. A. D. Lewis, and the Chemical Development Department under Dr. A. W. Ruddy. In particular we wish to thank Messrs. F. Turner, J. M. Daly, and P. J. Storino and Dr. S. Ringel for the microbiological testing, Mr. R. Novack for large-scale preparation of intermediates, and Messrs. R. Puchalski and T. Wildemann and Mrs. U. Zeek for analytical and spectral data.

(7) The synthesis of this compound is described in a forthcoming U. S. Patent by J. Shavel, Jr., and G. Bobowski.