Nucleic Acids. 11. Synthesis of 5′-Esters of 1-β-D-Arabinofuranosylcytosine Possessing Antileukemic and Immunosuppressive Activity[1]

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With the goal of obtaining derivatives of the potent antileukemic, antiviral, and immunosuppressive nucleoside, 1-β-D-arabinofuranosylcytosine (cytarabine, ara-C), possessing superior therapeutic properties, a series of 5′-esters have been synthesized. In our earlier work the 5′-*O*-trityl ether of ara-C was converted into its N^4-trichloroethoxycarbonyl (TCEC) derivative, and after detritylation, the N^4-TCEC compound was acylated at the 5′ position. The resultant N^4-TCEC 5′-ester was treated with Zn dust to obtain the desired 5′-ester. Yields were 3–5%. In our later syntheses, a greatly simplified synthetic route was employed which utilized protonation for protection of the N^4-amino group. Thus, ara-C·HCl was acylated at the 5′ position with an acid chloride, and the resultant 5′-ester·HCl was converted to the free base. Yields were 40–80%. This method should have general application for the synthesis of 5′-esters of nucleosides bearing reactive amino groups. A variety of aromatic and aliphatic carboxylate and sulfonate esters have been prepared. Of these, the palmitoyl, benzoyl, *p*-methoxybenzoyl, and 1-adamantoyl esters showed marked superiority as immunosuppressive and antileukemic agents compared to the parent compound when administered as a single dose in the mouse.

The 5′-ester of 1-β-D-arabinofuranosylcytosine[2,3] (cytosine arabinoside, cytarabine, aracytidine, ara-C) with adamantane-1-carboxylic acid (5′-adamantoyl ara-C), first synthesized by Neil, *et al.*,[4] has been shown to possess superior therapeutic properties (compared to ara-C) in the treatment of L1210 leukemic mice[4] and to possess greater immunosuppressive activity in this species[5] and in the rat.[6,7] Furthermore, in contrast to the parent compound, which exhibits short duration of action, 5′-adamantoyl ara-C possesses long-lasting immunosuppressive and antileukemic activity after a single injection.[4-7] We have undertaken a synthetic program designed to determine whether these properties are unique to the adamantoyl ester, or whether other derivatives of ara-C might possess these therapeutically superior properties. A further goal of our program was to discover ara-C derivatives possessing oral activity equal to or greater than the activity of ara-C when given parentally (ara-C possess low oral activity). In the course of this program, we have prepared a series of 5′-esters of ara-C, including the acetyl, 1-adamantoyl, benzoyl, 2,6-dimethylbenzoyl, 2,4,6-trimethylbenzoyl, *p*-methoxybenzoyl, 3,4,5-trimethoxybenzoyl, octanoyl, palmitoyl, pivaloyl, β-chloropivaloyl, isopropylcarbonyl, methoxycarbonyl, cyclobutylcarbonyl, cyclohexylcarbonyl, (3-carboxymethyladamantane-1)acetyl, 3-quinuclidinoyl, *p*-toluenesulfonyl, and 2,4,6-triisopropylbenzenesulfonyl derivatives. Of these 19 ara-C esters, all but 4 were active (within a 10-fold range in concn) in suppressing the incorporation of thymidine into the DNA of peripheral human lymphocytes *in vitro* (Table I). Thus, esterases present in human serum are able to cleave these 5′-esters to biologically active ara-C. Large differences in immunosuppressive activity seen *in vivo* following administration of these esters are probably due to differences in absorptive and destructive and depot effects of the esters rather than differences in their activities. The esters inactive or insoluble in this test were (3-carboxymethyladamantane-1)acetyl, 2,6-dimethylbenzoyl, 2,4,6-trimethylbenzoyl and *p*-toluenesulfonyl-ara-C.

TABLE I

5′-Ester	ID_{50} range,[a] μM	Av ID_{50}[c] μM
Acetyl	0.39–0.49	0.44
Methoxycarbonyl	0.43–0.60	0.52
Isopropylcarbonyl	0.45–0.61	0.53
Cyclobutylcarbonyl	0.37–0.68	0.54
Octanoyl	0.65–0.73	0.69
Cyclohexylcarbonyl	0.65–0.88	0.76
Pivaloyl	0.61–1.2	0.90
Benzoyl	0.76–1.1	0.99
H (nonesterified ara-C)	0.86–2.5	1.5
Palmitoyl	0.90–2.2	1.6
Adamantoyl	1.1–2.7	1.8
2,4,6-Triisopropylbenzenesulfonyl	1.4–2.6	2.0
3-quinuclidinoyl	0.4–>6.6	2.6
p-Methoxybenzoyl	1.6–4.0	2.7
3,4,5-Trimethoxybenzoyl	0.77–>6.6	4.7
β-Chloropivaloyl	1.2–>8.3	5.4
(3-Carboxymethyladamantane-1)-acetyl	5.0–>6.3	>6
2,6-Dimethylbenzoyl	>7.5	>7.5
2,4,6-Trimethylbenzoyl	Insol[b]	
p-Toluenesulfonyl	Insol[b]	

[a] All assays, all samples of blood. [b] Too insol in the lymphocyte medium to be assayed. [c] Average of all values.

When these 19 esters were administered to mice as a single ip injection, the palmitoyl, benzoyl, *p*-methoxybenzoyl, and adamantoyl derivatives possessed high immunosuppressive (inhibition of hemagglutinin titers) and antileukemic (L1210) activities.[8,9] The remaining derivatives, as well as ara-C, possessed greatly reduced activity under the same conditions. From these results, we conclude that the increased potency and long-lasting effects observed previously with 5′-

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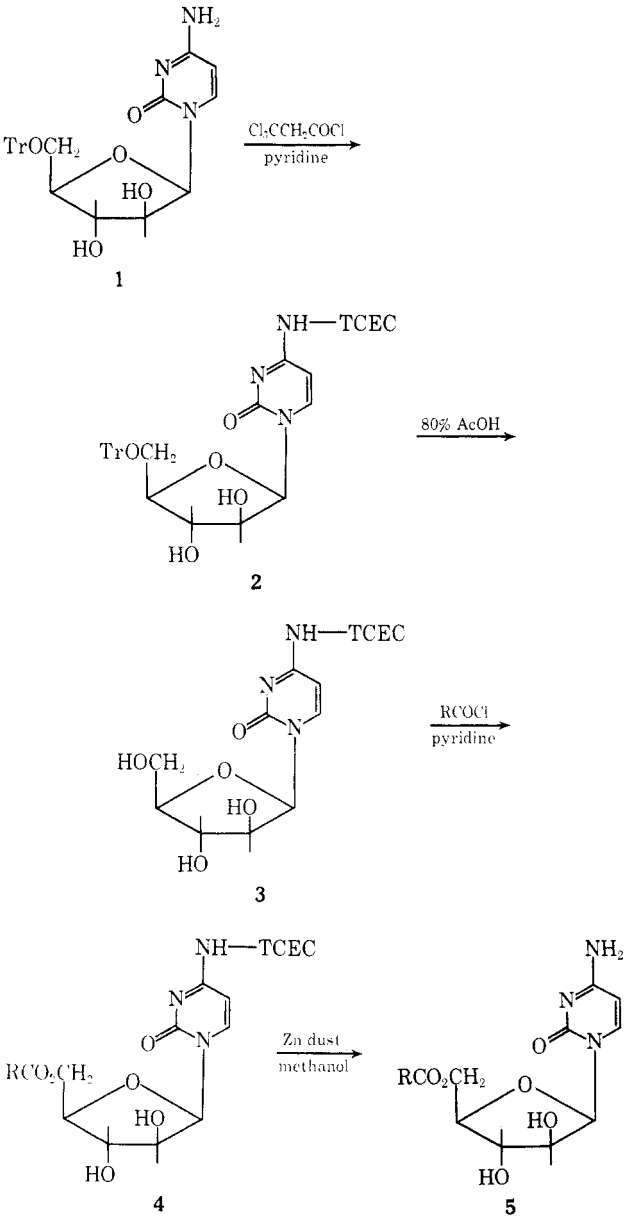
adamantoyl ara-C were not due to properties unique to the adamantane moiety, but would be exhibited by any group that would appropriately affect the rate of dissolution, lipophilicity, rate of hydrolysis, resistance to cytidine deaminase, and possibly other properties of these nucleoside derivatives.

In our search for an orally active drug, we have investigated the effects of such parameters as water solubility, distribution between H_2O and octanol, rates of hydrolysis at the 5′ position, and deamination by aminohydrolase. These results will be the subject of future publications, but it can be reported that several of the derivatives reported in this paper have exhibited significant oral activity.

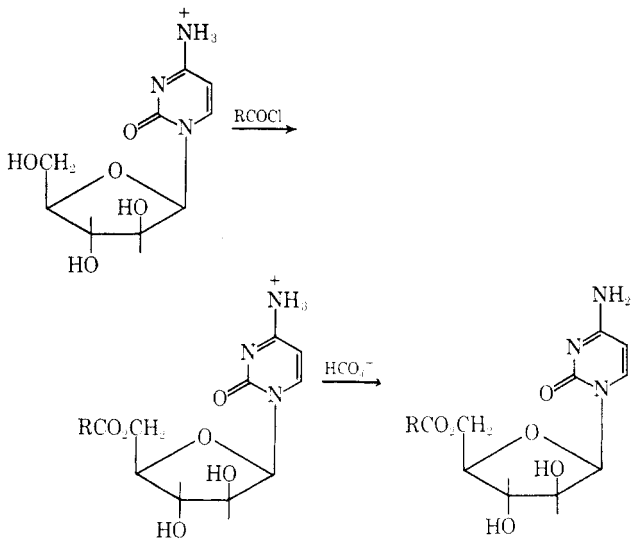
In our first syntheses, the 5′-esters were prepared by a route which began with the 5′-trityl derivative of ara-C (**1**). This compound was converted into its N^4-2,2,2-trichloroethoxycarbonyl derivative **2**, which



Tr = trityl; TCEC = 2,2,2-trichloroethoxycarbonyl

was then detritylated to **3**. The N^4-trichloroethoxycarbonyl derivative **3** was acylated at the 5′ position, using either an acid chloride or anhydride, to give **4**. Removal of the trichloroethoxycarbonyl group with Zn dust in MeOH gave the desired 5′-ester **5** after purification by column chromatography. The yields, based on ara-C, varied from 3 to 5%.

Subsequently, we have developed a greatly simplified procedure which involves a single synthetic step beginning with ara-C·HCl. We have found that protonation provides adequate protection for the N^4-amino group of cytosine against acylation. A solution of the hydrochloride of ara-C in DMF or dimethylacetamide was treated with the acid chloride to give the hydrochloride of the 5′-ester. Evaporation of the solvent and trituration of the product with dil aq $NaHCO_3$ (except in the cases of the water-sol Ac and quinuclidinoyl esters) yielded the crystalline 5′-esters. One recrystallization was sufficient to obtain the pure ester in yields of 40–80%. In the case of the Ac derivative, purification by column chromatography was necessary.



The dihydrochloride of the 5′-quinuclidinate crystallized in nearly pure state from the reaction mixture. The acid chloride of the racemic form of quinuclidine-3-carboxylic acid had been used for the preparation of this derivative. In order to seek information that might help to determine whether this ester had separated in the form of the racemic mix or as one of the diastereoisomers, the 100-MHz nmr spectrum of the dihydrochloride was examined. This spectrum, however, failed to yield any information concerning this question. It was then reasoned that mutually repulsive charges on the protonated N^4-amino group of the cytosine moiety and the protonated N of the quinuclidine moiety may have prevented the orientation that would be possible with the free base. The dihydrochloride was therefore converted to the free base by passage over an ion-exchange resin. Examination of the corresponding spectrum of the free base showed that the peaks for the 1′, 5, and 6 protons appear as pairs of doublets, due apparently to the influence of the asymmetric center at the 3 position of the quinuclidine moiety. We thus conclude that this derivative crystallized as a diastereoisomeric pair.

It was found that pivaloyl chloride, adamantoyl chloride, and benzoyl chloride formed complexes with DMF which are insoluble in that solvent. In these

TABLE II

5′-Ester	Composition	Reagent	Recrystn solvent	Mp, °C	Yield, %[a]	Analyses
Acetyl	$C_{11}H_{15}N_3O_6 \cdot 0.5H_2O$	AC[b]	MeOH–C_6H_6	115–117.5	4.1	C, N; H[e]
Octanoyl	$C_{17}H_{27}N_3O_6 \cdot H_2O$	AC	MeOH	123–124	13.5	C, H; N[f]
Palmitoyl	$C_{25}H_{43}N_3O_6$	AC	MeOH	143–146	7.3	C, H; N[g]
Pivaloyl	$C_{14}H_{21}N_3O_6$	AC	MeOH	255 dec	10.4	C, H, N
β-Chloropivaloyl	$C_{14}H_{20}ClN_3O_6$	AC	MeOH	238–240	35	C, H, N, Cl
Methoxycarbonyl	$C_{11}H_{15}N_3O_7$	AC	MeOH	188.5–190	13	C, H, N
Isopropylcarbonyl	$C_{13}H_{19}N_3O_6 \cdot 0.5H_2O$	AA[c]	H_2O	206–208	15	C, H, N
Cyclobutylcarbonyl	$C_{14}H_{17}N_3O_6$	AA	Me_2CO	200–200.5	16	C, H, N
Cyclohexylcarbonyl	$C_{16}H_{23}N_3O_6 \cdot 0.5H_2O$	AC	MeOH–Me_2CO	231 dec	19	C, H, N
Benzoyl	$C_{16}H_{17}N_3O_6 \cdot H_2O$	AA	MeOH	200.5–201.5	18	C, H, N
2,6-Dimethylbenzoyl	$C_{18}H_{21}N_3O_5 \cdot 0.5H_2O$	AC	MeOH	238–240	16	C, H, N
2,4,6-Trimethylbenzoyl	$C_{19}H_{23}N_3O_6 \cdot 0.5H_2O$	AC	MeOH	255–256	17	C, H, N
p-Methoxybenzoyl	$C_{17}H_{19}N_3O_7$	AC	MeOH	225–227	11	C, H, N
3,4,5-Trimethoxybenzoyl	$C_{19}H_{23}N_3O_9 \cdot H_2O$	AC	MeOH	137–139	26	C, H, N
(3-Carboxymethyladamantane-1)-acetyl	$C_{23}H_{31}N_3O_8$	AC[d]	Me_2CO	141–146	6.5	C; H;[h] N[i]
p-Toluenesulfonyl	$C_{16}H_{19}N_3O_7S$	AC	MeOH	171–174	24	C, H, N, S
2,4,6-Triisopropylbenzenesulfonyl	$C_{24}H_{35}N_3O_7S$	AC	MeOH–H_2O	228 dec	23	C, H, N, S

[a] The yields are based on the amt of N-TCEC-ara-C used. [b] Acid chloride. [c] Acid anhydride. [d] The diacid chloride was used. [e] Calcd, 5.48; found, 5.95. [f] Calcd, 10.85; found, 11.32. [g] Calcd, 62.34; found, 62.86. [h] Calcd, 6.54; found, 7.01. [i] Calcd, 8.80; found, 8.24.

cases, use of dimethylacetamide as solvent yielded the 5′-esters in good yield. The use of a 50–100% excess of the acid chlorides of benzoic and adamantane-1-carboxylic acids afforded a considerable improvement in yield. These acid chlorides are sufficiently hindered so that no significant reaction occurs at the 2′ or 3′ position. The use of dimethylacetamide as reaction solvent, instead of DMF, increased the yield of the palmitoyl ester from 50 to 80%.

Experimental Section[10]

Incorporation of Thymidine into PHA-Stimulated Human Lymphocytes.—The effects of ara-C and the 5′-esters on the synthesis of DNA in phytohemagglutinin (PHA)-stimulated human lymphocytes were assessed by measuring the incorporation of tritiated thymidine. Human venous blood was defibrinated with glass beads, and red cells were removed by settling for 30–45 min at 37°. Total white cell counts were made in 2% AcOH–H_2O soln; viable leukocyte counts were made with tryptan blue stain; differentital white cell counts were made using Giemsa stain. Cells and autologous serum were added to Minimal Essential Medium, Eagle's (MEM), supplemented with antibiotics and L-glutamine, to give final concns of 0.5×10^6 viable lymphocytes per ml and 17–18% (v/v) serum. Sterile PHA-P soln (Difco) was added at a ratio of 0.1 ml/64 ml of suspension. Aliquots (1 ml) of the suspension, with and without PHA, were distributed to screw-capped tubes. Incubations were at 37° for 68–72 hr. Test compds, 0.1-ml aliquots, were added after the first 24 hr of incubation, and tritiated thymidine, 0.1-ml aliquots (8 μCi, 12 nmoles), was added just 2 hr before the end of incubation. Test compds were dissolved at a concn of 2 mg/ml in 10^{-2} M HCl, and dilns were prepd serially in supplemented MEM. At the end of the incubation, the tube contents were washed serially with 10-ml aliquots of saline, 10% trichloroacetic acid (TCA), and 5% TCA. The ppts were heated with 1.0-ml aliquots of 5% TCA for 15 min at 88–90°, and the radioactivity in 0.25-ml aliquots of the clear supernatant liquid was detd in a scintillation-type counter. Each ID_{50} (inhibitory dose, 50%) value was calcd from 3-point assays with 4 replicates per point; lymphocytes from 3 individuals were used. The range of incorporation was from 23–82 dpm in nonstimulated controls to 2300–5500 dpm in the PHA-stimulated controls.

Synthesis of 5′-Esters of Ara-C *via* the N^4-Trichloroethoxycarbonyl Derivative. 5′-Trityl-N^4-trichloroethoxycarbonyl Ara-C.—5′-Trityl ara-C (194 g, 0.4 mole) was dissolved in 4 l. of freshly distd anhyd pyridine. The soln was cooled to 3° and treated with 84.4 g (0.4 mole) of TCEC chloride.[11] The soln was stirred at 3° for 4 hr and then allowed to stand at room temp for 18 hr. The pyridine was distd *in vacuo* at 40° bath temp, and the gummy residue was triturated with 1 l. of CH_2Cl_2. A solid (23.7 g) sepd and was removed by filtn. Tlc showed that this was starting material. The org soln was washed 3 times with 0.1 N HCl and once with satd salt soln. The CH_2Cl_2 soln was dried (Na_2SO_4) and then allowed to evap slowly, whereupon crystals were deposited. These were collected, washed with cold CH_2Cl_2, and dried, giving 64.5 g. Tlc of the mother liquor showed, in addn to the desired product, spots moving faster than the product, apparently, the N,2′- and N,3′-dialkylated products. The solvent was removed *in vacuo*, and the residue was treated with a mixt of 1 l. of THF and 1 l. of 0.3 N NaOH. After 1.5 hr, the faster moving material had disappeared. The mixt was acidified to pH 6.5 with concd HCl. The THF was distd *in vacuo* and the aq soln was extd with CH_2Cl_2. The org soln was washed and dried as above and then allowed to slowly evap. The resultant cryst product was collected and washed to give 42.5 g of product. Further evapn of the mother liquor yielded an addnl 45.5 g of impure material. This material was triturated with 500 ml of hot Me_2CO and the insol residue was removed by filtn. This was found to be starting material. The Me_2CO soln was evapd *in vacuo* and the residue was recrystd from CH_2Cl_2 as above to yield an addnl 19 g of product. The total yield was 126 g (48%). A sample was recrystd twice from MeOH for anal., mp 235° dec. *Anal.* ($C_{31}H_{28}Cl_3N_3O_7$) C, H, N; Cl: Calcd, 16.11; found, 15.54.

N^4-Trichloromethoxycarbonyl Ara-C.—5′-Trityl-N^4-trichloroethoxycarbonyl ara-C (116 g, 0.175 mole) was treated with 1 l. of 80% (v/v) AcOH for 48 hr at 25°. The material which had been deposited during this period was removed by filtn, and the filtrate was evapd to dryness *in vacuo*. The last traces of acid were removed by several codistns *in vacuo* with EtOH. The glassy residue was crystd from EtOH to give 62.5 g of product. Nmr anal. indicated that 10–15% of this material consisted of triphenylcarbinol. The product was purified by chromatog over silica gel, eluting with cyclohexane–EtOAc–EtOH (5:3:1). For anal. the material was recrystd from CH_2Cl_2, mp 145–148° dec. *Anal.* ($C_{12}H_{14}Cl_3N_3O_7$) C, H, N; Cl: Calcd, 25.41; found, 24.82.

N^4-Trichloroethoxycarbonyl 5′-Esters of Ara-C.—N^4-Trichloroethoxycarbonyl ara-C (0.02 mole) was dissolved in 50 ml of dry pyridine and a 10% excess of either the acid chloride or acid anhydride was added. After the mixt had been stirred overnight at room temp, 25–30 ml of H_2O was added, and the solvent was evapd *in vacuo*. The crude N^4-trichloroethoxycarbonyl 5′-ester was purified by chromatog over silica gel, eluting with cyclohexane–EtOAc–95% EtOH (5:3:1). The sepn was followed by tlc. The purified derivative was recovered by evapn *in vacuo* of pooled

(10) Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of theoretical values.

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TABLE III

5′-Ester	Composition	Reaction solvent	Recrystn solvent	Mp, °C	Yield, %	Analyses
Palmitoyl	$C_{25}H_{43}N_3O_6$	DMA	MeOH	147–149	80	C, H, N
Octanoyl	$C_{17}H_{27}N_3O_6$	DMF	EtOAc	158–161	55	C, H, N
Acetyl	$C_{11}H_{15}N_3O_6$	DMF	*n*-BuOH	184–185	38	C, H, N
Pivaloyl	$C_{14}H_{21}N_3O_6$	DMA	*n*-BuOH	260–261	55	C, H, N
Benzoyl	$C_{16}H_{17}N_3O_6 \cdot H_2O$	DMA	*n*-BuOH[a]	205–206	77	C, H, N[b]
Cyclohexylcarbonyl	$C_{16}H_{23}N_3O_6$	DMF	EtOAc	232 dec	53	C, H, N
1-Adamantoyl	$C_{20}H_{27}N_3O_6$	DMA	EtOAc	291 dec	70	C, H, N
3-Quinuclidinoyl[c]	$C_{17}H_{24}N_4O_6 \cdot 2HCl$	DMA	EtOH	188 dec	55	C, H, N, Cl

[a] After soln in hot BuOH, addn of 2–3% of H_2O induced rapid crystn. [b] Anal. for the anhyd material; when dried at 60° *in vacuo*, the wt loss was 4.82% (calcd for 1 H_2O: 4.93%). [c] Prepd using rac quinuclidine-3-carboxylic acid; isolated as the di·HCl by crystn from the reaction mixt.

fractions. The residue was dissolved in MeOH, 3 g of Zn dust was added, and the mixt was refluxed for 15 min. The 5′-ester so obtained was purified by chromatog over silica gel, eluting with MEK–Me_2CO–H_2O (72:20:8). The purified 5′-ester was recovered by evapn *in vacuo* of pooled fractions and recrystd. Results and anal. data are summarized in Table II.

In the cases of the 2,6-dimethylbenzoyl, β-chloropivaloyl, and (3-carboxymethyl-adamantane-1)acetyl esters, a considerable amt of unreacted N^4-trichloroethoxycarbonyl ara-C remained after treatment with the acid chloride. Further treatment with up to a 1 mole excess of these sterically hindered acid chlorides effected more nearly complete reaction without significant reaction at the 2′ or 3′ position.

Direct Synthesis of 5′-Esters of Ara-C.—The HCl of ara-C (0.01 mole) was dissolved in 25 ml of DMF or suspended in 50 ml of DMA, 0.011 mole of the acid chloride was added, and the mixt was stirred overnight at room temp. In the cases of the prepn of the 5′-benzoyl and 5′-adamantoyl esters, a second portion of the acid chloride was added and the reaction was allowed to continue for an addnl 24 hr. The reaction mixt was concd *in vacuo* to an oil, and the oil was thoroughly triturated with EtOAc–Et_2O (1:1). The oil was then thoroughly triturated with 1 *N* $NaHCO_3$. The cryst solid was collected, washed several times with H_2O, and dried. One recrystn yielded the pure ester. Results and anal. data are summarized in Table III.

Because of its soly in H_2O, the 5′-acetyl ester could not be purified as described above. After concn of the reaction mixt, the resultant oil was first triturated with Et_2O and then dissolved in H_2O. The pH was adjusted to 1.5, and the soln was extd several times with equal vols of EtOAc. The pH of the aq soln was then adjusted to 7, and the solvent was evapd *in vacuo*. The oil was dissolved in EtOH, and the NaCl was removed by filtn. The solvent was evapd *in vacuo* to leave an oil. The crude product was purified by chromatog over silica gel, using MEK–Me_2CO–H_2O (72:20:8) as the solvent. The purified ester had a mp of 184–185°, and was apparently obtained in an anhyd form, in contrast to the hemihydrate previously obtained for this ester [mp 115–117.5° (Table II)].

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Quantitative Structure–Activity Relationships in Leucomycin and Lincomycin Antibiotics

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The *in vitro* antibacterial activity of members of the leucomycin complex increase with increasing partition coefficient and removal of esterification of the 3 hydroxyl of the macrolide ring. In the series of 25 NCH_3 and NC_2H_5 lincomycins an optimum log *P* of 1.1 was calculated for *in vitro* activity *vs. Sarcina lutea* and 0.4 for *in vivo* activity *vs Staphylococcus aureus*. The *in vitro* activity of the NH lincomycins is positively correlated with log *P* (optimum >2.7). Electronic and steric factors also influence the activity of these antibiotics. An optimum partition coefficient is indicated in the clindamycins.

The antibiotics lincomycin and leucomycin are both considered to act by binding to the 50S ribosome to prevent bacterial protein synthesis. The relative *in vitro* antibacterial activity of various individual members of the leucomycin complex has recently been reported.[1] Similarly, the activity of a large number of alkyl analogs of lincomycin has been studied by Magerlein, *et al.*[2–4] It was our interest to investigate the quantitative structure–activity relationships in each series of compounds and to compare the results from these studies to form a general concept of the patterns which govern activity in this type of molecule. For this purpose the extrathermodynamic approach to structure–activity studies[5] was used.

Experimental Section

Partition Coefficients.—The π values [change in the logarithm of the 1-octanol–H_2O partition coefficient (log *P*) of a derivative compared to the parent compound] were calcd as outlined by Iwasa, *et al.*[5]

The log *P* value of leucomycin A1 (compound **1** in Table II) was calcd from the experimental observation of the log *P* value

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