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REPORT NO. 68066

THE SYNTHESIS OF NEW ANTIMALARIAL DRUGS ANALOGS OF PANTOTHENIC ACID

FINAL REPORT
(combined with Annual Report 3)

RAJ K. RAZDAN
BARBARA A. ZITKO
AVINASH C. MEHTA

March 1969

Supported by
U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Washington, D. C. 20315

Contract No. DA-49-193-MD-2879

ARTHUR D. LITTLE, INC.
Cambridge, Massachusetts 02140

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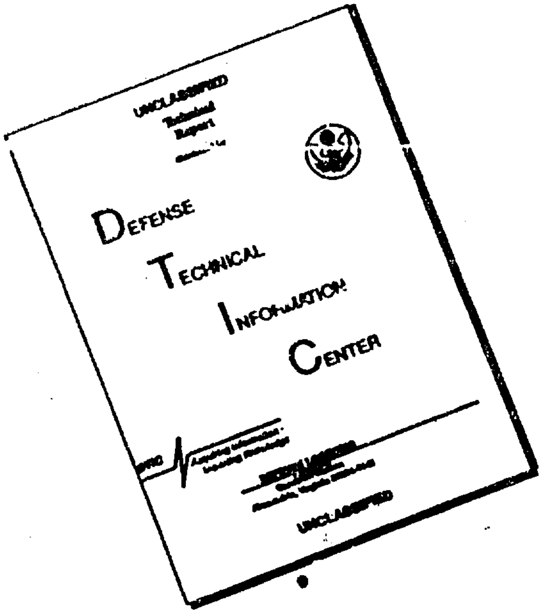

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Report No. 68066

The Synthesis of New Antimalarial Drugs
Analogs of Pantothenic Acid

Final Report
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Raj K. Razdan
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SUMMARY

During the three years of our work we have prepared and submitted for evaluation as potential antimalarials one hundred and eight compounds including repeat samples of which fifty are target compounds.

Except for WR 61467, AE 96096 and AF 14571 (pantoic acid derivatives of sulfadiazine, fanasil and kelfizina respectively) all of the target compounds so far tested in the Rane mice and bird screen have shown only marginal activity at best. The present synthetic program on antagonists of pantothenic acid was based on the demonstrated antimalarial activity of SN 14622 (WR 29,224) in avian malaria and more recently in Trager's in vitro screen, from the World War II program. Unfortunately, SN 14622 is completely inactive in the present WRAIR screens in mice (P. berghei), chicks (P. gallinaceum) and mosquitoes. In our opinion, the nonreproducibility of the activity of SN 14622, particularly in the present WRAIR chick screen is due to the different test procedure being used by Rane. We consider this screening procedure an improper one for our compounds. We suggest that the drug-diet method, used for testing SN 14622, should be repeated and used as a standard protocol method for these compounds. A few of our compounds were tested by Dr. Trager in his in vitro system with P. coatneyi in monkey erythrocyte suspension and he has found WR 54036 (an amide of pantoyltaurine) to be very active, much more so than SN 14622. We have been informed that on the basis of Dr. Trager's screen it has been selected for advanced screening in the monkey.

In the Rane screen in mice, WR 61467 has been found to be curative at 320 mg/kg and is active at 160 mg/kg. It is more active than sulfadiazine. Similarly, AE 96096 and AF 14571 are active at 40 mg/kg and 160 mg/kg respectively. We would recommend advanced biological evaluation of these compounds for (a) testing against resistant strains as possible candidates and (b) comparative evaluation against sulfas which are at present being administered in combination with pyrimethamine.

FOREWORD

In the middle of February 1966 work was started in our laboratories on the synthesis of "Analogs of Phenylpantothenone" and "Amides of Pantoyltaurine" as potential antimalarials under Contract DA-49-193-MD-2879. The first and the second annual reports were submitted in February of 1967 and 1968 respectively. The present final report covers the progress of work until March 1969, the termination date of the contract. The work carried out during this period was partly the subject of our proposals for renewal, dated July 24, 1967 and July 22, 1968.

Experimental details for only the compounds synthesized during the third year of our contract are given in this report. However, reference to the experimental details of the compounds synthesized in the previous two years may be obtained from the table of contents in this report.

Cumulative tables for the biological activity of all the compounds submitted so far to WRAIR for screening are included in this report.

Drs. T. R. Sweeney and B. Poon of the Department of Organic Chemistry, Walter Reed Army Institute of Research, continued to act as technical officers for this agency.

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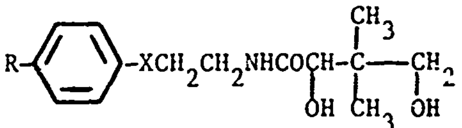
I. INTRODUCTION AND BACKGROUND

The primary objective with which the U.S. Army Medical Research and Development Command had launched this research program, i.e., to find an effective antimalarial against resistant strains of P. falciparum, has not yet been achieved and vigorous research in the various aspects of malaria chemotherapy is being continued. However, encouraging results have been obtained on recent studies on volunteers infected with chloroquine-resistant P. falciparum with the use of a combination of sulfadiazine (or a longer acting sulfonamide) with pyrimethamine. Similarly a mixture of cycloguanil embonate and diacetyl derivative of diphenylsulfone (CI 564) has shown promising results.

Background

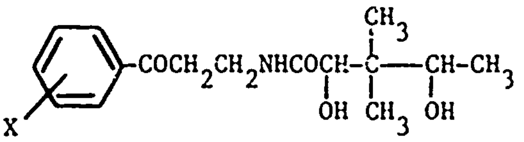
As a part of this program we have carried out the synthesis of analogs of pantothenic acid as potential antimalarials under Contract No. DA-49-193-MD-2879.

The biological rationale for the preparation of these compounds was based on the elegant work of Trager[1] who had shown that the addition of calcium pantothenate to an appropriate medium containing duck erythrocytes parasitized with P. lophurae increased the survival period of the parasite. Hence, the testing of pantothenic acid antagonists as potential antimalarials was initiated in the World War II program, and activity against P. gallinaceum and P. lophurae was found in phenylpantothenone (1, X = CO; R = H, Cl, etc.),[2,3] amides of pantoyltaurine (1, X = SO_2NH; R = H, Cl, etc.),[4] and in other related compounds (1, X = S, SO, SO_2,; R = H, Cl).[5]



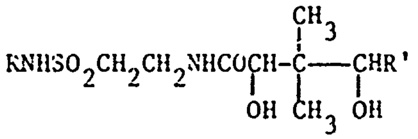
1

During the course of the program, we intended to synthesize compounds 2 and 3a as potential antimalarials in which the terminal $-CH_2OH$ of the pantoyl part has been replaced by $-CHOH-CH_3$, a group which is known to produce potent pantothenic acid antagonists.[6] In addition, we proposed to synthesize more examples in the series of amides of pantoyltaurine, 3b.



2

Analogs of phenylpantothenone



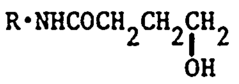
$$\mathrm{RNHSO_2CH_2CH_2NHCO\underset{OH}{C}H-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OH}{C}HR'}$$

3

a) (R' = CH_3), amides of ω-methylpantoyltaurine

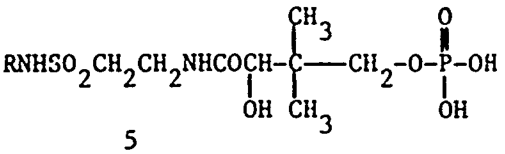
b) (R' = H), amides of pantoyltaurine

Recently, Dr. Trager[7] has demonstrated very elegantly that the plasmodium in fact utilize Coenzyme A for their growth. Thus, the beneficial effect observed by him earlier of the addition of calcium pantothenate is an indirect one. We therefore proposed to synthesize simpler analogs of type 4 where only the pantoic acid part of the molecule [$COCHOHC(CH_3)_2CH_2OH$] has been changed. The important part of 4 is the terminal hydroxyl group. This is necessary because it will then be available for phosphorylation, etc., to be converted biosynthetically to the corresponding Coenzyme A derivatives, whereas this conversion would be blocked in the absence of the hydroxyl group.



$$\mathrm{R\cdot NHCOCH_2CH_2\underset{OH}{C}H_2}$$

4

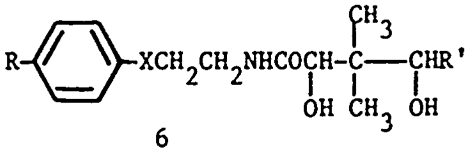


$$\mathrm{RNHSO_2CH_2CH_2NHCO\underset{OH}{C}H-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-O-\overset{O}{\underset{OH}{P}}-OH}$$

5

In addition we proposed to synthesize a few examples of phosphate esters of 3b, e.g., 5 (R = 4-chlorophenyl). The preparation of these compounds would be, in a way, a step further toward the synthesis of the corresponding Coenzyme A analogs.

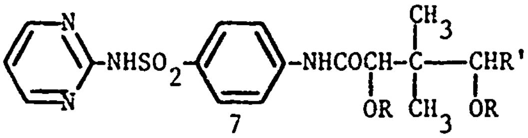
In view of the current interest in the antimalarial activity of the sulfone DDS against the resistant strain of P. falciparum, we had also proposed the synthesis of related sulfone derivatives of type 6.



6

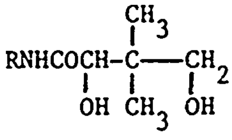
X = S, SO, SO_2; R' = H, CH_3

Some pantoic acid derivatives were also proposed in which some of the known antimalarials (e.g., sulfadiazine, etc., and 8-aminoquinolines) would be synthesized with the added pantoic acid side chain (e.g., 7), and thus hopefully their metabolic pathway would be changed.[8]



7

We had also proposed the synthesis of compounds of type 8, some of which are known antipantothenates.[9]



$$\mathrm{RNHCO}\underset{\mathrm{OH}}{\mathrm{CH}}-\overset{\mathrm{CH_3}}{\underset{\mathrm{CH_3}}{\mathrm{C}}}-\underset{\mathrm{OH}}{\mathrm{CH_2}}$$

8

Work carried out in the present program of synthesis of antipantothenates has led to an amide of pantoyltaurine[8a] (WR 54036) which is very active in Trager's *in vitro* screen although inactive in the Rane screen. We have been informed that this compound has been selected for advanced screening in the monkey.[10] Whereas a pantoic acid derivative[8a] of sulfadiazine (WR 61467) has been found to be curative at 320 mg/kg, it is active at 160 mg/kg in the Rane screen and is inactive in Trager's *in vitro* screen. It is more active than sulfadiazine. Similarly pantoic acid derivatives of Fanasil (AE 96096) and Kelfizina (AF 14571) are active at 40 mg/kg and 160 mg/kg respectively in the Rane screen. Further data on these compounds are not yet available and are awaited with interest.

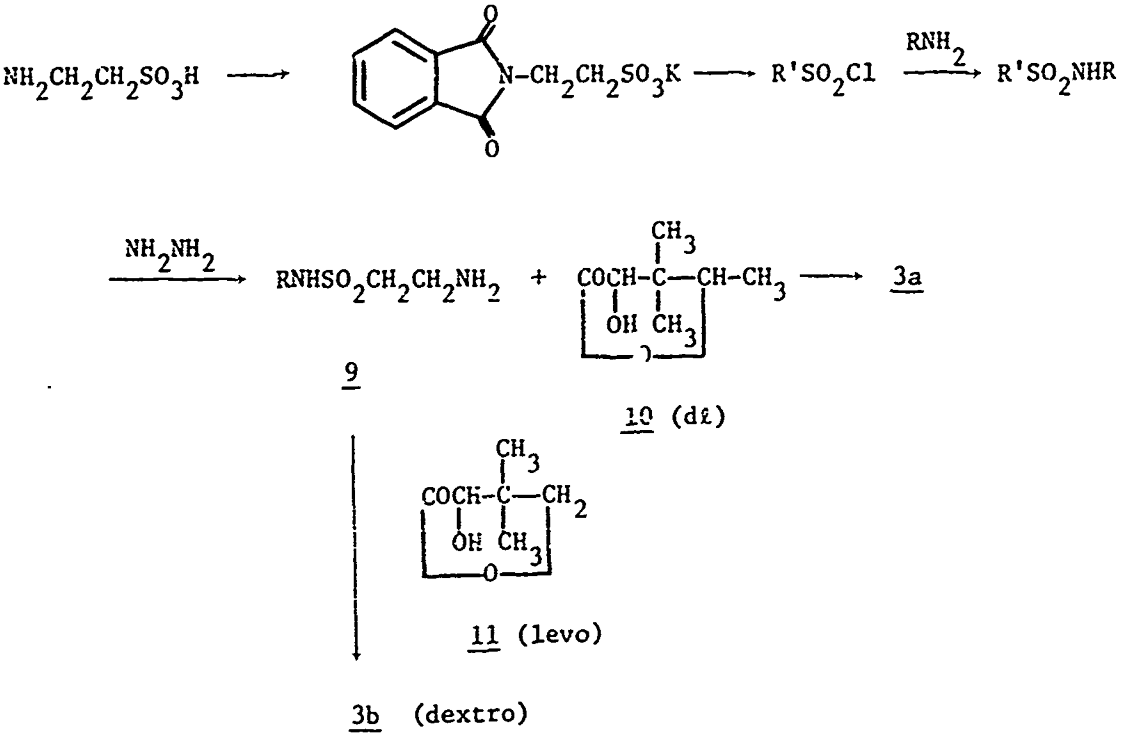
II. SYNTHESIS OF COMPOUNDS

A. Analogs of Phenylpantothenones (2)

Because of the extreme acid-base sensitivity of these compounds,[8a p 7-11] the original scheme had to be abandoned and an alternative five-step synthesis was developed to give their diacetates. The three compounds submitted for biological testing have shown no activity in any of the malaria screens (Table IA).

B. Amides of ω-Methylpantoyltaurine (3a) and Amides of Pantoyltaurine (3b)

All but one of the 17 sulfonamides 9 originally suggested[8a p 11-13] have been prepared. The sulfonamides 9 were synthesized as shown below and then were condensed with lactones 10 or 11 to give the target compounds 3a and 3b respectively. The lactone 11 condensed smoothly with the sulfonamides 9, but there was no reaction when lactone 10 was used. However, it was found that the condensation occurred when the sulfonamide 9 was used as its potassium salt.



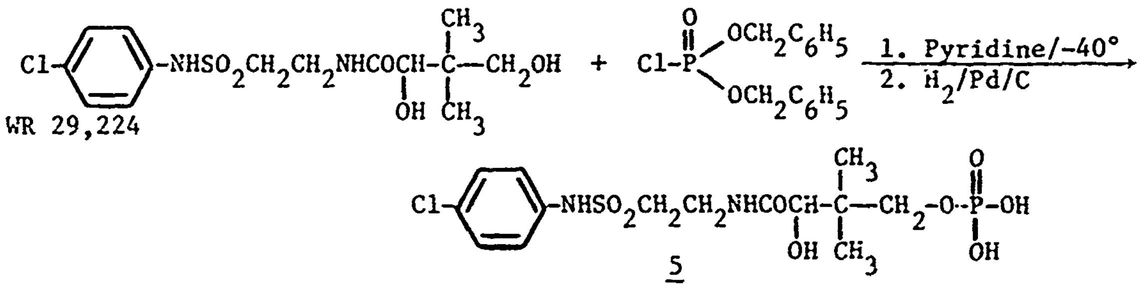
To date twenty-two target compounds have been submitted for testing. Two compounds, viz WR 54036 and WR 35393, have been found to be very active in Dr. Trager's screen (see discussion of biological activity).

The structures and biological activity of all the amides of ω-methylpantoyltaurines 3a, amides of pantoyltaurines 3b, sulfonamides 9 and the corresponding phthalimides submitted by us for testing are given in Tables IB, IC, ID and IE respectively.

C. Other Analogs (4 and 8) and Phosphate Esters (5)

Compounds of type 4 and 8 were prepared by the condensation of various amines with γ-butyrolactone and 11 respectively.[8b p 7]

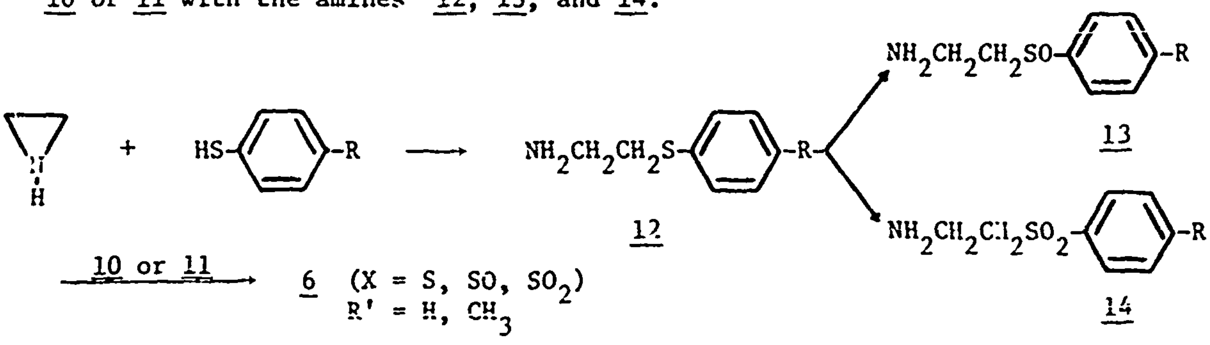
Only one example of 5 was prepared. It was synthesized as shown below. It is the phosphate ester of SN 14622 (WR 29,224), the most active antipantothenate from the World War II program.



The structures and biological activity of these compounds is given in Table 3A.

D. Related Sulfone Derivatives (6)

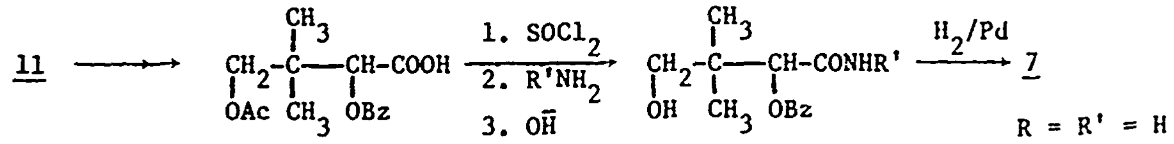
These compounds were prepared by the reaction of the lactones 10 or 11 with the amines[5] 12, 13, and 14.



Nearly all the suggested compounds[8b p 6] were prepared. A total of 15 compounds including six target compounds have been submitted for biological evaluation. The various ω-methylpantoylsulfones, pantoylsulfones, and their precursor sulfides, sulfoxides, and sulfones which we have synthesized are listed in Table 2A, 2B, 2C, 2D and 2E respectively.

E. Pantoic Acid Derivatives (7)

Since the attempted hydrolysis of the diacetate groups in WR 61467 (7, R = Ac, R' = CH_3) failed under a variety of conditions, the original synthetic scheme was abandoned[8b p 8-11] and an alternative synthesis as shown below was developed to give 16.



15 16

Derivatives of type 16 of sulfadiazine, Fanasil and Kelfizina have been prepared but in all cases the attempted debenzylation to give the target compound 7 (R = R' =H) have failed. The heterocyclic nucleus of the sulfas is reduced instead. However, compounds of type 16 are very important from the biological activity point of view, as they have the necessary terminal hydroxyl group (see p. 20).

Three compounds, WR 61467, AE 96096 and AF 14571, are active in the Rane screen. The biological data on a number of compounds in this series are not yet available.

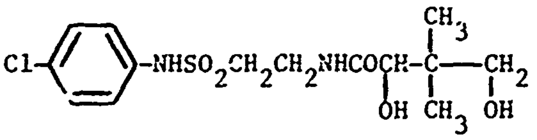
The list of pantoic acid derivatives we have synthesized are listed in Table 3B.

F. Miscellaneous

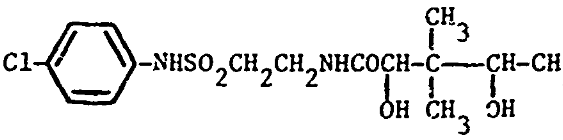
A few substituted dibenzyl anilinophosphonates were prepared by allowing the amine to react with dibenzyl phosphochloridate in refluxing benzene. They are listed in Table 3C.

III. BIOLOGICAL SCREENING DATA AND DISCUSSION OF RESULTS

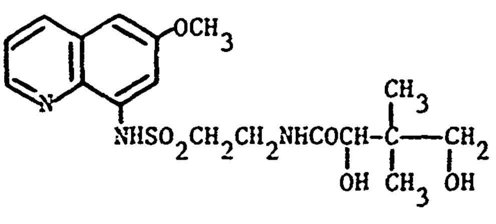
As discussed earlier, the present synthetic program on antagonists of pantothenic acid was based on the demonstrated antimalarial activity in avian malaria of phenylpantothenones and amides of pantoyltaurine. The most active compound, i.e., SN 14622 (WR 29,224) was reported to be ten times as active as quinine when tested against blood-induced P. gallinaceum infection in the chick.[4,11,12] More recently, Trager has shown the in vitro inhibitory effect of SN 14622 on P. lophurae, P. coatneyi, and P. falciparum developing intracellularly.[7] Unfortunately, SN 14622 is not being picked up[13] in the present WRAIR screens in mice (P. berghei), chicks (P. gallinaceum) and mosquitoes. Our target compounds so far tested, except WR 61467, AE 96096 and AF 14571, have shown marginal activity at best in mice and chicks. However, a few of our compounds were tested by Dr. Trager in his in vitro screen.[8b] He has found WR 35393 to be as active as SN 14622 and WR 54036 much more active than SN 14622 (Table 4a and 4b).



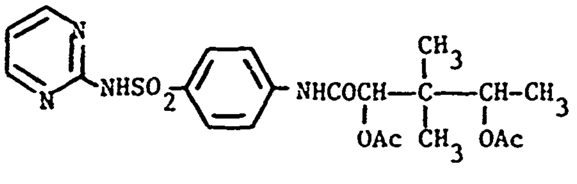
SN 14622 (WR 29,224)
(+ isomer)



WR 35393

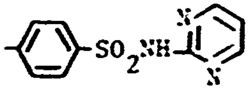


WR 54036 (+ isomer)



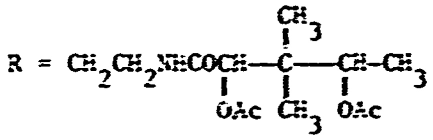
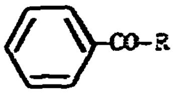
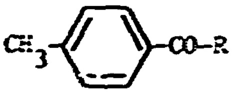
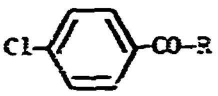
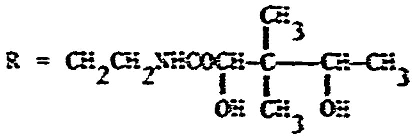
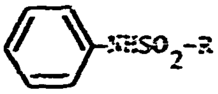
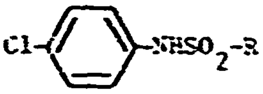
WR 61467

The non reproducibility of the activity of SN 14622 in the present WRAIR chick screen is both disappointing and puzzling. To us it seems the difference lies in the test procedure. In the present screen the drug is administered to the chick either subcutaneously or per os immediately after infection as a single dose, whereas in the World War II program the drug-diet method was used[14] and the administration of the drug was begun one day before infection and was continued for four days after infection. Perhaps in the present test method the lack of activity is due to insufficient levels of the drug in the blood. We suggest that the method used for testing SN 14622 (see reference 14) should be repeated and used as a standard protocol method for these compounds. We have been informed, however, that WR 54036, which is most active in Trager's screen, has been selected for advanced screening in the monkey.[10] In view of the difference in activity in the two chick screens, we would recommend that due consideration be given to having adequate drug levels in the blood in the test procedure to be used in the monkey screen. This whole question has been brought to the attention of WRAIR.

Among pantoic acid derivatives WR 61467 is curative in mice (Rane screen) at 320 mg/kg and is active at 160 mg/kg. It is more active than sulfadiazine. It is inactive in Trager's *in vitro* screen (Table 4b). This latter inactivity of WR 61467 is perhaps due to the presence of the acetate group which is not hydrolyzed in the *in vitro* system and thus is not available for phosphorylation, etc. With the present data it is difficult to assess whether its activity is due to hydrolysis *in vivo* to sulfadiazine. Some light may be thrown on this aspect when some results from the Trager screen become available on compound 16 (R' = ), which has a free terminal hydroxyl group.

Similarly AE 96096 (Fanasil derivative) and AF 14571 (Kelfizina derivative) are active at 40 mg/kg and 160 mg/kg respectively in the Rane screen. Further data on these compounds is not yet available. We would recommend advanced biological evaluation of these for (a) testing against resistant strains as possible candidate compounds and (b) comparison with sulfas which are at present being administered in combination with pyrimethamine. These compounds will be most interesting if their activity is based on something different than hydrolysis *in vivo* to the corresponding sulfas.

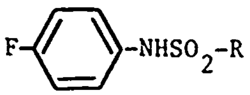
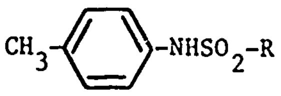
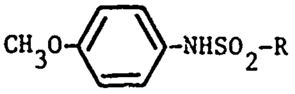
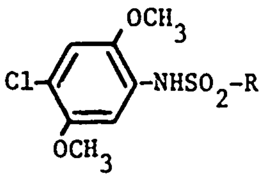
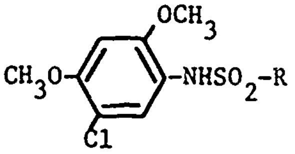
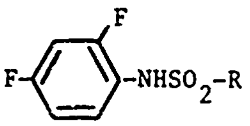
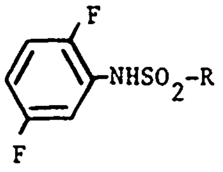
TABLE 1. Biological Results of Phenylpantothenones and Pantoyltaurine Derivatives

Identification	Compound	Mice Dose mg/kg	Survival Time, days Mean treated	 control	 change	Toxic Deaths
A. Analogs of Phenylpantothenone						
	 $R = CH_2CH_2NHCO\underset{OAc}{CH}-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OAc}{CH}-CH_3$					
ADL 14155-32 WR 40646		20 80 320	6.2 6.2 6.[illegible]	6.2 6.2 6.2	0.0 0.0 0.0	00 00 00
ADL 14155-25 WR 40647		10 40 160	6.2 6.4 6.4	6.2 6.2 6.2	0.0 0.2 0.2	00 00 00
ADL 14155-35 WR 45491		10 40 160	6.4 6.4 6.6	6.1 6.1 6.1	0.3 0.3 0.5	00 00 00
B. Amides of ω-Methylpantoyltaurine						
	 $R = CH_2CH_2NHCO\underset{OH}{CH}-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OH}{CH}-CH_3$					
ADL 14155-22 WR 35394		40 160 640	6.8 7.0 8.2	6.5 6.5 6.5	0.3 0.5 1.7	00 00 00
ADL 14155-26 WR 35393		40 160 640	7.6 8.4 9.2	6.5 6.5 6.5	1.1 1.9 2.7	00 00 00

Bird					Mosquito					
	Survival Time, days					Percent				
Dose	Mean			Toxic	Dose	Toxic	Abnormal	Suppression		Synthesis
mg/kg	treated	control	change	Deaths	% conc	Deaths	Oocysts	oocysts	sporozoites	on Page
										I (23)*
										I (23)
60	5.0	4.2	0.8	00						I (24)
120	5.0	4.2	0.8	00						
240	5.0	4.2	0.8	00						
120	4.0	3.6	0.4	00						I (25)
240	4.0	3.6	0.4	00						
480	4.0	3.6	0.4	00						
120	4.0	3.5	0.5	00						I (27)

*Annual Report I, p. 23

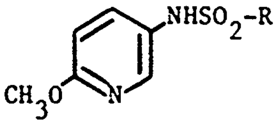
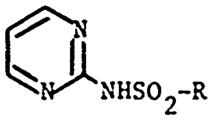
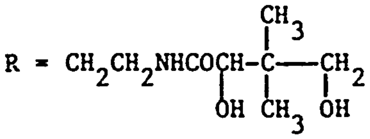
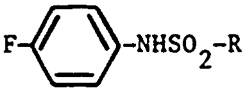
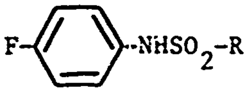
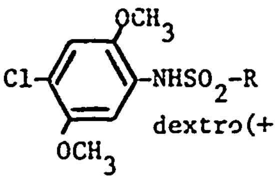
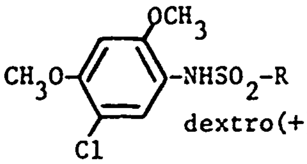
TABLE 1. (contd)

			Mice			
			Survival Time, days			
		Dose	Mean			Toxic
Identification	Compound	mg/kg	treated	control	change	Deaths
ADL 14155-27 WR 35395						
ADL 14155-28 WR 35392		40	6.4	6.1	0.3	00
		160	6.6	6.1	0.5	00
		640	7.0	6.1	0.9	03
ADL 14155-29 WR 52410						
ADL 14155-30 WR 40648		40	6.6	6.2	0.4	00
		160	6.6	6.2	0.4	00
		640	7.0	6.2	0.8	02
ADL 14155-31A WR 45492		40	6.4	6.1	0.3	00
		160	6.8	6.1	0.7	00
		640	6.8	6.1	0.7	00
ADL 14155-47 WR 74107		40	6.2	6.2	–	00
		160	6.4	6.2	0.2	00
		640	6.8	6.2	0.6	00
ADL 14155-48 WR 74110		40	6.2 (7.0)	6.1 (6.2)	0.1 (0.8)	00
		160	6.2 (7.0)	6.1 (6.2)	0.1 (0.8)	00
		640	6.4 (7.4)	6.1 (6.2)	0.3 (1.2)	00

Bird					Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
										I (28)
120	4.0	3.6	0.4	00						
240	4.0	3.6	0.4	00						I (29)
480	4.0	3.6	0.4	00						
										I (30)
										I (32)
										I (34)
120	4.0	3.6	0.4	00						
240	4.0	3.6	0.4	00						II (26)*
480	4.0	3.6	0.4	00						
120	4.0	3.6	0.4	00	0.1	17	0	0	0	II (25)

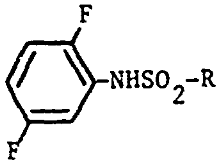
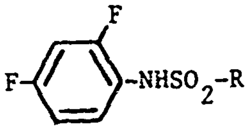
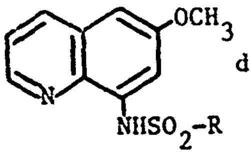
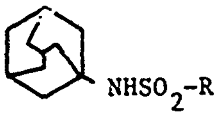
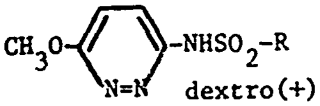
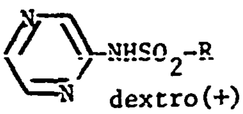
*Annual Report II, p. 26

TABLE 1. (contd)

Identification	Compound	Dose mg/kg	Mice			
			Survival Time, days			Toxic Deaths
			Mean			
			treated	control	change	
ADL 14155-49 WR 76219		40	6.2	6.1	0.1	00
		160	6.2	6.1	0.1	00
		640	6.2	6.1	0.1	00
ADL 15056-8 WR 91946		40	6.4	6.4	0.0	00
		160	6.6	6.4	0.2	00
		640	6.6	6.4	0.2	00
C. Amides of Pantoyltaurine						
	 R = $CH_2CH_2NHCOCH(OH)-C(CH_3)_2-CH_2OH$					
ADL 14155-34 WR 44247	 levo(-)					
ADL 14155-36 WR 44323	 dextro(+)					
ADL 14155-37 WR 52409	 dextro(+)	40	6.4	6.1	0.3	00
		160	6.4	6.1	0.3	00
		640	7.0	6.1	0.9	00
ADL 14155-38A WR 54035	 dextro(+)	40	6.2	6.1	0.1	00
		160	6.4	6.1	0.3	00
		640	6.4	6.1	0.3	00

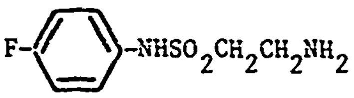
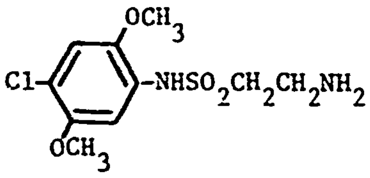
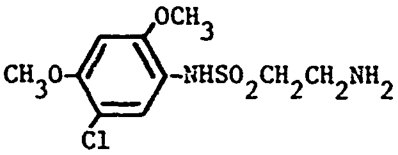
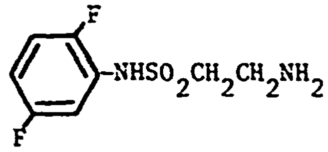
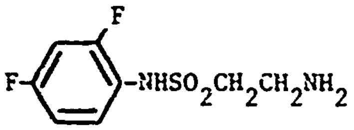
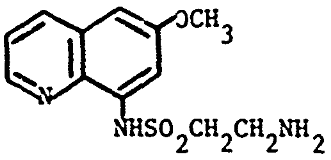
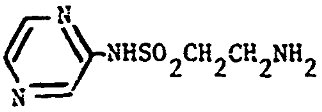
Bird					Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose ng/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
										II (27)
60	3.8	3.2	0.6	00						II (28)
120	3.8	3.2	0.6	00						
240	3.8	3.2	0.6	00						
										I (35)
										I (36)
120	4.0	3.5	0.5	00						I (36)
					0.001	9	-	-	-	I (37)
					0.01	11	-	-	-	
					0.1	9	0	0	0	

TABLE 1. (contd)

		Mice				
			Survival Time, days			
			Mean			
Identification	Compound	Dose mg/kg	treated	control	change	Toxic Deaths
ADL 14155-44 WR 66440	 dextro(+)					
ADL 14155-45 WR 66439	 dextro(+)					
ADL 14155-39 WR 54036	 dextro(+)	40 160 640	6.8 6.8 7.0	6.1 6.1 6.1	0.7 0.7 0.9	00 00 00
ADL 15056-4 WR 87796		40 160 640	6.2 6.2 6.2	6.1 6.1 6.1	0.1 0.1 0.1	00 00 00
ADL 15337-24 AC 64236	 dextro(+)	40 160 640	6.8 6.8 7.0	6.4 6.4 6.4	0.4 0.4 0.6	00 00 00
ADL 15337-35 AD 21709	 dextro(+)	10 40 60	6.4 6.6 6.6	6.1 6.1 6.1	0.3 0.5 0.5	00 00 00

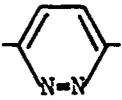
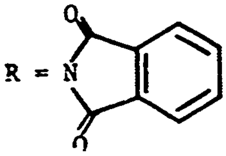
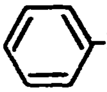
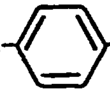
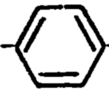
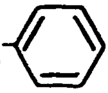
	Bird				Mosquito					
	Survival Time, days					Percent				
	Mean			Toxic	Dose	Toxic	Abnormal	Suppression		Synthesis
ng/kg	treated	control	change	Deaths	% conc	Deaths	Oocysts	oocysts	sporozoites	on Page
										I (39)
										I (40)
					0.001	6	-	-	-	
					0.01	9	-	-	-	I (42)
					0.1	31	-	-	-	
					0.1	0	0	0	0	II (30)
										II (32)
10	4.0	3.9	0.1	00						69
20	4.0	3.9	0.1	00						
40	4.0	3.9	0.1	00						
80	4.0	3.9	0.1	00						
160	4.0	3.9	0.1	00						
320	4.0	3.9	0.1	00						

TABLE 1. (contd)

		Mice				
			Survival Time, days			
		Dose	Mean			Toxic
Identification	Compound	mg/kg	treated	control	change	Deaths
D. 2-Amino-N-Substituted Sulfonamide						
ADL 14143-29 WR 40645		40	6.2	6.2	0.0	00
		160	6.4	6.2	0.2	00
		640	6.4	6.2	0.2	00
ADL 14143-52 WR 40649		40	6.2	6.2	0.0	00
		160	7.0	6.2	0.8	02
		640	0.0	6.2	0.0	05
ADL 14143-47 WR 61463		40	6.2	6.2	-	00
		160	6.2	6.2	-	00
		640	6.2	6.2	-	00
ADL 14421-33 WR 61466		20	6.4	6.2	0.2	00
		80	6.8	6.2	0.6	00
		320	6.8	6.2	0.6	00
ADL 14221-32 WR 61462		40	6.2	6.2	-	00
		160	6.2	6.2	-	00
		640	6.2	6.2	-	00
ADL 14421-12 WR 52112		40	6.4	6.2	0.2	00
		160	7.0	6.2	0.8	03
		640	-	6.2	-	05
ADL 14421-9 WR 45823		40	7.0	6.1	0.9	00
		160	7.2	6.1	1.1	00
		640	7.4	6.1	1.3	00

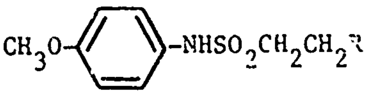
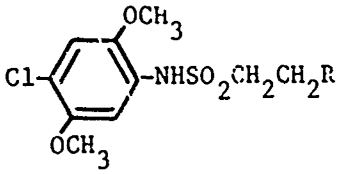
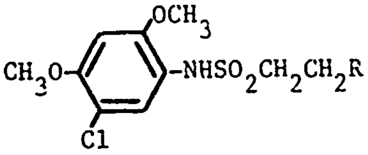
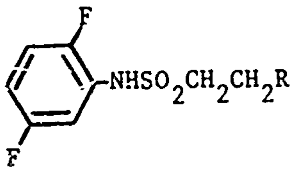
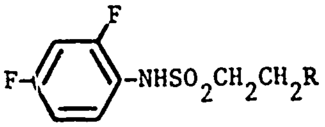
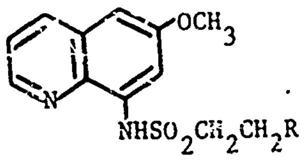
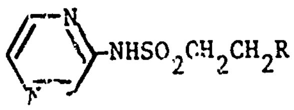
	Bird				Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on page
										I (28)
										I (32)
										I (33)
										I (38)
										I (40)
					0.1	57	0	0	0	I (41)
										I (43)

TABLE 1. (contd)

		Mice				
			Survival Time, days			
		Dose	Mean			Toxic
Identification	Compound	mg/kg	treated	control	change	Deaths
ADL 15537-20 AC 64245	CH_3O-  -$NHSO_2CH_2CH_2NH_2$	40	7.0	6.4	0.6	00
		160	7.2	6.4	0.8	00
		640	7.6	6.4	1.2	00
ADL 15337-27 AD 21736	 -$NHSO_2CH_2CH_2NH_2\cdot 2HCl$					
E. Phthalimides						
ADL 14143-49A WR 35396	 -$NHSO_2CH_2CH_2R$	40	7.2	6.5	0.7	00
		160	7.6	6.5	1.1	00
		640	8.4	6.5	1.9	00
ADL 14143-49B WR 38441	Cl-  -$NHSO_2CH_2CH_2R$	20	6.2	6.1	0.1	00
		80	6.4	6.1	0.3	00
		320	6.4	6.1	0.3	00
ADL 14143-27 WR 38443	F-  -$NHSO_2CH_2CH_2R$	20	6.2	6.1	0.1	00
		80	6.2	6.1	0.1	00
		320	7.0	6.1	0.9	02
ADL 14143-50A WR 38439	CH_3-  -$NHSO_2CH_2CH_2R$	20	6.8	6.1	0.7	00
		80	6.8	6.1	0.7	00
		320	7.0	6.1	0.9	00

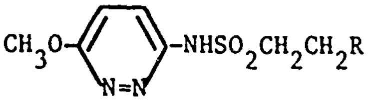
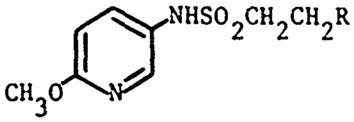
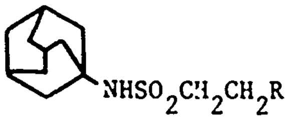
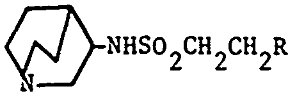
Bird					Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
										II (31)
										70
										I (25)
										I (26)
										I (27)
										I (29)

TABLE 1. (contd)

		Mice				
			Survival Time, days			
			Mean			
Identification	Compound	Dose mg/kg	treated	control	change	Toxic Deaths
ADL 14143-50B WR 38440		20	6.6	6.1	0.5	00
		80	6.6	6.1	0.5	00
		320	7.2	6.1	1.1	00
ADL 14143-42 WR 38442		40	6.2	6.1	0.1	00
		160	6.2	6.1	0.1	00
		640	7.0	6.1	0.9	03
ADL 14143-43 WR 52405						
ADL 14421-31 WR 61464		40	6.2	6.2	-	00
		160	6.6	6.2	0.4	00
		640	6.6	6.2	0.4	00
ADL 14421-27 WR 61465		40	6.4	6.2	0.2	00
		160	6.4	6.2	0.2	00
		640	6.4	6.2	0.2	00
ADL 14421-4 WR 52408		40	6.4	6.1	0.3	00
		160	6.6	6.1	0.5	00
		640	7.4	6.1	1.3	00
ADL 14143-51 WR 44[illegible]11						

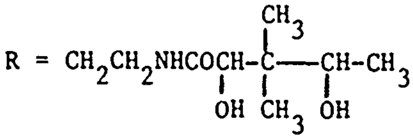
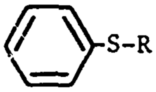
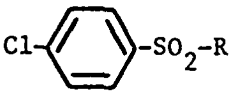
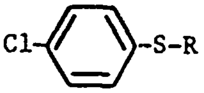
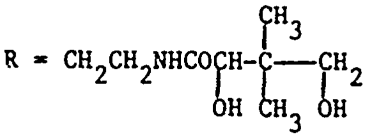
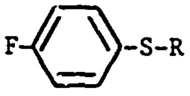
Bird					Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
										I (30)
										I (31)
										I (33)
										I (38)
										I (39)
					0.001	6	-	-	-	I (41)
					0.01	9	-	-	-	
					0.1	6	0	0	0	
										I (43)

TABLE 1. (contd)

Identification	Compound	Mice				
			Survival Time, days			
		Dose mg/kg	Mean treated	Mean control	change	Toxic Deaths
ADL 14421-3 WR 44313						
ADL 14421-19 WR 74108		40	6.2	6.2	-	00
		160	6.2	6.2	-	00
		640	6.2	6.2	-	00
ADL 14421-43 WR 74109		20	6.2	6.2	-	00
		80	6.2	6.2	-	00
		320	6.2	6.2	-	00
ADL 15337-26 AD 21745						

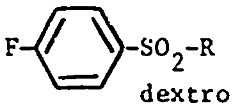
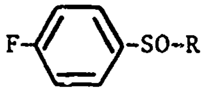
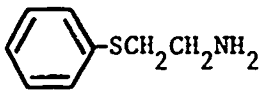
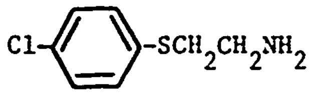
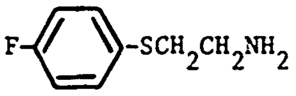
Bird					Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
										I (43)
120	4.0	3.6	0.4	00						II (26)
										II (29)
										70

TABLE 2. Biological Results of Related Sulfone Derivatives

Identification	Compound	Dose mg/kg	Mice			
			Survival Time, days			
			Mean			Toxic Deaths
			treated	control	change	
A. ω-Methylpantoylsulfones						
	 $R = CH_2CH_2NHCO\underset{OH}{CH}-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OH}{CH}-CH_3$					
ADL 15056-2 WR 83970						
ADL 15056-3 WR 91945		20 80 320	6.8 6.8 7.0	6.4 6.4 6.4	0.4 0.4 0.6	00 00 00
ADL 15056-9 WR 92073		40 160	6.6 6.8	6.2 6.2	0.4 0.4	00 00
B. Pantoylsulfones						
	 $R = CH_2CH_2NHCO\underset{OH}{CH}-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OH}{CH_2}$					
ADL 15056-10 WR 91947	 dextro(+)	40 160 640	6.4 6.4 6.6	6.4 6.4 6.4	0.0 0.0 0.2	00 00 00

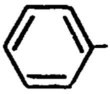
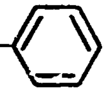
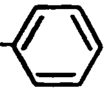
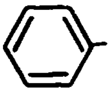
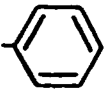
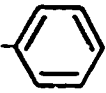
Bird					Mosquito					
	Survival Time, days						Percent			
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
										II (33)
60	4.0	3.2	0.8	00						
120	4.0	3.2	0.8	00						II (34)
240	4.0	3.2	0.8	00						
30	4.0	3.3	0.7	00						
60	4.0	3.3	0.7	00						II (35)
120	4.0	3.3	0.7	00						
60	3.8	3.2	0.6	00						
120	4.0	3.2	0.8	00						II (36)
240	4.0	3.2	0.8	00						

TABLE 2. (contd)

		Mice				
			Survival Time, days			
			Mean			
Identification	Compound	Dose mg/kg	treated	control	change	Toxic Deaths
ADL 15056-16 AC 64227	 dextro(+)	40	7.0	6.4	0.6	00
		160	7.0	6.4	0.6	00
		640	7.4	6.4	1.0	00
ADL 15056-17 AC 64183	 dextro(+)	20	7.0	6.4	0.6	00
		80	7.4	6.4	1.0	00
		320	7.4	6.4	1.0	00
C. Sulfides ·HCl						
ADL 14421-62 WR 34649		40	7.2	6.1	1.1	00
		160	7.5	6.1	1.4	01
		640	-	6.1	-	05
ADL 14421-61 WR 37764		40	6.4	6.1	0.3	00
		160	6.6	6.1	0.5	00
		640	7.0	6.1	0.9	02
ADL 15056-12 WR 91948						

Bird					Mosquito					
	Survival Time, days					Percent				
Dose	Mean			Toxic	Dose	Toxic	Abnormal	Suppression		Synthesis
mg/kg	treated	control	change	Deaths	% conc	Deaths	Oocysts	oocysts	sporozoites	on Page
					0.1	0	0	0	0	II (37)
										II (38)
					0.1	6	0	0	0	II (32)
					0.1	0	0	0	0	II (35)
										II (36)

TABLE 2. (contd)

		Mice				
			Survival Time, days			
		Dose	Mean			Toxic
Identification	Compound	mg/kg	treated	control	charge	Deaths
D. Sulfoxides ·HCl						
ADL 15119-7 WR 03735	$-SOCH_2CH_2NH_2$	40	6.2	6.2	-	00
		160	6.4	6.2	0.2	00
		640	6.4	6.2	0.2	00
ADL 15119-1 WR 87797	Cl-$-SOCH_2CH_2NH_2$	40	6.2	6.2	-	00
		160	6.2	6.2	-	00
		640	6.2	6.2	-	00
ADL 15119-10 WR 90191	F-$-SOCH_2CH_2NH_2$	40	6.6	6.2	0.4	00
		160	7.0	6.2	0.8	00
		640	7.0	6.2	0.8	00
E. Sulfones ·HCl						
ADL 14421-65 WR 83969	$-SO_2CH_2CH_2NH_2$	40	6.2	6.2	-	00
		160	6.4	6.2	0.2	00
		640	6.4	6.2	0.2	00
ADL 14421-63 WR 28376	Cl-$-SO_2CH_2CH_2NH_2$	40	6.4	6.1	0.3	00
		160	6.4	6.1	0.3	00
		640	7.0	6.1	0.9	03
ADL 15119-8 AC 64209	F-$-SO_2CH_2CH_2NH_2$	40	6.8	6.4	0.4	00
		160	6.8	6.4	0.4	00
		640	7.0	6.4	0.6	00

Bird					Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
					0.1	51	0	25	50*	II (39)
					0.1	3	0	0	0	
					0.1	14	0	0	0	II (39)
					0.1	0	0	0	0	II (38)
					0.1	9	0	25	0	II (39)
										II (33)
					0.1	3	0	0	0	II (37)

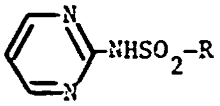
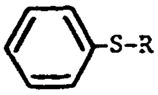
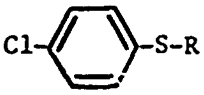
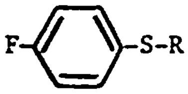
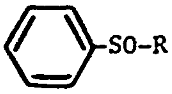
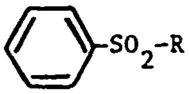
*Partial Sporozoite Suppression

TABLE 3. Biological Results of Other Analogs, Pantoic Acid Derivatives and Miscellaneous Compounds

		Mice				
			Survival Time, days			
		Dose	Mean			Toxic
Identification	Compound	mg/kg	treated	control	change	Deaths

A. Other Analogs

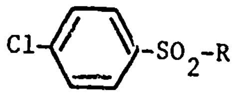
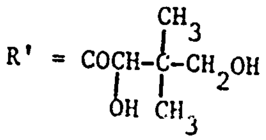
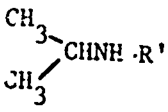
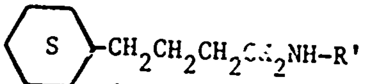
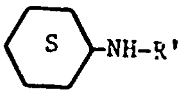
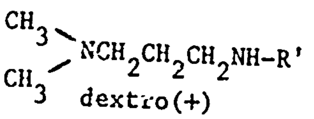
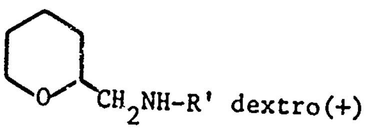
$R = CH_2CH_2NHCOCH_2CH_2CH_2OH$

Identification	Compound	Dose mg/kg	treated	control	change	Toxic Deaths
ADL 15056-7 WR 90192		40	6.2	6.2	–	00
		160	6.4	6.2	0.2	00
		640	6.4	6.2	0.2	00
ADL 15056-1 WR 83971		40	6.6	6.2	0.4	00
		160	6.6	6.2	0.4	00
		640	6.8	6.2	0.6	00
ADL 14421-75 WR 84131		40	6.4	6.2	0.2	00
		160	6.6	6.2	0.4	00
		640	6.8	6.2	0.6	00
ADL 15119-11 WR 87798		40	6.2	6.2	–	00
		160	6.4	6.2	0.2	00
		640	6.4	6.2	0.2	00
ADL 15056-14 AC 64254		40	7.0	6.4	0.6	00
		160	7.2	6.4	0.8	00
		640	7.6	6.4	1.2	00
ADL 15119-6 WR 84130		40	6.2	6.2	–	00
		160	6.2	6.2	–	00
		640	6.2	6.2	–	00

Bird						Mosquito					
	Survival Time, days							Percent			
	Mean										
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	Suppression oocysts	Suppression sporozoites	Synthesis on Page
60	4.0	3.7	0.3	00	0.1	3	0	0	0	II (40)
60	4.0	3.7	0.3	00						II (40)
60	4.0	3.7	0.3	00	0.1	9	0	0	0	II (41)
120	4.0	3.7	0.3	00						
240	4.0	3.7	0.3	00						
					0.1	17	0	0	0	II (41)
					0.1	3	0	0	25*	II (41)
					0.1	17	0	25	0	
60	4.0	3.7	0.3	00	0.1	29	0	0	0	II (42)
120	4.0	3.7	0.3	00						
240	4.0	3.7	0.3	00						

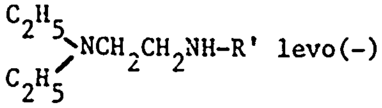
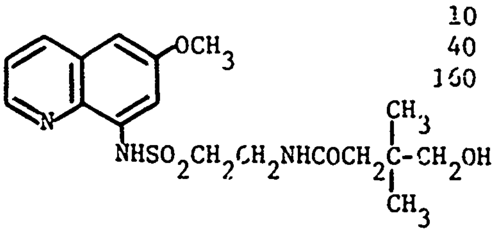
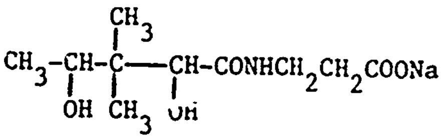
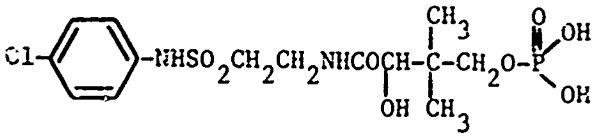
*Partial Sporozoite Suppression

TABLE 3. (contd)

		Mice				
			Survival Time, days			
			Mean			
Identification	Compound	Dose µg/kg	treated	control	change	Toxic Deaths
ADL 14155-52 WR 77537		40 160 640	6.2 6.2 6.2	6.2 6.2 6.2	- - -	00 00 00
	 $R' = \mathrm{CO\underset{OH}{CH}-\overset{CH_3}{\underset{CH_3}{C}}-CH_2OH}$					
ADL 15056-20 AE 96087	 dextro(+)	20 80 320	6.2 6.2 6.2	6.2 6.2 6.2	0.0 0.0 0.0	00 00 00
15056-21 AF 14606	 dextro(+)	10 40 160	6.2 6.4 6.4	6.1 6.1 6.1	0.1 0.3 0.3	00 00 00
15337-67 AF 14580	 dextro(+)	20 80 320	6.2 6.2 6.2	6.1 6.1 6.1	0.1 0.1 0.1	00 00 00
15337-68 AF 14599		20 80 320	6.2 6.4 6.4	6.1 6.1 6.1	0.1 0.3 0.3	00 00 00
15337-69 AS 34783						

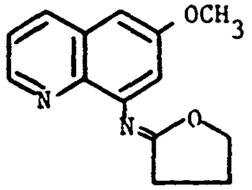
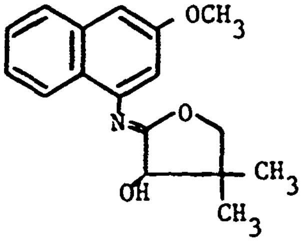
Bird					Mosquito					
Dose mg/kg	Survival Time, days Mean treated	Survival Time, days Mean control	Survival Time, days change	Toxic Deaths	Dose % conc	Toxic Deaths	Percent Abnormal Oocysts	Suppression oocysts	Suppression sporozoites	Synthesis on Page
30	4.0	3.6	0.4	00						
60	4.0	3.6	0.4	00						II (42)
120	4.0	3.6	0.4	00						
7.5	4.0	3.3	0.7	00						
15	4.0	3.3	0.7	00						
30	4.0	3.3	0.7	00	0.1	34	0	25	0	71
60	4.0	3.3	0.7	00						
120	4.0	3.3	0.7	00						
240	4.0	3.3	0.7	00						
										71
					0.1	57	0	0	0	71
					0.1	57	0	0	0	72
										72

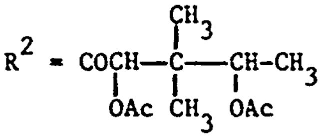
TABLE 3. (contd)

			Mice			
			Survival Time, days			
		Dose	Mean			Toxic
Identification	Compound	mg/kg	treated	control	change	Deaths
15337-71 AS 34809	 $(C_2H_5)_2NCH_2CH_2NH\text{-}R'$ levo(-)					
15056-19 AD 88937		10	6.2	6.1	0.1	00
		40	6.4	6.1	0.3	00
		160	6.4	6.1	0.3	00
15337-42 AE 86536	 $CH_3\text{-}\underset{OH}{CH}\text{-}\overset{CH_3}{\underset{CH_3}{C}}\text{—}\underset{OH}{CH}\text{-}CONHCH_2CH_2COONa$					
$15458\text{-}8R_2$ AE 09655						

	Bird				Mosquito					
	Survival Time, days						Percent			
Dose	Mean			Toxic	Dose	Toxic	Abnormal	Suppression		Synthesis
mg/kg	treated	control	change	Deaths	% conc	Deaths	Oocysts	oocysts	sporozoites	on Page
										73
10	3.8	3.8	0.0	00						73
20	3.8	3.8	0.0	00						
40	4.0	3.8	0.2	00						
80	4.0	3.8	0.2	00						
160	4.0	3.8	0.2	00						
320	4.0	3.8	0.2	00						
10	4.0	3.0	1.0	00						74
20	3.8	3.0	0.8	00						
40	4.0	3.0	1.0	00						
80	4.0	3.0	1.0	00						
160	4.0	3.0	1.0	00						
320	4.0	3.0	1.0	00						
2.5	3.0	3.0	0.0	00						75
5	3.0	3.0	0.0	00						
10	3.0	3.0	0.0	00						
20	3.0	3.0	0.0	00						
40	3.0	3.0	0.0	00						
80	3.4	3.0	0.4	00						

TABLE 3. (contd)

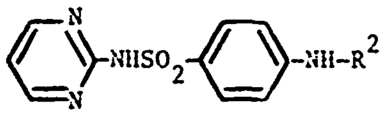
		Mice				
			Survival Time, days			
		Dose	Mean			Toxic
Identification	Compound	mg/kg	treated	control	change	Deaths
B. Pantoic Acid Derivatives						
ADL 15337-22 AC 64192		40 160 640	7.0 7.0 7.0	6.4 6.4 6.4	0.6 0.6 0.6	00 00 00
ADL 15337-32 AD 21727						



$$R^2 = \underset{OAc}{COCH}-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OAc}{CH}-CH_3$$

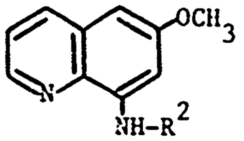
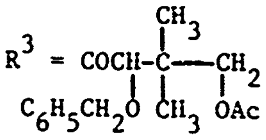
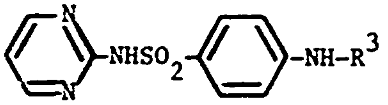
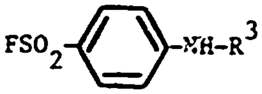
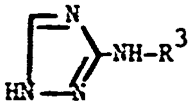
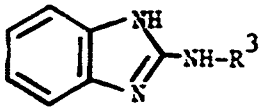
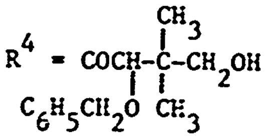
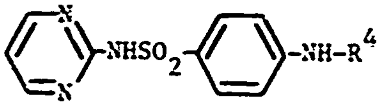
ADL 14155-43

WR 61467

	cures	Dose mg/kg	treated	control	change	Toxic Deaths
	00 00 00 00 04 04	20 40 80 160 320 640	8.6 9.4 10.6 14.0 - -	6.2 6.2 6.2 6.2 6.2 6.2	2.4 3.2 4.4 7.8 - -	00 00 00 00 00 01

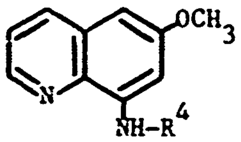
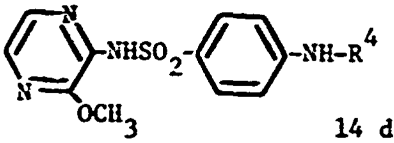
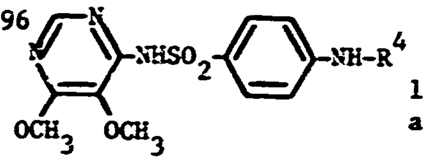
Bird					Mosquito					
	Survival Time, days					Percent				
Dose	Mean			Toxic	Dose	Toxic	Abnormal	Suppression		Synthesis
mg/kg	treated	control	change	Deaths	% conc	Deaths	Oocysts	oocysts	sporozoites	on Page
					0.01	6	0	0	0	II (44)
					0.1	100				
										75
					0.0001	6	-	-	-	
					0.01	6	-	-	-	I (44)
					0.1	3	0	0	0	

TABLE 3. (contd)

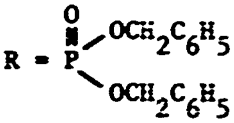
Identification	Compound	Dose mg/kg	Bird			
			Survival Time, days			Toxic Deaths
			Mean			
			treated	control	change	
ADL 14155-46 WR 68826						
	 $$R^3 = \underset{C_6H_5CH_2O}{COCH}-\overset{CH_3}{\underset{CH_3}{C}}-\underset{OAc}{CH_2}$$					
15337-51 AD 88955						
15337-70 AS 34792						
15337-72 AS 34818						
15897-2 AT 14982						
	 $$R^4 = \underset{C_6H_5CH_2O}{COCH}-\overset{CH_3}{\underset{CH_3}{C}}-CH_2OH$$					
15337-53 AD 88964		10	6.4	6.1	0.3	00
		40	6.4	6.1	0.3	00
		160	7.6	6.1	1.5	00

Bird					Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
					0.001	20	-	-	-	II (43)
					0.01	0	-	-	-	
					0.1	46	0	25	0	
										77
										78
										78
										79
10	3.6	3.0	0.6	00						80
20	3.8	3.0	0.8	00						
40	3.8	3.0	0.8	00						
80	3.4	3.0	0.4	00						
160	4.0	3.0	1.0	00						
320	4.0	3.0	1.0	00						

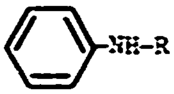
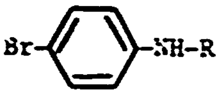
TABLE 3. (contd)

Identification	Compound		Dose mg/kg	Mice Survival Time, days Mean treated	control	change	Toxic Deaths
15337-60 AE 86554			20	6.4	6.2	0.2	00
			80	6.6	6.2	0.4	00
			320	6.6	6.2	0.4	00
15337-62 AF 14571			10	6.6	6.1	0.5	00
			20	7.2	6.1	1.1	00
			40	8.2	6.1	2.1	00
			80	8.8	6.1	2.7	00
		14 day alive	160	11.7	6.1	5.6	00
			320	12.0	6.1	5.9	00
15337-63 AE 96096			20	9.8	6.1	3.7	00
		14 day alive	40	15.5	6.1	9.4	00
			80	15.7	6.1	9.6	00
			160	-	6.1	-	00
			320	-	6.1	-	00
			640	-	6.1	-	00

C. Miscellaneous

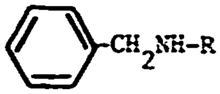
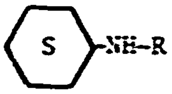
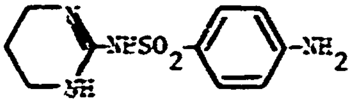


$R = P(=O)(OCH_2C_6H_5)_2$

Identification	Compound	Dose mg/kg	treated	control	change	Toxic Deaths
ADL 15458-1 AC 64218		40	7.2	6.4	0.8	00
		160	7.2	6.4	0.8	00
		640	7.6	6.4	1.2	00
15458-12 AE 48983						

Bird					Mosquito					
	Survival Time, days					Percent				
	Mean			Toxic	Dose	Toxic	Abnormal	Suppression		Synthesis
Dose mg/kg	treated	control	change	Deaths	% conc	Deaths	Oocysts	oocysts	sporozoites	on Page
										80
										81
15	4.0	3.3	0.7	00						
30	4.0	3.3	0.7	00						
60	4.0	3.3	0.7	00	0.1	29	0	0	0	82
120	4.0	3.3	0.7	00						
240	4.0	3.3	0.7	00						
480	4.0	3.3	0.7	00						
10	3.6	3.3	0.3	00						
20	3.6	3.3	0.3	00						
40	3.6	3.3	0.3	00	0.1	3	0	0	0	II (44)
80	3.6	3.3	0.3	00						
160	4.0	3.3	0.7	00						
320	4.0	3.3	0.7	00						
										84

TABLE 3. (contd)

		Mice				
			Survival Time, days			
		Dose	Mean			Toxic
Identification	Compound	mg/kg	treated	control	change	Deaths
15458-13 AE 48974						
15458-14 AE 48965						
15458-18 AS 34774						
15337-58 AE 86545						

Bird					Mosquito					
	Survival Time, days					Percent				
	Mean							Suppression		
Dose mg/kg	treated	control	change	Toxic Deaths	Dose % conc	Toxic Deaths	Abnormal Oocysts	oocysts	sporozoites	Synthesis on Page
										84
10	3.6	3.3	0.3	00						
20	3.6	3.3	0.3	00						
40	3.6	3.3	0.3	00						85
80	3.6	3.3	0.3	00						
160	3.6	3.3	0.3	00						
320	3.6	3.3	0.3	00						
										85
										86

Table 4a

Activity of Compounds in Trager's In Vitro Screen[a]

Flask No.	Addition	Conc	Parasites per 10,000 red cells[b]						
			Day 1						
		µg/ml	R	Tr	ES	LS	G	Abnormal[c]	Total
1	H_2O		0	2	6	34	1	1	44
2			0	2	1	27	0	1	31
3	WR 54036A	75	0	11	11	3	2	10	37
4			0	14	1	0	0	10	25
5	WR 54036A	25	0	4	9	36	0	0	49
6			1	9	12	27	0	0	49
7	WR 35393B	75	0	12	6	9	0	7	34
8			0	8	7	10	0	-	32
9	SN 14622	75	0	4	4	8	0	7	23
10			0	3	13	29	0	9	54
11	WR 68826A	25	0	2	2	38	2	1	45
12			0	2	2	42	0	1	48

a) W. Trager, Rockefeller University, Personal Communication.

b) At time 0 count was 45 to 55 per 10,000 red cells, of which nearly all were young uninucleate trophozoites.
R = rings; Tr = 1-nucleate; ES = Binucleate forms; LS = Forms with 3 or more nuclei; G = Gametocytes.

c) The abnormal parasites were chiefly rather large 1-nucleate forms with a large nucleus, one or more large pigment masses and some small vacuoles. They still showed a good differential stain.

Flask No.	Addition	Conc	Day 1	Parasites per 10,000 red cells						
				Day 2						
		µg/ml	Total[d]	R	Tr	ES	LS	G	Abnormal	Total
1	H_2O		31	43	11	0	2	1	0	57
2			12	66	4	0	2	0	0	72
3	WR 54036A	75	9	0	0	0	0	0	5	5
4			17	0	0	0	0	0	4	4
5	WR 54036A	25	18	0	1	1	1	0	1	4
6			8	0	1	1	1	0	1	4
7	WR 35393B	75	12	4	0	1	1	0	4	10
8			16	0	1	0	3	0	6	10
9	SN 14622	75	25	1	1	0	5	0	2	9
10			4	0	0	0	2	0	3	5
11	WR 68826A	25	13	32	1	0	4	0	0	37
12			10	43	0	0	5	1	1	50

d) On day 1, after centrifugation and resuspension of the cells in fresh medium, they received, per flask, 0.3 ml of fresh uninfected monkey blood thereby reducing the count of parasites per 10,000 red cells to about one-third to one-half its previous value.

Table 4b

Flask No.	Addition	Conc µg/ml	Parasites per 10,000 red cells[e] Day 1 R	Tr	ES	LS	G	Abnormal[f]	Total Normal
1	H_2O		0	5	10	9	0	0	24
2			0	4	13	8	0	0	25
3	WR 54036A	37	0	12	15	2	0	3	29
4			0	9	14	0	0	3	23
5	WR 54036A	75	0	8	4	0	0	7	12
6			0	6	4	0	0	9	10
7	WR 61467	75	0	4	10	12	0	2	26
8			0	3	7	13	2	3	25
9	WR 61467	150	0	6	13	12	1	1	32
10			0	11	22	30	4	1	47

e) At time 0 count was 36 to 42 per 10,000 red cells of which 10 to 17 were rings and the rest young uninucleate trophozoites.
R = rings; Tr = 1-nucleate; ES = 2-3 nuclei; LS = Forms with 4 or more nuclei; G = gametocytes.

f) Abnormalities were of several types, still clearly recognizable as parasites, usually with 1 nucleus.

Flask No.	Addition	Conc µg/ml	Day 1 Total[d]	Parasites per 10,000 red cells Day 2 R	Tr	ES	LS	G	Abnormal	Total Normal
1	H_2O		11	19	1	2	8	4	0	34
2			8	22	0	0	6	5	0	33
3	WR 54036A	37	22	0	4	0	1	0	8	5
4			13	0	4	1	0	2	5	7
5	WR 54036A	75	8	1	1	0	0	0	4	2
6			4	0	1	0	0	0	5	1
7	WR 61467	75	14	19	0	0	5	1	3	25
8			12	10	1	0	6	3	1	20
9	WR 61467	150	15	14	0	1	7	2	2	24
10			18	16	0	0	7	1	4	24

IV. EXPERIMENTAL DETAILS

Melting points are uncorrected. Analyses were by Spang Microanalytical Laboratories, Ann Arbor, Mich., and Galbraith Microanalytical Laboratories, Knoxville, Tenn. Nmr spectra were obtained on a Varian, Model A-60 spectrometer. Peak positions are reported in terms of parts per million from tetramethylsilane. Ultraviolet absorption spectra were determined on a Beckman, DK-1A recording spectrophotometer. Infrared spectra were recorded on a Perkin-Elmer 237 spectrometer.

Copies of all spectra are on file at Arthur D. Little, Inc., and are available on request.

(+)-N-[2-[(2-Pyrazinyl)sulfamoyl]ethyl]-2,4-dihydroxy-3,3-dimethylbutyramide (AD 21709)

3.0 g (0.015 mole) of 2-amino-N-(2-pyrazinyl)ethanesulfonamide[8a] p 43 was suspended in absolute alcohol and an alcohol solution containing one equivalent of freshly prepared potassium ethoxide was added. After refluxing for one hour, the solution was cooled and ethanol was removed on the vacuum rotary evaporator. After drying for two hours *in vacuo*, the potassium salt was powdered and combined with 2.2 g (0.017 mole) of (-)-α-hydroxy-β,β-dimethyl-γ-butyrolactone (Pfaltz and Bauer, Inc.). The mixture was heated at 115-120° for 24 hr. The residue was dissolved in a small amount of water and neutralized with dilute (15%) hydrochloric acid. This solution was evaporated to dryness and the residue extracted with absolute alcohol. The extract was evaporated to a brown gum. Trituration with ethanol gave 0.8 g of beige solid which was removed by filtration. The filtrate was concentrated and chromatographed through a column of silicic acid (100 mesh) using increasing quantities of methanol in chloroform. The fraction eluted with 25% methanol/chloroform contained the amide (0.6 g). This fraction was combined with the beige solid and recrystallized several times from ethanol/ether. Total yield was 1.3 g (26%) of white powder, $[\alpha]_D^{23}$ +16.9 (ethanol), mp 162-165°. Anal. Calcd for $C_{12}H_{20}N_4O_5S$: C, 43.37; H, 6.06; N, 16.83. Found: C, 43.46; H, 5.83; N, 16.51.

The amide showed ultraviolet absorption bands at λ_{max}^{EtOH} 297 mμ (log ε 3.54), 282 mμ (log ε 3.58), 245 mμ (log ε 3.79) and 218 mμ (log ε 3.99) and infrared bands (KBr) at 3400, 1645 and 1055 cm^{-1}.

A 1.3 g sample (15337-35) was submitted on April 22, 1968, for testing in the WRAIR malaria screen.

N-[2-[(3-Quinuclidinyl)sulfamoyl]ethyl]phthalimide Hydrochloride (AD 21745)

To 20.0 g (0.1 mole) of 3-aminoquinuclidine dihydrochloride suspended in chloroform was added with vigorous stirring an aqueous solution of 8.0 g (0.2 mole) of sodium hydroxide. The chloroform layer was separated, washed, dried and evaporated to give 11.0 g of 3-aminoquinuclidine (beige solid - very hygroscopic). Finely powdered 2-phthalimidoethanesulfonyl chloride (24.0 g, 0.088 mole) was added slowly and with stirring to a pyridine solution (75 ml) of 3-aminoquinuclidine (11.0 g, 0.088 mole). The reaction mixture was cooled and stirred vigorously during the addition and for another one hour. During this time the orange solution changes to a solid yellow-white mass. Ethyl ether was added and the mixture stirred at room temperature for one hour. The mixture was filtered and the solid was washed well with ether. After drying *in vacuo*, the solid was recrystallized first from water and then methanol to give 17.0 g (45%) white powder, mp 258-260°.
Anal. Calcd for $C_{17}H_{21}N_3O_4S\cdot HCl$; C, 51.06; H, 5.54; N, 10.51. Found: C, 50.95; H, 5.48; N, 10.46.

Nmr spectrum (DMSOd_6) 2.0 (multiplet, area 4), 3.33 (multiplet, 8), 3.9 (multiplet, 4), 7.98 (singlet, 4), 8.15 (broad, 1 D_2O exchange).

A 0.5 g sample (15337-26) was submitted on April 22, 1968, for testing in the WRAIR malaria screen.

2-Amino-N-(3-quinuclidinyl)ethanesulfonamide Dihydrochloride (AD 21736)

To 17.0 g (0.024 mole) of N-[2-[(3-quinuclidinyl)sulfamoyl] ethyl]phthalimide hydrochloride suspended in hot absolute ethanol was added one equivalent of freshly prepared potassium ethoxide solution. After filtration, the solution was adjusted to 125 ml of 95% ethanol and 2.45 g (0.042 mole) of hydrazine hydrate (85%) was added. The mixture was refluxed with stirring for three hours and the excess ethanol was removed on the rotary evaporator. The residue was suspended in approximately 75 ml of warm water and made acid to Congo red with dilute (15%) hydrochloric acid. After stirring for fifteen minutes, the mixture was cooled and filtered. The water was evaporated to give a clear viscous oil which solidified upon trituration with methanol. This solid recrystallized from methanol-water as 9.0 g of white granules, mp 247-249°.
Anal. Calcd for $C_9H_{19}N_3O_2S\cdot 2HCl$: C, 35.30; H, 6.91; N, 13.72. Found: C, 35.41; H, 6.92; N, 13.73.

A 0.5 g sample (15337-27) was submitted on April 22, 1968, for testing in the WRAIR malaria screen.

(+)2,4-Dihydroxy-3,3-dimethyl-N-isopropylbutyramide (AE 96087)

4.0 g (0.03 mole) of (-)-α-hydroxy-β,β-dimethyl-γ-butyrolactone was heated with excess isopropylamine at 110° for 4 hr with occasional stirring. A solution of resulting clear viscous liquid in a small quantity of ethyl acetate was chromatographed through a column of silicic acid (100 mesh) with the same solvent. The fraction which showed one spot in tlc and had bulk of the material was collected. It was washed with 1N hydrochloric acid solution followed by sodium bicarbonate solution and finally with water. After drying the solvent was removed to leave 3.6 g (64%) of a golden gum $[\alpha]_D^{20}$ +47.4° (ethanol).
Anal. Calcd for $C_9H_{19}NO_3$: C, 57.11; H, 10.12; N, 7.4. Found: C, 56.89; H, 10.13; N, 7.33.

It showed infrared bands (KBr) at 3350 and 1640 cm^{-1}. A 2.9 g sample (15056-20) was submitted on August 30, 1968 for testing in the WRAIR malaria screen.

(+)-2,4-Dihydroxy-3,3-dimethyl-N-[(4-cyclohexyl)butyl]butyramide (AF 14606)

2.6 g (0.02 mole) of (-)-α-hydroxy-β,β-dimethyl-γ-butyrolactone was combined with 3.50 g (0.0225 mole) of 4-cyclohexylbutylamine and heated at 100° for three hours. The viscous residue was dissolved in chloroform and chromatographed using silicic acid (100 mesh). The desired product was eluted with 5% methanol/chloroform, and evaporation of solvents gave 3.8 g of a colorless oil. Analysis indicated trace amounts of lactone present. The compound was purified by dissolving in ethyl acetate and washing with dilute hydrochloric acid followed by sodium bicarbonate solution and water. After drying over sodium sulfate the solvent was evaporated, and the colorless residue was dissolved in a small quantity of ethyl ether. Petroleum ether was added and the mixture was cooled until the compound separated into an oily layer. This process was repeated an additional two times. Total yield was 3.5 g (64%) of colorless gum with $[\alpha]_D^{23}$ +40.1 (95% ethanol).
Anal. Calcd for $C_{16}H_{31}NO_3$: C, 67.33; H, 10.95; N, 4.91. Found: C, 67.03; H, 11.09; N, 4.79.

The amide showed infrared bands at 3380 and 1650 cm^{-1}.

A 2.5 g sample (15056-21) was submitted on September 30, 1968, for testing in the WRAIR malaria screen.

(+)-2,4-Dihydroxy-3,3-dimethyl-N-cyclohexylbutyramide (AF 14583)

3.25 g (0.025 mole) of (-)-α-hydroxy-β,β-dimethyl-γ-butyrolactone was combined with 2.50 g (0.025 mole) of cyclohexylamine and heated at 110-120° for four hours with occasional stirring. The reaction mixture crystallizes upon cooling. Two recrystallizations from

methylene chloride/petroleum ether gave 4.5 g (78%) of white crystals, mp 100-102°, $[\alpha]_D^{20}$ +46.2° (95% ethanol).
Anal. Calcd for $C_{12}H_{23}NO_3$: C, 62.85; H, 10.11; N, 6.11. Found: C, 62.62; H, 10.15; N, 6.07.

The amide showed ultraviolet bands at 3370, 3250 and 1640 cm^{-1}.

A 2.5 g sample (15337-67) was submitted on September 30, 1968, for testing in the WRAIR malaria screen.

(+)-2,4-Dihydroxy-3,3-dimethyl-N-[3,3(dimethylamino)propyl]butyramide (AF 14599)

3.25 g (0.025 mole) of (-)-α-hydroxy-β,β-dimethyl-γ-butyrolactone was heated with excess 3-dimethylaminopropylamine (3.5 g, 0.027 mole) at 110-120° for 3 hours with occasional stirring. The viscous residue was triturated several times with petroleum ether. The washings were decanted and the colorless gum was dissolved in ether. With cooling and scratching, a white crystalline solid appeared. Recrystallization was difficult and the compound was purified as an oil. The solid was dissolved in benzene and petroleum ether was added until formation of a distinct oily layer. After decanting the solvents, the viscous oil was dissolved in ether and crystallized with cooling. The compound was obtained as 1.4 g (24%) white crystals, mp 66.5-71°.
Anal. Calcd for $C_{11}H_{24}N_2O_3$: C, 56.87; H, 10.41; N, 12.05. Found: C, 56.59; H, 10.32; N, 11.91.

The amide showed infrared bands at 3400, 3300 and 1630 cm^{-1}.

A 1.3 g sample (15337-68) was submitted on September 30, 1968, for testing in the WRAIR malaria screen.

(+)-2,4-Dihydroxy-3,3-dimethyl-N-(2-tetrahydropyranylmethyl)butyramide (AS 34783)

3.25 g (0.025 mole) of (-)-α-hydroxy-β,β-dimethyl-γ-butyrolactone was heated with 2.90 g (0.025 mole) of 2-aminomethyltetrahydropyran at 110-120° for 4 hours with occasional stirring. After cooling, the residue was dissolved in a small quantity of chloroform and passed through a column of Florisil (60-100 mesh). The compound was eluted with 5% ethanol/chloroform. Evaporation of the solvents left a colorless viscous residue which was dissolved in ether. Petroleum ether was added until the material separated out as an oily layer. The solvents were decanted, and the whole procedure repeated an additional two times. Tlc showed one spot, and the sample was dried to give 2.25 g (37%) of colorless oil, $[\alpha]_D^{23}$ +44.1 (95% ethanol).
Anal. Calcd for $C_{12}H_{23}NO_4$: C, 58.75; H, 9.45; N, 5.71. Found: C, 58.81; H, 9.62; N, 5.79.

The amide had infrared bands at 3400 (broad) and 1650 cm^{-1}.

A 2.1 g sample (15337-69) was submitted on December 2, 1968, for testing in the WRAIR malaria screen.

(-)-N-[2-(Diethylamino)ethyl]2,4-dihydroxy-3,3-dimethylbutyramide (AS 34809)

2.64 g (0.02 mole) of (-)-α-hydroxy-β,β-dimethyl-γ-butyrolactone was heated with 2.32 g (0.02 mole) of N,N-diethylethylenediamine at 110° for 4 hours. The clear viscous residue was dissolved in chloroform and passed through a column of Florisil (60-100 mesh). The fraction eluted with 10% methanol/chloroform contained the desired compound. The solvents were evaporated to leave a viscous oil, which was dissolved in a small amount of ether. Petroleum ether was added until the compound separated and a distinct layer formed. The solvents were decanted and the whole procedure again repeated. After drying there remained 1.45 g (29%) of colorless oil, $[\alpha]_D^{23}$ -36.2 (95% ethanol).
Anal. Calcd for $C_{12}H_{26}N_2O_3 \cdot 1/2\ H_2O$: C, 56.45; H, 10.57; N, 10.97.
Found: C, 56.57; H, 10.78; N, 10.97. The amide showed infrared bands at 3350 and 1645 cm^{-1}.

A 1.4 g sample (15337-71) was submitted on December 2, 1968, for testing in the WRAIR malaria screen.

β,β-Dimethyl-γ-butyrolactone

It was prepared according to a literature procedure[15] as a light yellow solid, mp 55-57° (lit. 55-57°) in 27% yield.

3,3-Dimethyl-4-hydroxy-N-(6-methoxy-8-quinolyl)butyramide (AD 88937)

3.75 g (.013 mole) of 2-amino-N-(6-methoxy-8-quinolyl)ethanesulfonamide was suspended in absolute ethanol and on alcohol solution containing one equivalent of freshly prepared potassium ethoxide was added. After refluxing for 1 hr, the solution was cooled and ethanol was removed on a vacuum rotary evaporator. The potassium salt thus obtained was further dried for 2 hr in vacuo. The solid was powdered and heated with 1.65 g (.014 mole) of β,β-dimethyl-γ-butyrolactone at 115° for 4 hr with occasional stirring. The viscous residue was suspended in water and neutralized with dilute hydrochloric acid. The resulting mixture was extracted with ethyl acetate, washed, dried and evaporated to leave a gum. This gum was chromatographed through a column of silicic acid (100 mesh) and eluted with 50:50 ethyl acetate/benzene followed by ethyl acetate alone. On elution with ethyl acetate a major fraction was collected which on concentration in vacuo left a gum. It solidified on tituration with ether. The solid was filtered and recrystallized from chloroform/ether/petroleum ether mixture to give 1.3 g (26%) of a yellow solid, mp 123-125°.

Anal. Calcd for $C_{18}H_{25}N_3O_5S$: C, 54.67; H, 6.37; N, 10.63. Found: C, 54.86; H, 6.20; N, 10.55.

The amide showed ultraviolet absorption bands at λ_{max}^{EtOH} 330 mμ (log ε 3.59), 242 mμ (log ε 4.55) and infrared bands (KBr) at 3380, 1625, 1300, 1140 cm^{-1}.

A 1.25 g sample (15056-19) was submitted on May 29, 1968, for testing in the WRAIR malaria screen.

Sodium ω-Methylpantothenate[6b] (AE 86536)

A mixture of 2.22 g of the sodium salt of β-Alanine (0.02 moles) and 3.16 g (0.022 moles) of freshly distilled ω-methylpantolactone was heated at 110-120° for 3 hours. The product was dissolved in 150 ml of isopropanol; the solution was cooled and filtered to remove a small quantity of white solid. The volume of isopropanol was reduced to 50 ml and the remaining solution was stored at 0°C for several weeks. During this time solid was removed by filtration and the mother liquor was again stored in the cold. Total yield of white solid was 1.0 g (19%), mp 147-150° (lit. 160-161.5°). Attempts at purification (crystallization, chromatography) failed and the compound remained slightly impure.
Anal. Calcd for $C_{10}H_{18}O_5NNa$: C, 47.05; H, 7.11; N, 5.49. Found: C, 45.75; H, 6.81; N, 5.73.

The amide showed in infrared absorption band (KBr) at 1625 cm^{-1}.

A 0.9 g sample (15337-42) was submitted on July 30, 1968, for testing in the WRAIR malaria screen.

Dibenzylphosphonate

It was prepared according to a literature procedure.[16]

N[2-[(4-Chlorophenyl)sulfamoyl]ethyl]-2,4-dihydroxy-3,3-dimethylbutyramide-4-dibenzylphosphate

1.82 g (0.005 mole) of WR 29,224 (SN 14622) was dissolved in 50 ml of anhydrous pyridine and the solution cooled in a dry ice bath. A solution of dibenzylchlorophosphoridate[17] (from 2.62 g, 0.01 mole of dibenzylphosphonate and 1.35 g of N-chlorosuccinimide) in 30 ml of dry benzene was then added and the solution was thawed and rapidly frozen in dry ice bath and left at that temperature for 18 hr. Water (10 ml) was added and the reaction mixture left at room temperature for 2 hr. Pyridine, water and benzene from the reaction mixture were removed on the rotary evaporator under reduced pressure at a bath temperature less

than 35°. The residual oily liquid was extracted with ethyl acetate. The extract was washed three times each with 2N sulfuric acid, 10% sodium bicarbonate and saturated sodium sulfate and finally dried over sodium sulfate. Removal of the solvent on the rotary evaporator under reduced pressure at less than 35° bath temperature gave a syrupy residue. The residue was treated with a mixture of ether and benzene (1:1) and the solvent removed on the rotary evaporator. This process was repeated three times. Finally the last traces of the solvent were removed directly on the vacuum pump when the residue started becoming a fluffy solid. This, when macerated with dry ether, changed into a white crystalline solid (1.05 g), mp 117-119° with early sintering at 80-85°. Tlc in $CHCl_3$/MeOH::33:66 showed a single spot.
Anal. Calcd for $C_{28}H_{34}ClN_2O_8PS$: C, 53.80; H, 5.45; N, 4.48. Found: C, 53.85; H, 5.42; N, 4.39.

It showed infrared bands (KBr) at 3340, 1645, 1485, 1330, 1242, 1140, 1020 cm^{-1}. Nmr spectrum ($CDCl_3$) 0.87, 1.0 (singlet, 6), 3.24, 3.7 (broad, 6), 3.97 (singlet, 1), 4.57 (broad, D_2O exchange, 1), 4.97, 5.11 (singlet, 4), 7.3 (multiplet, 14), 7.74 (broad, D_2O exchange, 1), 8.96 (broad, D_2O exchange, 1).

N[2-[(4-Chlorophenyl)sulfamoyl]ethyl]-2,4-dihydroxy-3,3-dimethylbutyramide-4-dihydrogenphosphate (AE 09655)

The above dibenzylphosphate (1 g) was dissolved in some methanol and the hydrogenation flask flushed with nitrogen before adding 2 g of 10% Pd-C. The mixture was hydrogenated at atmospheric pressure. Theoretical amount of hydrogen was absorbed in an hour. The hydrogenated mixture was filtered and the filtrate concentrated on the rotary evaporator at less than 50° bath temperature. Tlc of the residual mixture (460 mg) indicated the presence of three compounds. Using preparative tlc (silica gel C, 1 mm; 10% MeOH in $CHCl_3$ as developer) a pure compound (200 mg) was obtained.
Anal. Calcd for $C_{14}H_{22}ClN_2O_8PS$: C, 37.80; H, 4.95; N, 6.30. Found: C, 37.43; H, 5.35; N, 6.28.

It showed infrared bands (KBr) at 3400-3250, 1650, 1490, 1325, 1140, 1030 cm^{-1}.

A 1.0 g sample of 15456-82$_2$ (95% pure on the basis of elemental and mass spectrum analyses) was submitted on June 10, 1968, for testing in the WRAIR malaria screen.

4,4-Dimethyl-2-[(6-methoxy-8-quinolyl)imino]tetrahydrofuran-3-ol (AD 21727)

Three grams (0.017 mole) of 8-amino-6-methoxyquinoline and 4.5 g (0.035 mole) of (-)-α-hydroxy-β,β-dimethyl-γ-butyrolactone (Pfaltz and Bauer, Inc.) were combined and heated in a sealed tube at 25° for

24 hr. The contents of the tube were dissolved in chloroform and filtered. The chloroform was evaporated and a large quantity of ethyl ether added. Filtration removed additional polymeric material. A small amount (0.4 g) of impure product was obtained after concentration of the filtrate and trituration with ethyl acetate. The solid was purified by column chromatography (silicic acid - 100 mesh) using ethyl acetate, chloroform and ethanol. The fractions eluted with ethyl acetate and chloroform contained starting material and some dark-colored impurities. Evaporation of the ethanol fraction and recrystallization from methylene chloride/ether gave 0.1 g (3%) beige powder, mp 202-204°C. Chromatography was attempted on the filtrate from the ethyl acetate trituration but no additional material could be obtained.
Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.11; H, 6.34; N, 9.79. Found: C, 67.16; H, 6.25; N, 9.70.

Nmr spectrum (DMSOd_6): 1.11, 1.2 (singlets, area 6), 3.51, 3.84 (doublet, 2), 3.9 (singlet, 3), 4.08 (singlet, 1), 5.61 (broad, 1 D_2O exchange), 7.34 (multiplet, 3), 8.28 (doublet, 1), 8.7 (multiplet, 1).

The compound showed ultraviolet absorption at λ_{max}^{EtOH} 332 mμ (log ε 3.72), 283 mμ (log ε 3.55) and 230 mμ (log ε 4.53) and a characteristic infrared band (KBr) at 1705 cm^{-1}.

A 0.1 g sample (15337-32) was submitted on April 22, 1968, for testing in the WRAIR malaria screen.

±2-Benzyloxy-3,3-dimethylbutyro-γ-lactone[18]

(±)Pantolactone (11, 130 g, 1 mole) was added to a solution of 23 g of sodium in 400 ml of absolute alcohol and the mixture stirred at room temperature for 1.5 hr. Alcohol was removed on the rotary evaporator and the residual solid macerated with dry ether, filtered as quickly as possible and dried for 48 hr in a vacuum dessicator.

106 g of the dried sodium salt was suspended in 500 ml of dry xylene and 95 ml of benzyl chloride was added. The mixture was refluxed with stirring for 2 hr, cooled and diluted with water. The organic layer was separated, washed first with 150 ml of 2N H_2SO_4 and then with water and finally dried over anhydrous sodium sulphate. Removal of xylene on the rotary evaporator under reduced pressure gave 118 g of a yellow oily residue which was used directly without further purification in the next step.

±2-Benzyloxy-3,3-dimethyl-4-acetoxybutyramide

A mixture of above benzyloxylactone (66 g) and 150 ml of liquid ammonia was left at room temperature in a steel bomb for 18 hr. The reaction mixture which had solidified to a hard cake was broken into small pieces which were macerated with dry ether and filtered as quickly

as possible. The solid material (44 g) was transferred immediately to a 500 ml R.B. flask and 200 ml of pyridine followed by 75 ml of acetic anhydride were added and the reaction mixture stirred at room temperature for 24 hr. Pyridine and acetic anhydride were removed under reduced pressure and to the residual oily liquid excess of ether was added. The ether extract was washed successively with 2N H_2SO_4, aq $NaHCO_3$ and water and finally dried over anhydrous sodium sulphate. Ether was removed first on the rotary evaporator and finally on the vacuum pump when 31 g of a crystalline solid, mp 61-66°, was obtained. It was recrystallized from ether/pet. ether to give colorless crystals, mp 64-66°.
Anal. Calcd for $C_{15}H_{21}NO_4$ requires: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.55; H, 7.68; N, 15.13.

It showed bands (Nujol mull) at 3410, 3275, 1730, 1675 cm^{-1}. Nmr spectrum ($CDCl_3$): 1.03, 1.05 (singlet, 6), 1.97 (singlet, 3), 3.75 (singlet, 1), 3.87, 4.12 (J = 11 cps, 2), 4.39, 4.68 (J = 12 cps, 2), 6.48 (broad, D_2O exchange, 2), 7.35 (singlet, 5).

2-Benzyloxy-3,3-dimethyl-4-acetoxy butyric acid (15)

To a solution of 5.0 g (0.018 moles) of 2-benzyloxy-3,3-dimethyl-4-acetoxy butyramide in 25 ml of glacial acetic acid was added 9 ml of isoamyl nitrite (Eastman). The mixture was heated at reflux for 40 min, 3 ml of isoamyl nitrite were added and the heating continued for an additional hour. The solution was cooled and the volatile material removed on the rotary evaporator *in vacuo*. Water was added to the residue, and the mixture was made alkaline with 1N sodium hydroxide solution. After extracting with chloroform, the aqueous layer was acidified with dilute (15%) hydrochloric acid and again extracted with chloroform. This extract was washed, dried and evaporated. The residue dissolved in sodium bicarbonate solution and repurified in the same way gave 2.5 g (50% yield) of red-orange oil.
Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.18. Found: C, 64.16; H, 7.20.

Nmr spectrum ($CDCl_3$): 1.05 (singlet, area 6), 1.96 (singlet, 3), 3.85 (singlet, 1), 3.86, 4.05 (doublet, J = 10, 2), 4.35, 4.73 (doublet, J = 11, 2), 7.38 (singlet, 5), 10.06 (singlet, 1, D_2O exchange).

2-Benzyloxy-3,3-dimethyl-4-acetoxy-N-[4-(2-pyrimidinylaminosulfonyl)-phenyl]butyramide (AD 88955)

15.0 g (0.054 moles) of 2-benzyloxy-3,3-dimethyl-4-acetoxy butyric acid were combined with 32 ml of thionyl chloride and heated on the steam bath for 1 hr. After cooling, the excess thionyl chloride was removed *in vacuo*. The residue was dissolved in benzene (500 ml) and added slowly with cooling to a pyridine solution (250 ml) of 13.2 g (0.053 moles) sulfadiazine. The reaction mixture was stirred overnight at

room temperature and heated for 4 hr on the steam bath. After cooling, the solvents were removed on the rotary evaporator. The residue was treated with water and extracted with chloroform. The extract was washed, dried and evaporated to give 22 g of brown gum. The gum was chromatographed on silicic acid (100 mesh) and eluted with chloroform. Recrystallization from ethyl acetate/petroleum ether gave 4.95 g (19%) white powder, mp 161-163°.
Anal. Calcd for $C_{25}H_{28}N_4O_6S$: C, 58.59; H, 5.51; N, 10.93. Found: C, 58.85; H, 5.58; N, 10.89.

The amide showed an ultraviolet adsorption band at λ_{max}^{EtOH} 263 mμ (log ε 4.45) and infrared bands (KBr) at 1735, 1690, 1160 cm^{-1}. Nmr spectrum ($CDCl_3$): 1.03, 1.06 (singlets, area 6), 1.9 (singlet, 3), 3.94 (multiplet, 3), 4.57 (singlet, 2), 6.98 (triplet, J = 5, 1), 7.23 (singlet, 5), 7.68 (doublet, J = 8.5, 2), 8.04 (doublet, J = 8.5, 2), 8.64 (doublet, J = 5, 2), 8.71 (singlet, 1), 10.16 (broad, 1, D_2O exchange).

A 0.5 g sample (15337-51) was submitted on May 29, 1968, for testing in the WRAIR malaria screen.

4-Acetoxy-2-benzyloxy-3,3-dimethyl-4'-fluorosulfonylbutyranilide (AS 34792)

6.0 g (0.021 mole) of 2-benzyloxy-3,3-dimethyl-4-acetoxybutyric acid (15) was reacted with 3.75 g (0.021 mole) of sulfanilyl fluoride according to the method of Baker.[19] The starting materials were added to xylene and the mixture was refluxed for 5 hours. Hydrogen chloride was evolved and the solvent was allowed to distill slowly. The remaining solution was concentrated to a dark brown oil. Ether was added to the residue, the solution was cooled and a dark brown solid crystallized. Additional solid was obtained from the mother liquor by the same procedure. Two recrystallizations from methylene chloride/n-hexane gave 1.20 g (13%) white solid, mp 93-97°.
Anal. Calcd for $C_{21}H_{24}FN_6O_6S$: C, 57.66; H, 5.53; N, 3.20. Found: C, 57.46; H, 5.54; N, 3.26.

The compound showed an ultraviolet absorption band at λ_{max}^{EtOH} 265 mμ (log ε 4.35) and infrared bands (KBr) at 3300, 1715 and 1690 cm^{-1}.

A 1.15 g sample (15337-70) was submitted on December 2, 1968, for testing in the WRAIR malaria screen.

4-Acetoxy-2-benzyloxy-3,3-dimethyl-N-(1H-1,2,4-triazol-3-yl)butyramide (AS 34818)

6.0 g (0.021 mole) of 2-benzyloxy-3,3-dimethyl-4-acetoxybutyric acid (15) and 20 ml of thionyl chloride were combined and heated on the steam bath for one half hour. The excess thionyl chloride was removed on the rotary evaporator, and finally *in vacuo*. A solution of 1.8 g (0.021 mole) of 3-amino-1,2,4-triazole in 100 ml of pyridine was added

with stirring and cooling to the acid chloride. After stirring overnight at room temperature, the pyridine was removed. The residue was added to water and extracted with chloroform. The extract was washed with sodium bicarbonate solution and water, dried over sodium sulfate and evaporated to give a dark oil. The oil was chromatographed using Florisil (60-100 mesh) and methanol/chloroform to elute. The desired compound was obtained as a yellow oil from the 5% methanol/chloroform fractions. The oil was crystallized several times from chloroform/n-hexane to give 0.6 g (9%) colorless crystals, mp 106-107°.
Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.40; N, 16.17. Found: C, 58.83; H, 6.45; N, 16.28.

The compound showed an ultraviolet absorption band at λ_{max}^{EtOH} 265 mμ (log ε 3.63) and infrared bands (KBr) at 3460, 1735, 1720 and 1635 cm^{-1}.

A 0.6 g sample (15337-72) was submitted for testing in the WRAIR malaria screen.

4-Acetoxy-N-(2-benzimidazolyl)-2-benzyloxy-3,3-dimethylbutyramide (AT 14982)

6.0 g (0.021 mole) of 2-benzyloxy-3,3-dimethyl-4-acetoxybutyric acid was combined with 20 ml of thionyl chloride and heated on the steam bath for one half hour. The excess thionyl chloride was removed on the rotary evaporator and finally *in vacuo*. A pyridine solution of 2-aminobenzimidazole (3.0 g, 0.022 mole) was added to the acid chloride with cooling and stirring. The mixture was stirred overnight at room temperature and the pyridine was removed on the rotary evaporator. Water was added to the residue and the mixture was extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate solution, water, dried over sodium sulfate and evaporated. The oily residue was dissolved in a small quantity of ether and cooled to give crystals. Recrystallization from methylene chloride/n-hexane gave 0.6 g (8%) of colorless crystals, mp 161-163°.
Anal. Calcd for $C_{22}H_{25}N_3O_4$: C, 66.82; H, 6.37; N, 10.62. Found: C, 66.74; H, 6.26; N, 10.54.

The amide showed ultraviolet adsorption bands at λ_{max}^{EtOH} 285 mμ (log ε 4.23), 292 mμ (log ε 4.20) and 250 mμ (log ε 3.98) and infrared bands (KBr) at 3270, 1745, 1685 and 1625 cm^{-1}.

A 0.6 g sample (15897-2) was submitted on February 4, 1969, for testing in the WRAIR malaria screen.

2-Benzyloxy-3,3-dimethyl-4-hydroxy-N-[4-(2-pyrimidinylaminosulfonyl)-phenyl]butyramide (AD 88964)

To a mixture of 4.45 g of 2-benzyloxy-3,3-dimethyl-4-acetoxy-N-[4-(2-pyrimidinylaminosulfonyl)phenyl]butyramide (AD 88955, 0.0087 moles) in 200 ml water and 225 ml methanol was added 19.5 ml of 1N NaOH solution (0.0195 moles). The solution was stirred at room temperature for 1 1/2 hr and neutralized with dilute (15%) hydrochloric acid. White solid appeared after neutralization and during the removal of methanol on the rotary evaporator. The desired compound was extracted into chloroform from the remaining aqueous fraction. The extract was washed, dried and evaporated to give a colorless, viscous oil. Trituration with ethyl ether and filtration gave 3.90 g (95%) of white powder, mp 170-172°. Anal. Calcd for $C_{23}H_{26}N_4O_5S$: C, 58.71; H, 5.57; N, 11.91. Found: C, 58.79; H, 5.69; N, 11.98.

The compound showed an ultraviolet adsorption band at λ_{max}^{EtOH} 263 mμ (log ε 4.42) and infrared bands (KBr) at 3500, 1680, 1155 cm^{-1}. Nmr spectrum (pyridine d_5): 1.2, 1.23 (singlets, area 6), 3.74 (singlet, 2), 4.32 (singlet, 1), 4.54 (doublet, J = 11, 1), 4.74 (doublet, J = 11, 1), 6.65 (triplet, J = 5, 1), 7.2 (multiplet, 5), 8.03, 8.38 (doublets, J = 8.5, 4), 8.35 (doublet, J = 5, 2), 9.5 (broad, 1, D_2O exchange), 10.15 (singlet, 1, D_2O exchange).

A 1.0 g sample (15337-53) was submitted on May 29, 1968, for testing in the WRAIR malaria screen.

2-Benzyloxy-3,3-dimethyl-4-hydroxy-N-(6-methoxy-8-quinolyl)butyramide (AE 86554)

12.0 g (0.043 moles) of 2-benzyloxy-3,3-dimethyl-4-acetoxybutyric acid (15) and 20 ml of thionyl chloride were combined and heated on the steam bath for one hour. The excess thionyl chloride was removed on the rotary evaporator. A solution of 7.5 g (0.043 moles) of 8-amino-6-methoxyquinoline in 140 ml of pyridine was added with stirring and cooling to the acid chloride. After stirring overnight at room temperature the pyridine was removed. The residue was added to water and extracted with chloroform. The extract was washed, dried and evaporated to give 22 grams of black oil. The product was purified by chromatography on silicic acid (100 mesh) using 2% ethyl acetate/chloroform. 7.7 grams of orange-brown oil were obtained (41% yield). The structure was confirmed by nmr and IR.

To a solution of 7.7 g (0.0176 moles) of 2-benzyloxy-3,3-dimethyl-4-acetoxy-N-(6-methoxy-8-quinolyl)butyramide in 300 ml of methanol was added 26.5 ml of 1N sodium hydroxide solution (0.0265 moles). The solution was stirred at room temperature for 1 1/2 hours. After neutralization with dilute (15%) hydrochloric acid, the methanol was removed on a rotary evaporator. The residue was treated with water and extracted with chloroform. This extract was washed, dried and evaporated to give 6.0 g orange oil. The oil was chromatographed on silicic acid (100 mesh) using increasing quantities of chloroform in benzene. The material was obtained as dark red crystals from the 1 benzene:4 chloroform fractions. Several recrystallizations from methylene chloride/n-hexane gave 1.25 g (18%) of white crystals, mp 105-107°.
Anal. Calcd for $C_{23}H_{26}N_2O_4$: C, 70.03; H, 6.64; N, 7.10. Found: C, 70.01; H, 6.51; N, 7.03.

The amide showed ultraviolet absorption bands at λ_{max}^{EtOH} 335 mμ (log ε 3.81), 305 mμ (log ε 3.72), 244 mμ (log ε 4.77) and 215 mμ (log ε 4.51), and infrared bands at 3475 and 1660 cm^{-1}.

A 0.75 g sample (15337-60) was submitted on August 1, 1968, for testing in the WRAIR malaria screen.

2-Benzyloxy-3,3-dimethyl-4-hydroxy-4'-[(3-methoxy-2-pyrazinyl)aminosulfonyl]butyranilide (AF 14571)

4.3 g (0.015 mole) of 2-benzyloxy-3,3-dimethyl-4-acetoxybutyric acid (15) and 10 ml of thionyl chloride were combined and heated on the steam bath for one half hour. The excess thionyl chloride was removed on the rotary evaporator. The residue was dissolved in benzene (150 ml) and added slowly and with cooling to a pyridine solution (75 ml) of 3-methoxy-2-sulfanilamidopyrazine (4.15 g, 0.0148 mole). After stirring overnight at room temperature the reaction mixture was heated on the steam bath for four hours. The solvents were removed on the rotary evaporator. Water was added to the residue and the mixture was extracted with chloroform. The extract was washed with dilute hydrochloric acid, sodium bicarbonate solution and water. After drying over sodium sulphate the solvent was evaporated to give 6.5 g of dark red-brown oil. The structure was confirmed by IR.

To a solution of 6.5 g of 4-acetoxy-2-benzyloxy-3,3-dimethyl-4'-[(3-methoxy-2-pyrazinyl)aminosulfonyl]butyranilide in 250 ml of water and 300 ml of methanol was added an excess of sodium hydroxide (30.0 ml 1N solution). The mixture was stirred at room temperature for 3 hours. After neutralization with dilute hydrochloric acid, methanol was removed on the rotary evaporator. The aqueous residue was shaken with chloroform, and the extract was washed, dried and evaporated to give 4.9 g red oil. A chloroform solution of the oil was chromatographed through silicic acid (100 mesh) and eluted with 5% methanol/chloroform. One fraction gave a single spot in tlc, although analysis showed the sample to be impure. The sample was dissolved in ethyl acetate and treated with charcoal (Norite A). The solution was washed with sodium bicarbonate solution and water and dried over sodium sulfate. Evaporation of the solvent left 0.65 g pale yellow oil which became foamy after drying *in vacuo*. An additional 0.3 g sample (slightly impure by tlc) was obtained. Anal. Calcd for $C_{24}H_{28}N_4O_6S$: C, 57.59; H, 5.64; N, 11.19. Found: C, 56.55; H, 5.66; N, 11.19.

The amide showed an ultraviolet band at λ_{max}^{EtOH} 260 mμ (log ε 4.31) and infrared bands (KBr) at 3500 (broad) 3370 and 1680 cm^{-1}. Nmr ($CDCl_3$) 0.94, 1.06 (singlet, area 6), 3.48 (s, 2), 3.95 (s, 3), 4.63 (s, 2), 7.36 (s, 5), 7.66 (doublet, J = 9, 2), 8.11 (d, J = 9, 2), 7.66 (s, 2).

This information indicated the correct structure, although the sample was somewhat impure by analysis. The 0.65 g sample (15337-62) was submitted on September 30, 1968, for testing in the WRAIR malaria screen.

2-Benzyloxy-3,3-dimethyl-4'-[(5,6-Dimethoxy-4-pyrimidinyl)aminosulfonyl]-4-hydroxybutyranilide (AE 96096)

4.5 g (0.016 moles) of 2-benzyloxy-3,3-dimethyl-4-acetoxybutyric acid (15) and 10 ml of thionyl chloride were combined and heated on the steam bath for one hour. The excess thionyl chloride was removed on the rotary evaporator. The residue was dissolved in 150 ml of benzene and added with cooling and stirring to a pyridine solution (75 ml) of 5,6-dimethoxy-4-sulfanilamidopyrimidine (4.65 g, 0.015 moles). The mixture was stirred overnight at room temperature and heated on the steam bath for [illegible] hours. The solvents were removed on the rotary evaporator, and water was added to the residue. The compound was taken up in chloroform, and the extract was washed with dilute hydrochloric acid, sodium bicarbonate solution and dried over sodium sulfate. Evaporation of the chloroform left 8.7 g of red-yellow oil. The structure of the compound was confirmed by IR ($CHCl_3$) although the sample was somewhat impure (tlc in 10% MeOH/$CHCl_3$).

To a mixture of 8.7 g of 2-benzyloxy-3,3-dimethyl-4'-[(5,6-dimethoxy-4-pyrimidinyl)aminosulfonyl]-4-acetoxybutyranilide in 300 ml water and 350 ml methanol was added 38.0 ml of 1N sodium hydroxide solution. The solution was stirred at room temperature for 1 1/2 hr and neutralized with dilute (15%) hydrochloric acid. The methanol was removed on the rotary evaporator and the remaining aqueous fraction was extracted with chloroform. The extract was washed, dried and evaporated to give 7.4 g of red-yellow oil. The oil was chromatographed using silicic acid (100 mesh) and chloroform. The compound was obtained as 3.6 g (43%) of yellow oil which changed to powdery foam after considerable drying *in vacuo*.
Anal. Calcd for $C_{25}H_{30}N_4O_7S$: C, 56.60; H, 5.70; N, 10.56. Found: C, 56.53; H, 5.69; N, 10.38.

The amide showed an ultraviolet absorption band at λ_{max}^{EtOH} 265 mμ (log ε 4.43) and infrared bands at 3475 and 1680 cm^{-1}.

A 2.0 g sample (15337-63) was submitted on August 30, 1968, for testing in the WRAIR malaria screen.

Dibenzyl p-bromoanilinephosphonate (AE 48983)

7.8 g (0.03 mole) of dibenzylphosphonate[16] was dissolved in 30 ml of dry benzene and (4.06 g; ca 0.03 mole) of N-chlorosuccinimide was added in small lots. The reaction mixture warmed up and was stirred at room temperature for 2 hr. Succinimide that had separated out was filtered through a sintered glass funnel and to the filtrate (10.32 g; 0.06 mole) of p-bromoaniline was added and the reaction mixture stirred for 4 hr. Amine hydrochloride that had precipitated was filtered and washed with hot benzene. The filtrate was washed with 50 ml of 1N HCl followed by aqueous $NaHCO_3$ and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent on the rotary evaporator gave an oily residue which on leaving in contact with methylene chloride and n-hexane solidified. After crystallization from methylene chloride and n-hexane twice analytically pure sample (1 g), mp 85-87°, was obtained.
Anal. Calcd for $C_{20}H_{19}BrNO_3P$: C, 55.54; H, 4.40; N, 3.24. Found: C, 55.36; H, 4.31; N, 3.20.

A 0.4 g sample (15458-12) was submitted on July 1, 1968, for testing in the WRAIR malaria screen.

Dibenzyl p-methoxyanilinephosphonate (AE 48974)

5.24 g (0.02 mole) of dibenzyl phosphonate[16] was dissolved in 20 ml of dry benzene and (2.67 g; 0.02 mole) of N-chlorosuccinimide was added in small lots. The reaction mixture was stirred at room temperature for 2 hr. Succinimide that had separated out was filtered through a sintered glass funnel and to the filtrate 4.92 g (0.04 mole) of p-methoxyaniline was added and the mixture stirred for 4 hr. Amine hydrochloride that had precipitated out was filtered and washed with hot benzene. The filtrate was washed with 50 ml of 1N HCl followed by aq $NaHCO_3$ and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent on the rotary evaporator gave an oily residue which on leaving in contact with methylene chloride and n-hexane solidified. After crystallization from methylene chloride and n-hexane analytically pure sample (2.82 g), mp 115-117°, was obtained.
Anal. Calcd for $C_{21}H_{22}NO_4P$: C, 65.80; H, 5.74; N, 3.65. Found: C, 65.68; H, 5.68; N, 3.59.

A 1.0 g sample (15458-13) was submitted on July 1, 1968, for testing in the WRAIR malaria screen.

Dibenzyl benzylaminephosphonate[20] (AE 48965)

5.24 g (0.02 mole) of dibenzylphosphonate was dissolved in 20 ml of dry benzene and (2.67 g; 0.02 mole) of N-chlorosuccinimide was added in small lots. The reaction mixture was stirred at room temperature for 2 hr. Succinimide that had separated out was filtered through a sintered glass funnel and to the filtrate (4.28 g; 0.04 mole) of benzylamine in 30 ml of dry benzene was added and the mixture stirred for 4 hr. Amine hydrochloride that had separated out was filtered and washed with hot benzene. The filtrate was washed with 50 ml of 1N HCl followed by aq $NaHCO_3$ and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent on the rotary evaporator gave a thick syrupy residue which on leaving in contact with methylene chloride and n-hexane solidified. After crystallization from methylene chloride and n-hexane, 3.27 g of a white crystalline solid, mp 82-85°, was obtained (lit.[20] mp 84-85°).

A 1.0 g sample (15458-14) was submitted on July 1, 1968, for testing in the WRAIR malaria screen.

Dibenzyl N-cyclohexylphosphoramidate[20] (AS 34774)

5.24 g (0.02 mole of dibenzylphosphonate[16] was dissolved in 20 ml of dry benzene and 2.67 g (0.02 mole) of N-chlorosuccinimide was added in small lots. The reaction mixture was stirred at room temperature for 2 hr. Succinimide that had separated out was filtered through a sintered glass funnel and to the filtrate 3.96 g (0.04 mole) of cyclohexylamine in 30 ml of dry benzene was added and the mixture stirred for 4 hr. Amine hydrochloride that had separated out was filtered and washed with hot benzene. The filtrate was washed with 50 ml of 1N HCl followed by aq $NaHCO_3$ and saturated sodium chloride solution and dried over anhydrous sodium sulfate. Removal of the solvent on the rotary evaporator gave a thick syrupy residue which on leaving in contact with methylene chloride and n-hexane solidified. After crystallization from methylene chloride and n-hexane 2.1 g of a white crystalline solid, mp 77-78°, was obtained (lit.[20] mp 79-80°).

A 2.1 g sample (15458-18) was submitted on December 2, 1968, for testing in the WRAIR malaria screen.

N^1-2-(3,4,5,6 -Tetrahydropyrimidinyl)sulfanilamide (AE 86545)

To 3.0 g of sulfadiazine (0.012 moles) in 250 ml of methanol and 12.0 ml of 1N sodium hydroxide solution was added 1.2 g of 10% Palladium on Charcoal (Engelhardt). The mixture was hydrogenated at atmospheric pressure; the theoretical uptake of hydrogen required 2.5 hours. The reaction mixture was filtered and the filtrate was concentrated to a volume of 50 ml. White. crystalline solid was obtained. The material was recrystallized by dissolving (with heating) in a large volume of methanol, reducing the volume to one-half and cooling. Yield of white crystals was 0.55 g (19%), mp 243-245°.
Anal. Calcd for $C_{10}H_{13}N_4O_2S$: C, 47.43; H, 5.17; N, 22.21. Found: C, 47.31; H, 5.46; N, 22.22.

The compound showed an ultraviolet absorption band at λ_{max}^{EtOH} 264 mμ (log ε 4.28) and infrared bands (KBr) at 3480, 1620, 1590, 1370, 1175 cm^{-1}. Nmr spectrum (DMSO d_6) 1.64 multiplet, area 2), 3.1 (multiplet 4), 5.46 (singlet, 2 D_2O exchange), 6.47 (doublet, 4, J = 9 cps), 7.29 (doublet, 4, J = 9 cps), 7.3 (2, D_2O exchange).

A 0.55 g sample (15337-58) was submitted on July 30, 1968, for testing in the WRAIR malaria screen.

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Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)

Arthur D. Little, Inc.
Cambridge, Massachusetts 02140

2a. REPORT SECURITY CLASSIFICATION

Unclassified

2b. GROUP

—

3. REPORT TITLE

The Synthesis of New Antimalarial Drugs
Analogs of Pantothenic Acid

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

Final report combined with Annual Report 3, March 1, 1968 thru March 31, 1969

5. AUTHOR(S) (First name, middle initial, last name)

Raj K. Razdan
Barbara A. Zitko
Avinash C. Mehta

6. REPORT DATE: 31 March 1969

7a. TOTAL NO. OF PAGES: 92

7b. NO. OF REFS: 20

8a. CONTRACT OR GRANT NO.: DA-49-193-MD-2879

9a. ORIGINATOR'S REPORT NUMBER(S): 68066

b. PROJECT NO.

c.

d.

9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report): —

10. DISTRIBUTION STATEMENT

Distribution of this document is unlimited.

11. SUPPLEMENTARY NOTES

Antimalarials

12. SPONSORING MILITARY ACTIVITY

U.S. Army Medical Research & Development Command (B. Poon, Proj. Officer)
Washington, D. C. 20315

13. ABSTRACT

The present synthetic program on antagonists of pantothenic acid was based on the demonstrated antimalarial activity of SN 14622 (WR 29,224) in avian malaria from World War II program. During the three years of our work we have prepared and submitted for evaluation one hundred and eight compounds. Unfortunately, SN 14622 is completely inactive in the present WRAIR screens in mice, chicks and mosquitoes. It appears that th nonproducibility of the activity of SN 14622 in the present chick screen is due to the different test procedure being used. A few of our compounds were tested in Dr. Trager' *in vitro* screen and of these WR 54036 has been selected for advanced screening in the monkey.

Three other compounds, WR 61467, AE 96096 and AF 14571 (derivatives of sulfonamides) have been found to be active in the Rane screen in mice at 160, 40, and 160 mg/kg respectively.

DD FORM 1 NOV 65 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

14. KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Antimalarials						
Pantothenic acid antagonists						
Biological activity						
Sulfadiazine derivatives						
Fanasil derivatives						
Kelfizina derivatives						
Phenylpantothenones						
ω-Methylpantoyltaurines						
Pantoyltaurines						
2-Amino-N-substituted sulfonamides						
Phthalimides						
ω-Methylpantoylsulfones						
Pantoylsulfones						
Pantoic acid derivatives						
Organic Synthesis						
Rane mice screen						
Rane bird screen						
Mosquito screen						