AD NUMBER

ADB145101

LIMITATION CHANGES

TO:

Approved for public release; distribution is unlimited.

FROM:

Distribution authorized to U.S. Gov't. agencies only; Proprietary Information; APR 1989. Other requests shall be referred to Army Medical Research and Development Command, Fort Detrick, MD.

AUTHORITY

USAMRDC ltr 6 Aug 1992

AD_____

SYNTHESIS OF IMPROVED ANTILEISHMANIAL AND ANTITRYPANOSOMAL DRUGS, TREATMENT AND PROPHYLAXIS

FINAL REPORT

By

A. Markovac
D.J. Dagli
A.B. Ash
C.L. Stevens

April 1989

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-84-C-4210

ASH STEVENS INC.
Detroit Research Park
5861 John C. Lodge Freeway
Detroit, Michigan 48202

UNCLASSIFIED
SECURITY CLASSIFICATION OF THIS PAGE

REPORT DOCUMENTATION PAGE

Form Approved OMB No. 0704-0188

1a. REPORT SECURITY CLASSIFICATION: Unclassified	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION / AVAILABILITY OF REPORT: Distribution limited to U.S. Government agencies only; Proprietary Information, April 30, 1989
2b. DECLASSIFICATION / DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S): 145R	5. MONITORING ORGANIZATION REPORT NUMBER(S)
6a. NAME OF PERFORMING ORGANIZATION: Ash Stevens Inc. / 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION
6c. ADDRESS (City, State, and ZIP Code): 5861 John C. Lodge Freeway, Detroit, Michigan 48202	7b. ADDRESS (City, State, and ZIP Code)
8a. NAME OF FUNDING / SPONSORING ORGANIZATION: U.S. Army Medical Research & Development Command / 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER: DAMD17-84-C-4210
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick, Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS: PROGRAM ELEMENT NO. 62770A / PROJECT NO. 3M1 / 62770A870 / TASK NO. AM / WORK UNIT ACCESSION NO. 030

11. TITLE (Include Security Classification)
(U) SYNTHESIS OF IMPROVED ANTILEISHMANIAL AND ANTITRYPANOSOMAL DRUGS, TREATMENT AND PROPHYLAXIS.

12. PERSONAL AUTHOR(S)
Markovac, A.; Dagli, D.J.; Ash, A.B.; Stevens, C.L.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
FINAL	FROM 9/1/84 TO 6/30/88	1989 April	84

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	
07	03		Antileishmanials, metabolites of 8-(6-diethylaminohexyl-amino)-6-methoxy-4-methylquinoline, WR 6026, RA 1,
06	01		ORGANIC compounds, DRUGS (JG)

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The work reported herein was directed at the preparation of improved antileishmanial and antitrypanosomal drugs. During the contract period (forty six months), 46 candidate drugs were submitted for biological testing. This program was divided into five phases of work: 1) Analogs of WR 6026 (eleven); 2) Potential metabolites and analogs of a known metabolite of WR 6026 (seven); 3) Bis-amidoxime and bis-amidines (four); 4) Dimethylaminomethyl ethylenes (similar to Burroughs Welcome 353 C) (seventeen); and 5) Amidoximino ethylenes (seven). Twenty eight of the target compounds prepared were directed against T. cruzi infections, while the remaining eighteen compounds were targeted against Leishmaniasis.

Trypanosoma cruzi

20. DISTRIBUTION / AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☐ UNCLASSIFIED/UNLIMITED ☒ SAME AS RPT. ☐ DTIC USERS	Unclassified

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Mary Frances Bostian	301-663-7325	SGRD-RMI-S

DD Form 1473, JUN 86 — Previous editions are obsolete. — SECURITY CLASSIFICATION OF THIS PAGE

FOREWORD

The work described herein was performed under Contract No. DAMD17-84-C-4210 for USAMRDC, Walter Reed Army Institute of Research, Division of Experimental Therapeutics,Walter Reed Army Medical Center. This Final Report covers the four-year period from September 1984 thru August 1988.

Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

ACKNOWLEDGMENT

The work was performed under the general direction of Dr. C.L. Stevens, Principal Investigator. Dr. A. Markovac served as Associate Investigator and Dr. D.J. Dagli as Senior Research Chemist, Dr. A.B. Ash served as Program Manager.

The timely advice and assistance of the COR, Dr. Robert R. Engle, is gratefully acknowledged.

TARGET COMPOUNDS SUBMITTED

FOUR YEARS: 9/01/84 TO 8/15/88

CONTRACT NO. DAMD17-84-C-4210

SNL NO.	ASI CODE NO.	BOTTLE NO.	WALTER REED NO.	EXPERIMENTAL ANNUAL REPORT PAGE NO.
		First Year (9/1/84 - 8/31/85)		
109	DJD-06-44	BK99121	253904	29
110	DJD-06-59A	BL00432	254019	31
111	DJD-06-81	BL03808	254238	34
112	DJD-06-99	BL05571	254391	36
113	AM-04-12	BL07691	254588	37
114	DJD-06-126	BL07682	254589	38
115	DJD-06-134	BL08401	254642	40
116	DJD-06-152	BL09533	254731	42
117	AM-04-20	BL09524	254729	43
		Second Year (9/1/85 - 8/31/86)		
118	KW-08-188	BL12503	254959	31
119	KW-08-211B	BK12790	254985	31
120	DJD-06-210	BL18247	255426	33
121	AM-04-28	BK40799	255566	36
122	DJD-06-268	BL19333	255593	37
123	DJD-06-270	BL19324	255594	37
124	RK-04-154	BL19315	255595	42
125	DJD-06-288	BL20336	255664	43
126	DJD-06-293	BL20345	255665	43
127	DJD-06-295	BL20354	255662	46
128	DJD-07-27	BL21780	255784	47
129	DJD-07-32	BL22205	255810	50
130	DJD-07-44	BL24003	255931	51

TARGET COMPOUNDS SUBMITTED (Continued)

SNL NO.	ASI CODE NO.	BOTTLE NO.	WALTER REED NO.	EXPERIMENTAL ANNUAL REPORT PAGE NO.
		Third Year (9/1/86 to 8/31/87)		
131	DJD-07-51	BL24012	255934	41
132	DJD-07-65	BL27862	256122	43
133	DJD-07-66	BL27853	256123	43
134	DJD-07-89	BL31768	256541	46
135	DJD-07-94	BL31777	256539	46
136	DJD-07-97	BL31759	256540	46
137	DJD-07-107	BL33137	256599	49
138	DJD-07-107A	BL33146	256600	49
139	DJD-07-117	BL35828	256782	51
140	DJD-07-118	BL35837	256780	53
141	DJD-07-123	BL35846	256781	53
142	DJD-07-128	BL35855	256779	53
143	DJD-07-153	BL45066	257305	57
144	DJD-07-161	BL48405	257566	59
		Fourth Year (9/1/87 to 8/15/88)*		
145	DJD-07-214	BL49993	257680	41
146	DJD-07-203	BL50021	257683	42
147	DJD-07-239	BL51297	254421	45
148	DJD-07-248	BL51304	257767	47
149	DJD-07-283	BL52196	258444	49
150	DJD-07-289	BL52749	258651	50
151	DJD-07-299	BL52954	258820	51
152	DJD-07-301	BL53308	259036	53
153	DJD-08-68	BL53602	259219	54
154	DJD-08-77	BL54207	215300	55

*Work completed June 30, 1988

TABLE OF CONTENTS

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

SYNTHESIS OF IMPROVED ANTILEISHMANIAL AND ANTITRYPANOSOMAL DRUGS

TREATMENT AND PROPHYLAXIS

1. INTRODUCTION AND BACKGROUND

Work performed under prior contract (1) will be reviewed first in general terms, followed by the approach taken under the current contract (2,3,4,5). Both contracts were targeted toward the two title parasites.

1.1 Prior Contract Work

Under the six and one-half year prior contract (1), a total of 56 target candidate drugs were submitted in several structural categories: 15 analogs of the active leishmaniacide WR 6026, 8-[(6-diethylaminohexyl)amino]-6-methoxy-4-methylquinoline, three 7-aminoquinolines, two 3-aminoquinolines, one 4-amino-2,6-disubstituted-pyridine, 20 aryl/heterocyclic bis(amidoximes) and bis(amidines), four clinical bis(amidines) together with the four corresponding bis(amidoxime) analogs and HOE 668 to include six structural modifications.

Promising new leads against L. donovani were obtained in the 8-aminoquinolines series by some 15 modifications of the basic WR 6026 structure, largely by incorporating additional methoxy groups in the 2- and/or 5-position, as well as various side chain modifications. Significant reductions in toxicity were achieved in a number of instances while retaining a high degree of activity; none were as active as WR 6026, however.

Another successful result was the acquisition of new candidate trypanosomiacides with a high degree of activity against T. rhodesiense. The drugs are effective when administered both PO as well as SC and possess excellent toxicity characteristics. For example, 2,6-bis(4-amidoximinophenyl)-4-methylpyridine, WR 248,936, is active at 0.83 mg/kg, both PO and SC, with a minimum toxic dose of 424 mg/kg or higher. On the other hand, no compounds active against the refractory T. cruzi, "Chagas disease", indigenous to South and Central America, were found and more attention was directed to this problem under the current contract.

1.2 Work Under the Current Contract

Work under the current contract, initiated September 1, 1984, represents a continuation and extension of work performed under the prior contract. The structures of all 46 compounds prepared to-date under the 46 month current contract are shown in Figure 1.

In the first year, nine compounds were prepared (2). Seven of these represented a continuation of prior phases of work: four modifications of the 8-aminoquinoline leishmaniacide, WR 6026, two new bis(amidoximes) and one new bis(amidine) as candidate tryanosomicides, and one bis(pyridylhydrazide) as a candidate leishmaniacide (6).

Also, in the first year, a new effort was initiated against forms of the refractory (Trypanosoma cruzi.) Thus McCabe and co-workers at Stanford University (7) stated that "Chagas disease, caused by infections of T. cruzi, affects millions of people in Central and South America and, at present, no chemotherapeutic agent has been accepted as completely effective for its treatment." Our literature search revealed a 1982 paper (8a) and related patents (8b,8c) by a group of workers at Wellcome Research Laboratories in England who described a series of 1,1-bis(aryl)-3-dimethylaminomethylethylenes which were active orally in mice against a Peruvian strain of T. cruzi. As a result, the first example of new congeners of the Wellcome compounds were prepared.

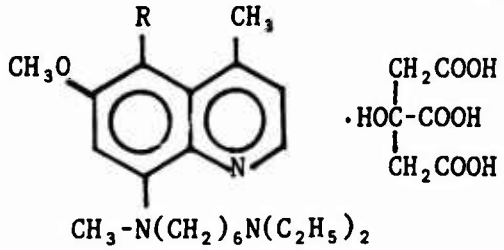
In the second year 11 of the 13 compounds were Wellcome-type compounds and the other two candidate drugs were candidate leishmaniacides (new 8-aminoquinolines).

In the third year, the first 12 of the 14 submissions were related to the Wellcome structures. No additional examples of these were planned and the balance of the contract work was targeted against strains of leishmaniasis, including the two 8-aminoquinolines submitted at the end of the third year.

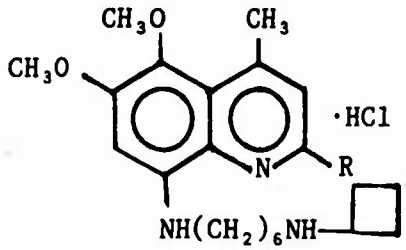
In the fourth and final year of the contract, the work was targeted against strains of leishmaniasis as suggested by the COR, Dr. Robert R. Engle. In the current year ten 8-aminoquinoline derivatives were submitted. These compounds are potential metabolites of WR 6026, the most active leishmaniacide, based on work pioneered by WRAIR scientists (J.D. Berman, A.D. Theohariaes and others, see Section 2.3).

FIGURE NO. 1

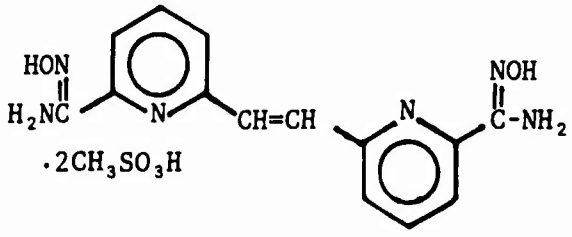
COMPOUNDS PREPARED UNDER THE CURRENT CONTRACT
(1 September 1984 - 31 August 1985)
Year No. 1 (9)



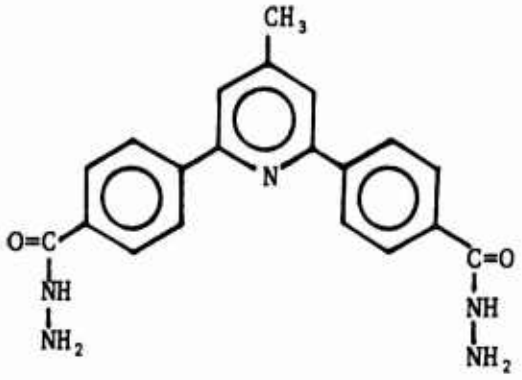
SNL-109, R = H, 10 g, DJD-06-44, WR 253904
SNL-111, R = OCH_3, 12 g, DJD-06-81, WR 254238



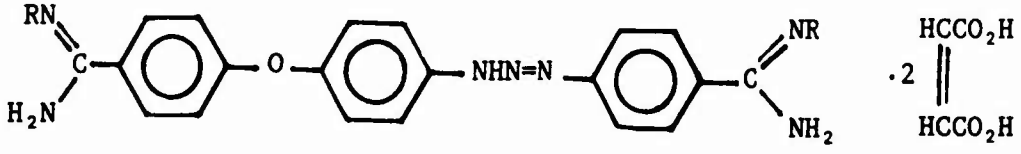
SNL-112, R = H, 11 g, DJD-06-99, WR 254391
SNL-114, R = OCH_3, DJD-06-126, WR 254589



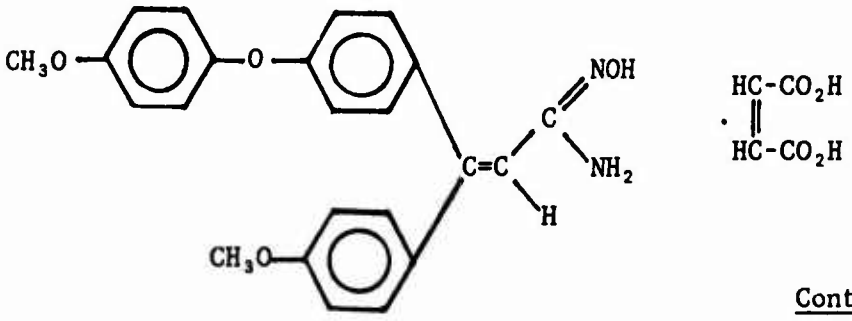
SNL-110, 9 g, DJD-06-59A, WR 254019



SNL-113, 7 g, AM-04-12, WR 254588



SNL-115, R = OH, 10 g, DJD-06-134, WR 254642
SNL-116, R = H, 4.5 g, DJD-06-152, WR 254731



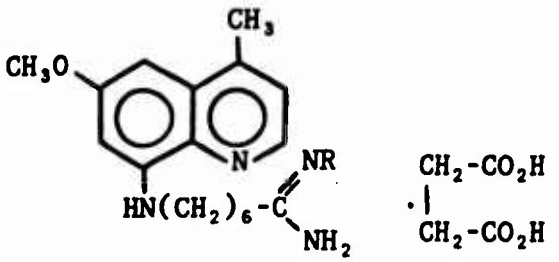
Continued

SNL-117, 4.5 g, AM-04-20, WR 254729

FIGURE 1, Continued

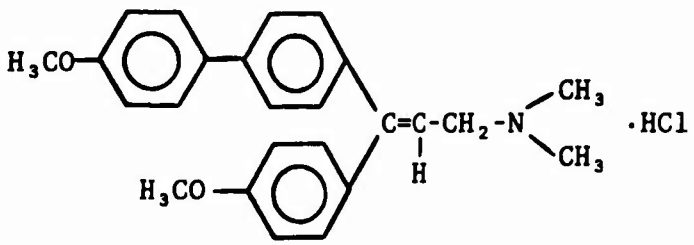
(1 September 1985 to 30 August 1986)

Year No. 2 (13)



SNL-118, R = OH, 5 g, KW-08-118, WR 254959

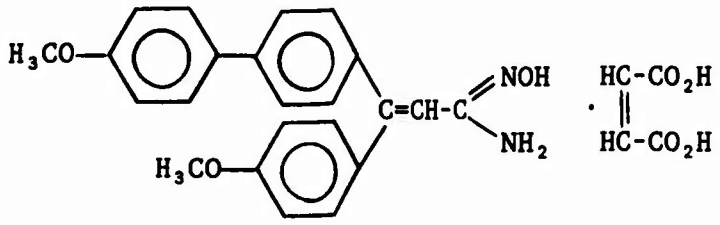
SNL-119, R = H, 6 g, KW-08-211B, WR 254985



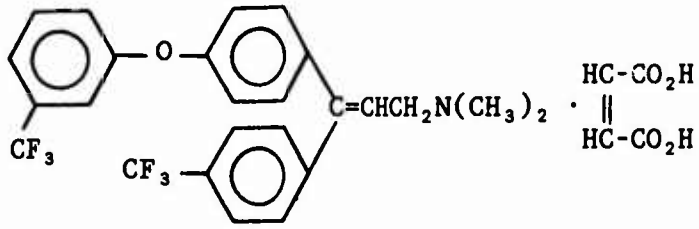
SNL-120, 4.5 g, DJD-06-210, WR 255426

FIGURE 1, Continued

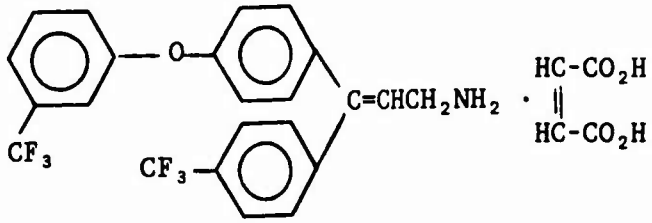
Year No. 2 (Continued)



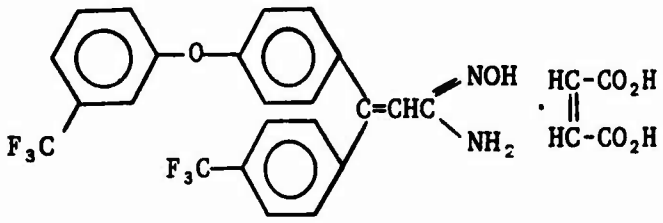
SNL-121, 5 g, AM-04-28, WR 255566



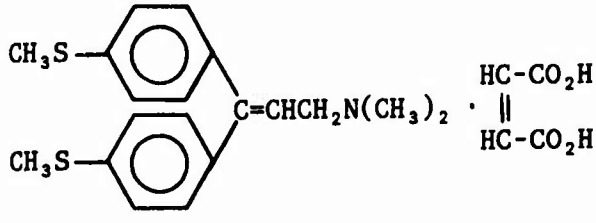
SNL-122, 7.5 g, DJD-06-268, WR 255593



SNL-123, 10 g, DJD-06-270, WR 255594



SNL-124, 5 g, RK-04-154, WR 255595

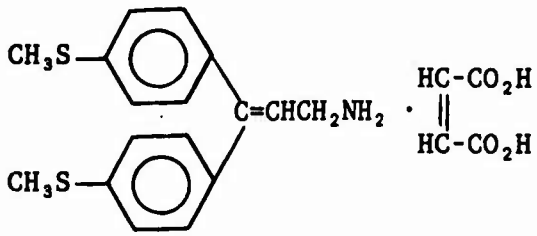


SNL-125, 4.5 g, DJD-06-288, WR 255664

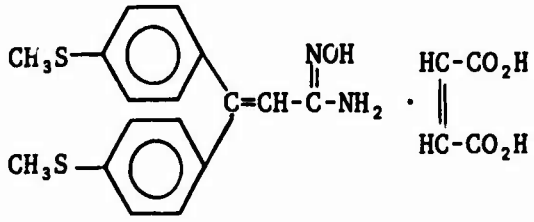
Continued

FIGURE 1, Continued

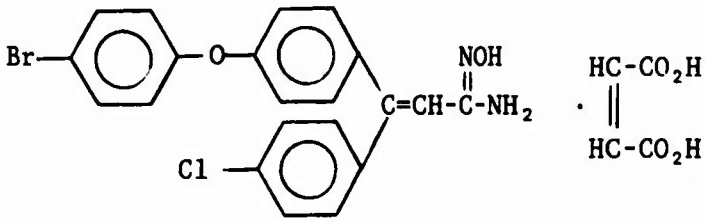
Year No. 2 (Continued)



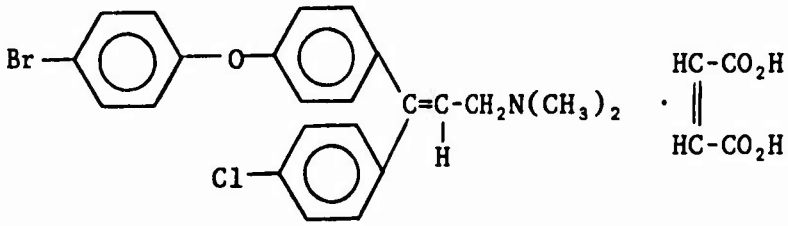
SNL-126, 4 g, DJD-06-293, WR 255665



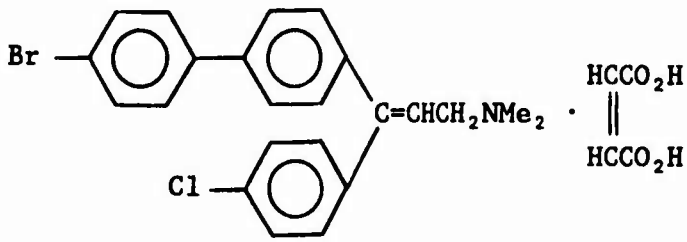
SNL-127, 4 g, DJD-06-295, WR 255662



SNL-128, 7.5 g, DJD-07-27, WR 255784



SNL-129, 6.5 g, DJD-07-32, WR 255810



SNL-130, 4.5 g, DJD-07-44, WR 255931

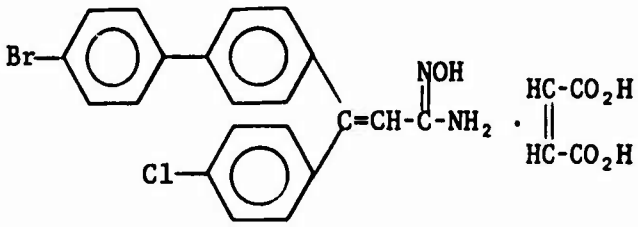
Wellcome Research Laboratories 353C

(As Tartrate salt)

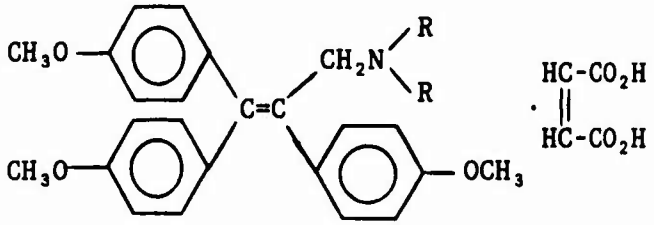
FIGURE 1, Continued

September 1, 1986 to 31 August 1987

Year No. 3 (14)

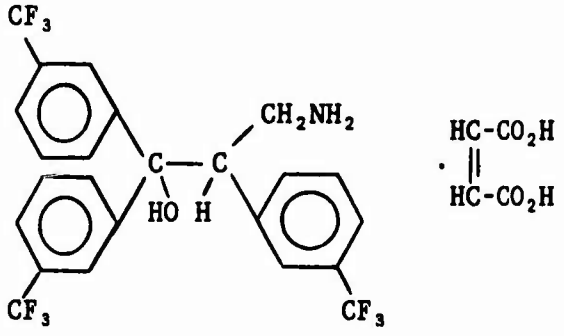


SNL-131, 4.5 g, DJD-07-51, WR 255934



SNL-132, R = CH_3, 5 g, DJD-07-65, WR 256122

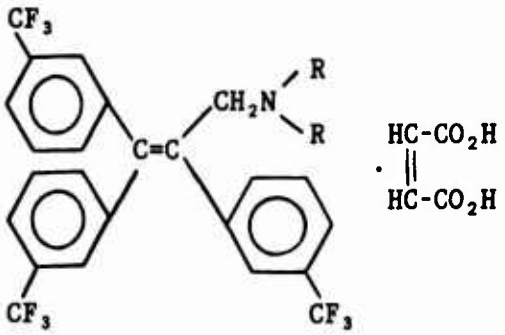
SNL-133, R = H, 5.8 g, DJD-07-66, WR 256123



SNL-134, 3.5 g, DJD-07-89, WR 256541

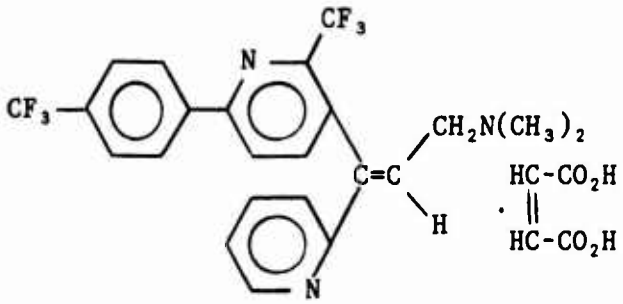
FIGURE 1, Continued

Year No. 3 (Continued)



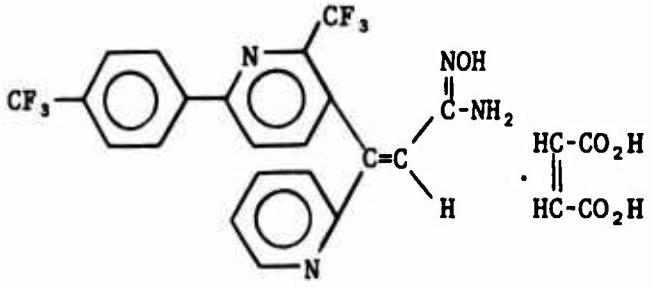
SNL-35, R = CH_3, 6.5 g, DJD-07-94, WR 256539

SNL-136, R = H, 4.5 g, DJD-07-97, WR 256540



SNL-137, Isomer A, 4.5 g, DJD-07-107, WR 256599

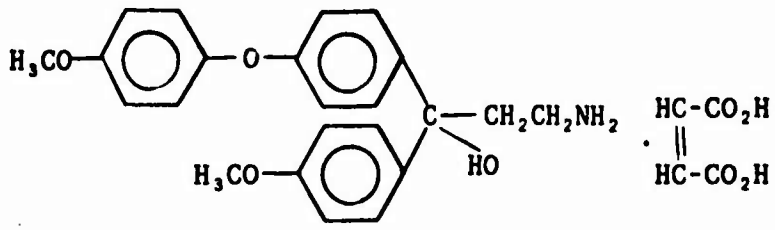
SNL-138, Isomer B, 8.5 g, DJD-07-107A, WR 256600



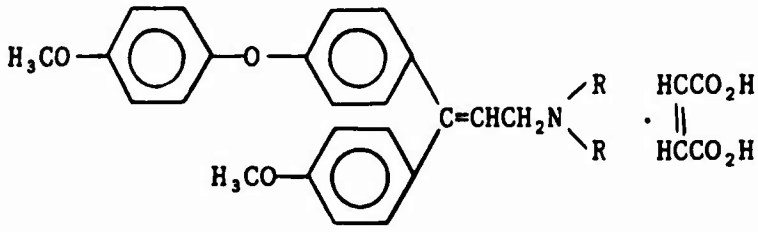
SNL-139, 10 g, DJD-07-117, WR 256782

FIGURE 1, Continued

Year No. 3 (Continued)

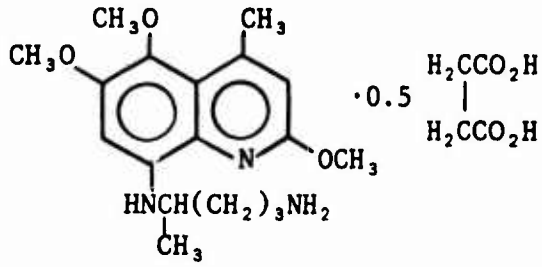


SNL-140, 3.5 g, DJD-07-118, WR 256780

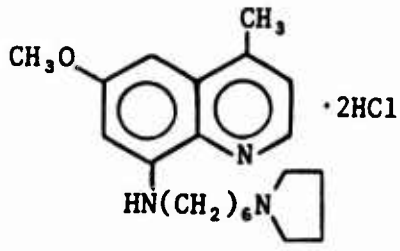


SNL-141, R = CH_3, 6 g, DJD-07-123, WR 256781

SNL-142, R = H, 5 g, DJD-07-128, WR 256779



SNL-143, 5.5 g, DJD-07-153, WR 257305

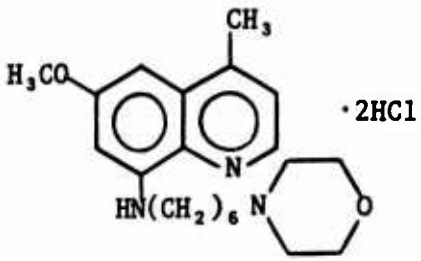


SNL-144, 5 g, DJD-07-161, WR 257366

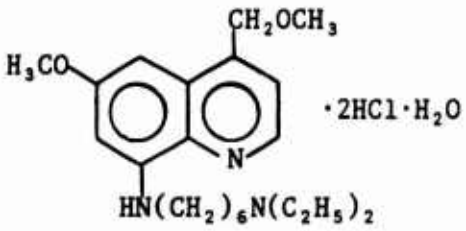
FIGURE 1, Continued

September 1, 1987 to August 15, 1988*

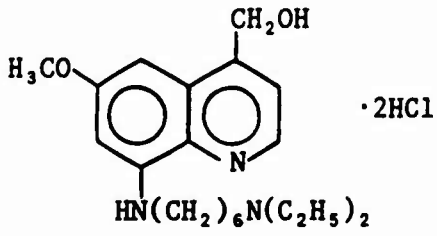
Year No. 4 (10)



SNL 145, 3.5 g, DJD-07-214, WR 257680



SNL 146, 10.3 g, DJD-07-203, WR 257683



Metabolite of WR 6026

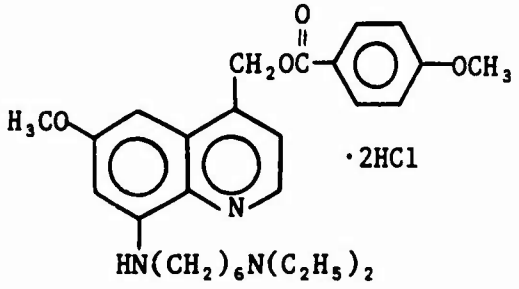
SNL 147, 6.0 g, DJD-07-239, WR 254421

*Work completed June 30, 1988

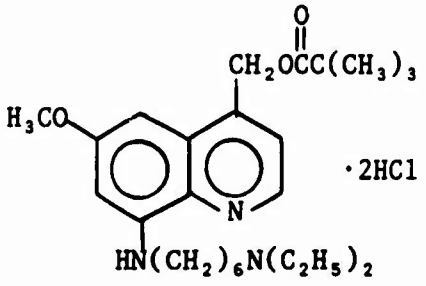
Year No. 4 (Continued)

September 1, 1987 to August 15, 1988

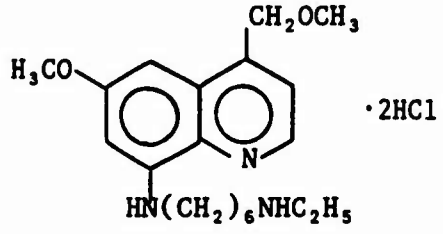
SNL 148, 7.0 g, DJD-07-248, WR 257767



SNL 149, 3.8 g, DJD-07-283, WR 258444



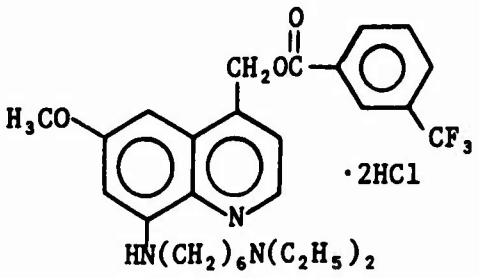
SNL 150, 5.0 g, DJD-07-289, WR 258651



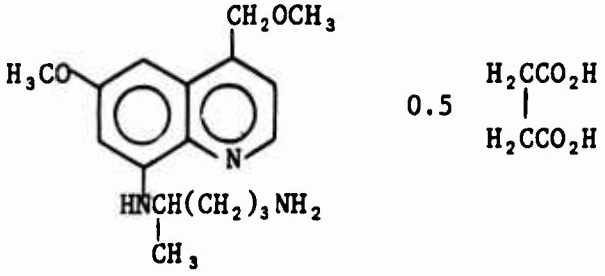
SNL-151, 5.8 g, DJD-07-299, WR 258820

Year No. 4 (Continued)

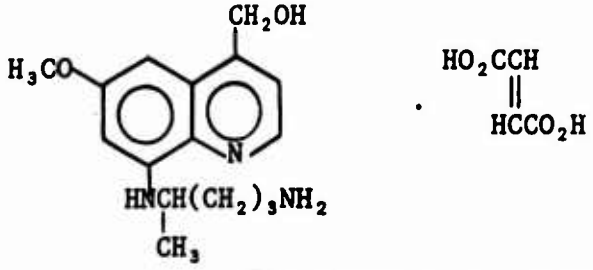
September 1, 1987 to August 15, 1988



SNL 152, 4.5 g, DJD-07-301, WR 259036



SNL 153, 6 g, DJD-08-68, WR 259219



(4-Hydroxymethyl Primaquine)

SNL 154, 5 g, DJD-08-77, WR 215300

2. DISCUSSION OF WORK COMPLETED. BIOLOGICAL RATIONAL AND DATA.

The 46 compounds submitted in the past three years and ten months of the current contract are shown in Figure 1, pages 6-15. These compounds will be discussed briefly, both in terms of the biological rationale leading to their preparation, as well as the activity data available at this writing. Biological data for the 56 target compounds submitted under the prior contract were summarized in the Final Summary Report (1) and portions of the data for these earlier compounds will be tabulated herein for comparative purposes.

The compounds submitted under the current contract were presented and discussed in four Annual Reports (2,3,4,5).

2.1 Leishmaniacides (8-Aminoquinolines)

The major effort has been directed at modified 8-aminoquinolines. Thus, under the current contract six new examples were prepared: SNL-109, 111, 112, 114, 118 and 119 (see Figure 1). The rationale for their preparation is the high activity of WR 6026 against L. donovani (Hanson) represented by a Glucantime index of 474 (IM) and 708 (PO). The available biological data are shown in Table 1.

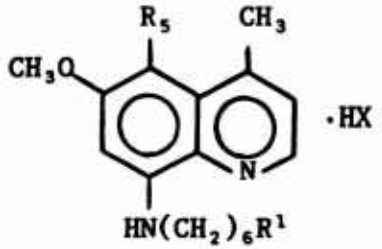
8-N^1-CH_3 Blocking Group: - The pair of 8-N^1-CH_3-blocked compounds, SNL-109 and 111, represent the use of a blocking N-methyl group to prevent the metabolic conversion of the drug to a 5,8- or a 7,8-iminoquinone in order to assess the impact upon the activity and/or toxicity relative to the parent (unblocked) compounds. Referring to Table 1, no data are yet available for SNL-109 which is WR 6026 containing a 8-N^1 blocking methyl group. However, SNL-111, which bears the toxicity-inducing (usually) 5-methoxy group (see data for WR 226,292), shows a minimum toxic dose of 832 mg/kg and a 100% suppression of parasites at 52 mg/kg (lowest dose tested). While the data are limited, the results are nevertheless promising.

8-N^6-Cyclobutyl Side Chain Group: - Similarly, in the case of analogs bearing a cyclobutyl side-chain group (Table 1), the original compound, SNL-07, showed both promising activity and reduced toxicity relative to WR 6026. Accordingly, in the case of SNL-112, the activating but toxicity-inducing 5-methoxy group was again added; no data are yet available. However, some data are available for SNL-114, the 2-methoxy derivative, which shows 100% suppression of parasites at a dosage of 52 mg/kg, coupled with a sharply reduced toxicity (high minimum toxic dose of 832 mg/kg). Data at dose levels below 52 mg/kg are required to explore this promising lead further.

TABLE 1

ANTILEISHMANIAL ACTIVITY OF ANALOGS OF WR 6026 (IN PART)

L. donovani, hamster (Hanson) (IM)



SNL No.	WR No., Bottle No.	R^1	R_5	Other Groups	Min. Curative Doses, % Suppression mg/kg/day (x4)		Min. Toxic Dose	Glucantime Index, G
	6,026	$-NEt_2$	H	—	99.6/0.20	84/0.05	52	474
	226,292	$-NEt_2$	$-OCH_3$	—	100/0.20	68/0.05	>13 <52	401
17(a)	242,896	$-NEt_2$	H	$2-OCH_3$	99.5/13	56/0.81	208(6/6T)	33
108(a)	254,123	$-NEt_2$	$-OCH_3$	$2-OCH_3$	100/52(a)		208(6/6T)	7(a)
				8-N^1-Methyl Blocked Analogs				
109(a)	253,904	$-NEt_2$	H	$8-N^1-CH_3$				
111	254,233	$-NEt_2$	$-OCH_3$	$8-N^1-CH_3$	100/52(a)		832(6/6T)	1(a)
				Cyclobutyl Sidechain Analogs				
07(a)	239,374	$-NH-C_4H_7$	H	—	99.2/0.81	74/0.20	208(6/6T)	188,174
112	254,391	$-NH-C_4H_7$	$-OCH_3$	—				
114	254,589	$-NH-C_4H_7$	H	$2-OCH_3$	100/52(a)		832(6/6T)	1(a)
				Amidoximino/Amidino Sidechain Groups				
118	254,959	$-C(NH_2)=NOH$	H	—	50/52		52, Non Toxic	
119	254,985	$-C(NH_2)=NH_2$	H	—				

(a) Prepared under prior Contract No. DAMD17-78-C-8001.

8-N^6-Amidoximino/Amidino Sidechain Groups: - The most recent modifications of WR 6026 are SNL-118 and 119 in which the exterior 8-amino group is replaced by an amidoximino and amidino group, respectively. No data are yet available.

Other: - Another candidate leishmaniacide of a different structural category is represented by 2,6-bis(4-hydrazidophenyl)-4-methylpyridine, SNL-113 (Fig. 1). This was prepared based on a suggestion by Peters and associates (6) who noted that the antituberculosis drug isoniazid had a remissive effect (tissue culture and animals) against L. mexicana, and a salutary clinical result in limited cases. While the clinical result was discounted later, the hydrazido group may be worth exploring as new leads are relatively scarce.

2.2 Trypanosomiacides (T. rhodesiense)

The early effort (1) was directed at exploring the effect of a wide variety of bis(amidines) and bis(amidoximes), primarily against T. rhodesiense (Rane/Ager).

Bis(amidoximes) and bis(amidines): - As reported in detail in the earlier work under the prior contract (1), considerable success against L. rhodesiense was achieved with a number of the title compounds as shown in Table 2 (for structures, see Figure 2). Thus a number of compounds were active (SC) over a range of 0.11 to 0.83 mg/kg and SNL-28 (WR 248,396), 2,6-bis-(4-amidinophenyl)-4-methyl-pyridine dihydrochloride, was curative (PO) at 1.66 mg/kg.

In the current program, the preparation of 1,2-ethylene-bis-(6-amidoximino-2-pyridyl), SNL-110 (Fig. 1), was based on the high activity against T. rhodesiense exhibited by the closely-related 2-amidoximino-6-(4-amidoximinostyryl)pyridine (SNL-36), WR 249,238, which gave a minimum curative dose of 6.55 mg/kg (x 1), both SC and PO (1). SNL-110 (WR 254,019) was curative (4/5C) at 26.5 mg/kg but it was inactive at 13 mg/kg (SC, no oral data). Also the new submissions, SNL-115 and 116 are triazene structures (Fig. 1) relating to the commercial drug diminazene(berenil) in terms of containing a phenoxy grouping; no data are available for these as yet.

Some 16 of the title bis(amidoximes) and bis(amidines) were tested against T. cruzi (Ager); none were active. The results, in part, led to the work discussed below directed specifically against T. cruzi (5,6).

TABLE 2

ANTITRYPANOSOMAL DATA. SELECTED BIS(AMIDOXIMES) AND BIS(AMIDINES)[a]

AO = Bis(amidoxime), AM = Bis(amidine)

SNL No.	For Structures, see Figure 2, next page: WR or BN No.	Type Cpd.	T. rhodesiense Rane/Ager, five mice (SC): Min. Curative Dose	100% Curative Dose(5/5C)	Min. Toxic Dose	Rane,[b] five mice, Min. Toxic Dose
			mg/kg(x1)			
			A. Bis(aryl) Heterocycles			
28	248,396	AO	0.83(5C)	0.83	>424	
29	248,535	AM	0.11(1C)	0.42	424	160(1T)
47	249,698	AM	0.21(2C)	0.83	424	640(5T)
54	250,262	AM	0.21(2C)	0.83	106	160(4T)
107	252,070	AM	0.11(1C)	0.42	106,212	NA
			B. HOE 668, SNL-77 and Thio Analog SNL-96			
77	245,720	AM	0.11(2C)	0.83	424	>640(0T)
96	251,336	AM	0.83(4C,5C)	0.83	212	
			C. Commercial Drugs and Bis(amidoxime) Analogs			
			Pentamidine Dimethanesulfonates			
63	250,385	AO	0.83(1C)	1.66	106	640(4T)
64	4,931	AM	0.83(2C)	1.66	106	640(5T)
			Diminazene (Berenil) Dimaleates			
67	250,483	AO	0.11(1C)	0.83	212	
68	27,800	AM	0.01(1C)	0.11	106	160(3T)

a) From prior Contract No. DAMD17-78 C-8001.

b) *P. berghei* antimalarial test.

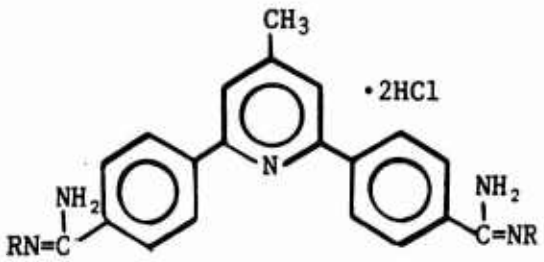
FIGURE 2

SELECTED ACTIVE ANTITRYPANOSOMAL STRUCTURES

From Prior Contract (1)

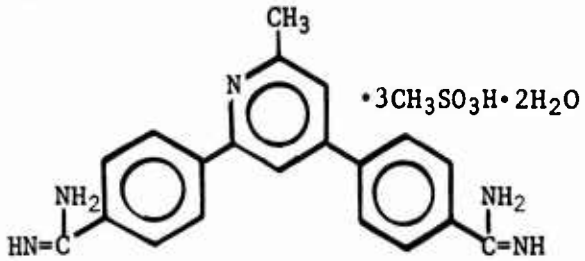
(T. rhodesiense, See Table 2, Section 2.2)

A. Bis(aryl) Heterocycles

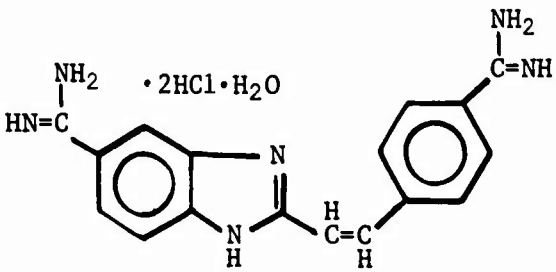


SNL-28, R = OH, WR 248,396, KW-II-98A

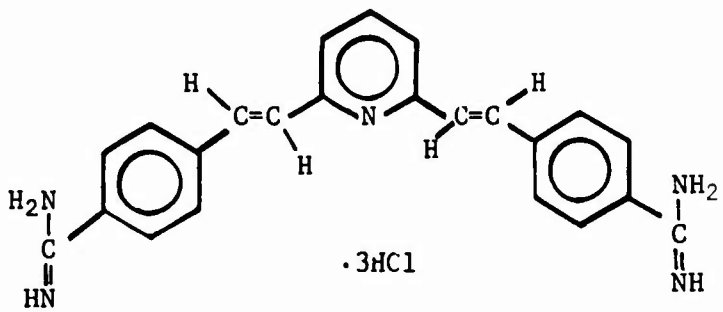
SNL-29, R = H, WR 248,535, KW-II-109A



SNL-54, WR 250,262, DJD-04-41

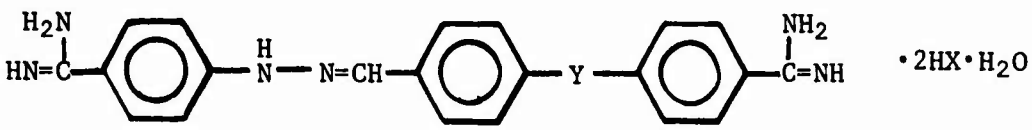


SNL-47, WR 249,698, KW-III-91A



SNL-107, WR 252,070, DJD-06-03

B. HOE 668 (SNL-77) and a Thio Analog (SNL-96)



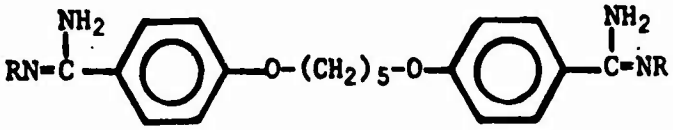
SNL-77, Y = O, WR 245,720, 2HX = Dimaleate, DJD-04-151

SNL-96, Y = S, WR 251,336, 2HX = Dihydrochloride, DJD-04-243

Continued

FIGURE 2 (Continued)

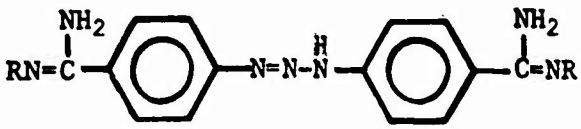
C. Commercial Bis(amidines) and their Bis(amidoxime) Analogs



SNL-63, R = OH, WR 250,385 •2HCl•0.5H_2O, DJD-04-59

SNL-64, R = H, WR 4,931 •2HCl (Pentamidine), DJD-04-63

WR 4,931, Commercial: Pentamidine Diisethionate



SNL-67, R = OH, WR 250,483 ·Dimaleate, DJD-04-94

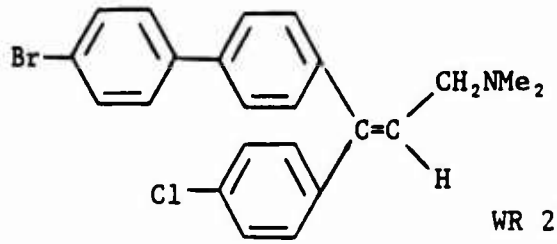
SNL-68, R = H, WR 27,800 ·Dimaleate (Diminazene; Berenil), DJD-04-95

WR 27,800, Commercial: Diminazene(Berenil) Diaceturate

2.3 Trypanosomiacides (T. cruzi)

As we noted earlier, and in our original proposal dated March 1984, "Chagas' disease", caused by infections of T. cruzi, affects millions of people in Central and South America. McCabe and co-workers (7) at Stanford University state that, "at present, no chemotherapeutic agent has been accepted as completely effective for its treatment. Nifurtimox and benznidazole are being used to treat human diseases but they are limited in application by significant side effects. It is controversial as to whether or not nifurtimox or benznidazole is curative."

In view of this, coupled with the fact the compounds reported above in section 2.2 were active only against T. rhodesiense, our attention was focused on candidate drugs which might be effective against South and Central American forms of trypanosomiasis. A 1982 paper (8a) by a group of workers at Wellcome Research Laboratories in England describe a powerful antitrypanocide which is effective orally against the refractory T. cruzi. Compound 353C cured 90% of T. cruzi



WR 255931

353C, tartrate salt; SNL-130, maleate salt

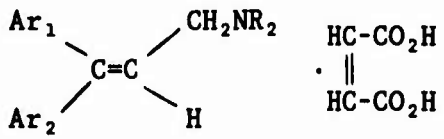
(Peruvian)-infected mice orally at a weekly dosage of 25 mg/kg. Compound 353C was one of the most active of the 130 1,1-diaryl-3-aminoprop-1-enes prepared by Wellcome (8a) and covered in two patents (8b and 8c). As a result, we prepared the eleven structural analogs shown in Figure 3. As another structural modification, two 1,1,2-triaryl-2-dimethylaminomethylethylenes and their primary amine precursors were prepared; these four compounds are shown in Figure 4.

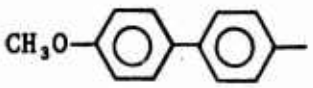
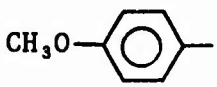
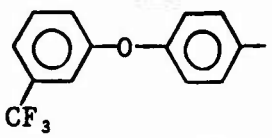
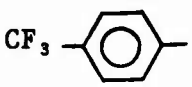
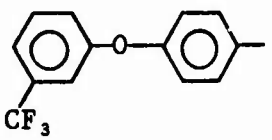
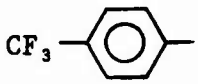
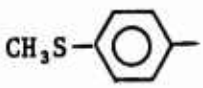
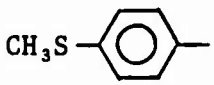
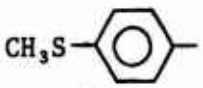
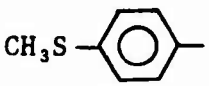
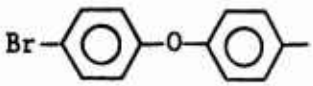
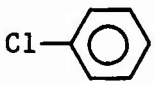
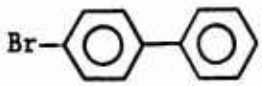
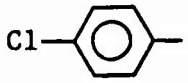
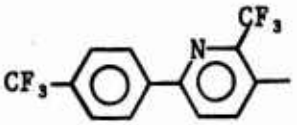
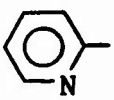
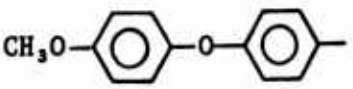
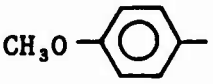
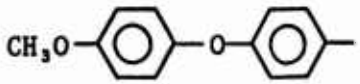
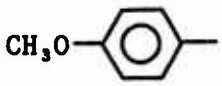
Inasmuch as the 3,3-diarylacrylonitriles were readily accessible from the intermediate 3-hydroxy-3,3-diarylpropionitriles, the nitrile group was converted to the amidoximine group in a number of cases. Seven 1,1-diaryl-2-(amidoximino)ethylenes were prepared as shown in Figure 5.

No test data are available for any of the Wellcome-type compounds (Figure 3 and 4) prepared in the course of the work against T. cruzi and/or other South American strains of trypanosomiasis.

FIGURE 3

1,1-DIARYL-2-(DIMETHYLAMINOMETHYL)ETHYLENES (11)

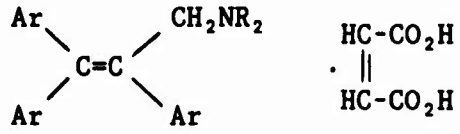


WR No. (SNL No.)	Ar_1	Ar_2	R
255,426 (120) (a)			CH_3
255,593 (122)			CH_3
225,594 (123)			H
255,664 (125)			CH_3
255,665 (126)			H
255,810 (129)			CH_3
255,931 (130) (b)			CH_3
256,599 (137) (c) } 256,600 (138) (d)			CH_3
256,781 (141)			H
256,779 (142)			H

(a) HCl Salt
(b) Burrough Welcome Compound 353C
(c) Isomer A
(d) Isomer B

FIGURE 4

1,1,2-TRIARYL-2-(DIMETHYLAMINOMETHYL)ETHYLENES (4)



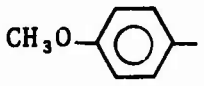
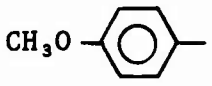
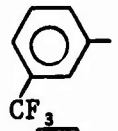
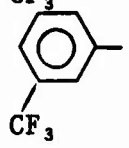
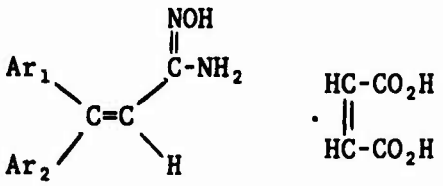
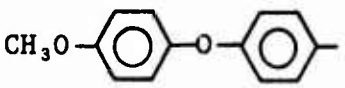
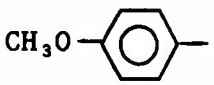
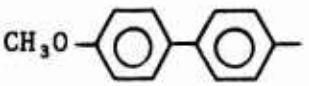
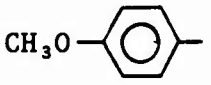
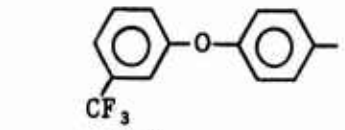
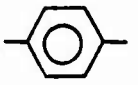
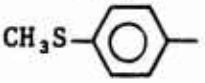
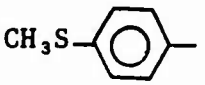
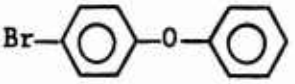
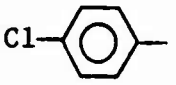
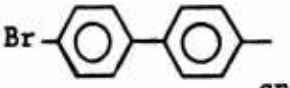
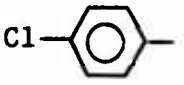
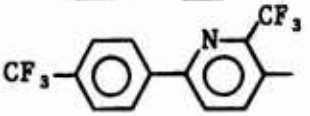
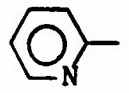
WR No. (SNL No.)	Ar	R
256,122 (132)		CH_3
256,123 (133)		H
256,539 (135)		CH_3
256,540 (136)		H

FIGURE 5

1,1-DIARYL-2-(AMIDOXIMINO)ETHYLENES (7)

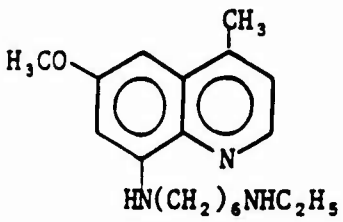


WR No. (SNL No.)	Ar_1	Ar_2
254,729 (117)		
255,566 (121)		
255,595 (124)		
255,662 (127)		
255,784 (128)		
255,934 (131)		
256,782 (139)		

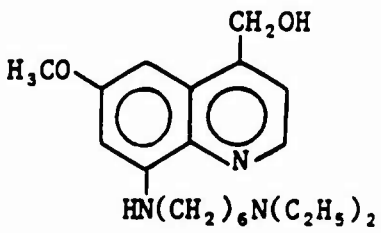
2.4 Leishmaniacides (Analogs of WR 6026)

There is considerable interest in WR 6026 since it is the most active leishmaniacide known today. All of the effort in the fourth and last year was devoted to exploring additional structural modifications represented by the 10 compounds shown earlier in Fig. 1, Year No. 4, pages 13-15, SNL-145 to 154, inclusive. SNL-145, the first of the ten submissions, represents another side chain modifcation of WR-6026(morpholino hexyl).

In a recent publication, Berman and Lee (9) suggested that the high activity of WR 6026 is due to it's biotransformation into a more potent leishmaniacide. These workers also have shown that WR 6026 lacks activity in vitro against amastigotes in macrophages. Recently Theoharides, Chung and Velaquez (WRAIR) undertook the study of metabolism of WR 6026 and identified two major metabolites of WR 6026 (10).



WR 211789 (14)
Metabolite 1



WR 254421, SNL-147
Metabolite 2

Since metabolite 2 is not known in the literature, we undertook the synthesis of this compound (SNL-147). Note also that SNL-146 is the methyl ether of SNL-147, both bearing the WR 6026 side chain. Similarly SNL-151 is the methyl ether of SNL-148 with a terminal ethylamine group on the side chain. Similarly SNL-149, 150 and 152 represent various esters of SNL-147 (metabolite 2). SNL-154 is 4-hydroxymethyl primaquine and SNL-153 is 4-methoxymethyl primaquine. Biological data thus far are limited to but the first four submissions. SNL-145, 146, 147 and 148 are 100 % curative against visceral leishmaniasis at 52 mg/kg (L. donovani Hahsen) and testing at lower dose levels is needed.

3. SYNTHESIS RESULTS AND DISCUSSION

The target compounds prepared during the term of the contract are discussed below.

3.1 8-[(6-Diethylaminohexyl-N^1-methyl)amino]-6-methoxy-4-methyl-quinoline Citrate (SNL-109, BK99121, WR 253904)

The reaction sequence used for the preparation of the title compound is shown in Chart No. 1.

Intermediate 1 and 2 were reported initially by K.N. Campbell and co-workers (11). 6-Methoxy-2-nitroaniline was condensed with methyl vinyl ketone under Skraup conditions to give the 8-nitroquinoline 1 (59%) which was hydrogenated using Raney nickel catalyst to give the 8-aminoquinoline 2 (90%). 6-Chlorohexanol was condensed with diethylamine to form diethylaminoheanol as reported by Worth (12). Treatment of the 6-aminoalcohol with thionyl chloride, as reported earlier in this program (13), gave the side chain reagent, N,N-diethylamino-6-chlorohexylamine 3 (65%). This was condensed with the 8-aminoquinoline 2 to give the highly active leishmaniacide, WR 6,026 (4, 65%) as the compound selected for blocking on the internal nitrogen atom in the 8-position.

The blocking 8-N^1-methyl group was introduced by a modification of the procedure developed originally by Borch and Hassid in 1972 (14). Thus intermediate 4 was methylated using cyanoborohydride-formaldehyde to give the target 8-N^1-methyl-8-aminoquinoline 5 as an oily free base. This oil was purified by column chromatography and converted to the crystalline citrate salt 5 (SNL-109) in 87% yield.

3.2 1,2-Bis[(6-amidoximino)-2-pyridyl]ethylene Dimethanesulfonate (SNL-110, BL00432, WR 254019)

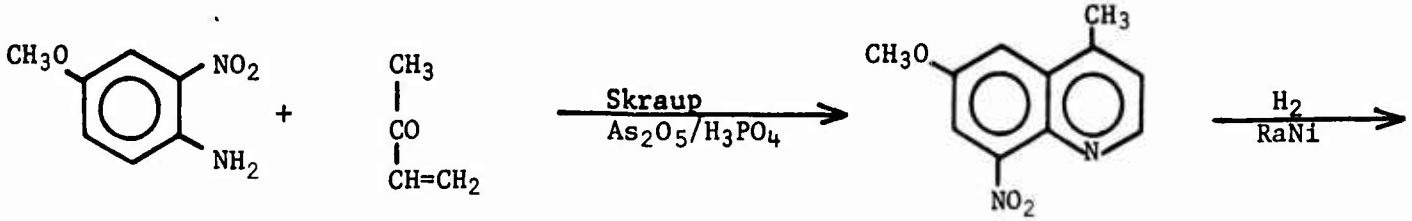
The reaction sequence used for the preparation of the title compound is shown in Chart No. 2.

The starting material for the title compound was the commercially-available 6-cyano-2-methylpyridine. One portion of this was brominated using N-bromosuccinimide in the presence of UV-light to give the corresponding crystalline 6-cyano-2-dibromethylpyridine (1) which was hydrolyzed with aqueous silver nitrate to form 6-cyano-2-formylpyridine (2), as reported by Eichinger and co-workers in 1982 (15).

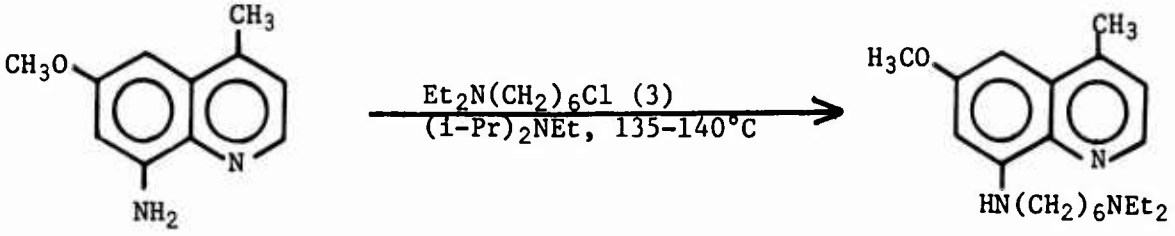
Bromination of a second portion of 6-cyano-2-methylpyridine under standard conditions (N-bromosuccinimide, carbon tetrachloride) afforded 2-bromomethyl-6-cyanopyridine as an oil. This was treated directly with triphenylphosphine to obtain the phosphonium salt 3 ((16) p. 15). Condensation of the aldehyde 2 with the salt 3 in the

CHART NO. 1

8-[(6-DIETHYLAMINOHEXYL-N^1-METHYL)AMINO]-6-METHOXY-4-METHYLQUINOLINE CITRATE (SNL-109, BK99121)

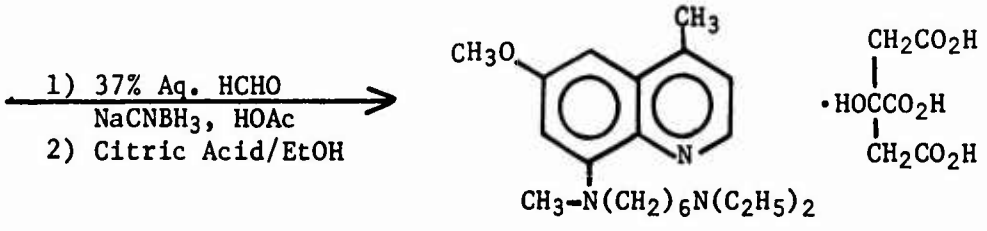


1 (59%)



2 (90%)

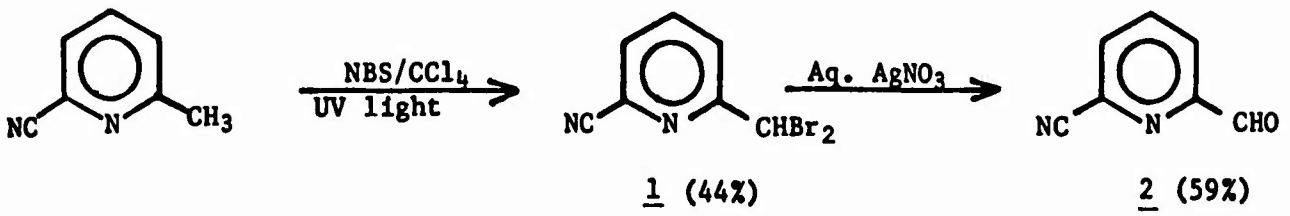
4 (65%), WR 6,026



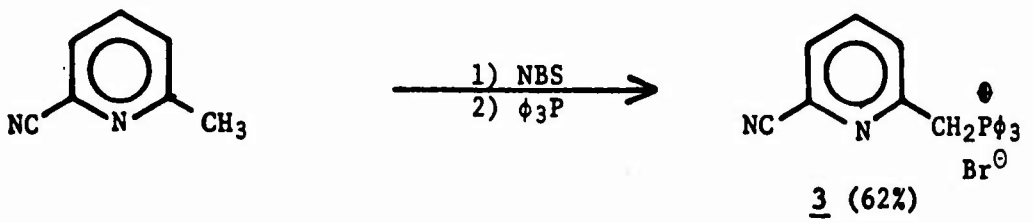
5 (81%) SNL-109, BK99121

CHART NO. 2

1,2-BIS[(6-AMIDOXIMINO)-2-PYRIDYL]ETHYLENE DIMETHANESULFONATE (SNL-110, BL 00432)

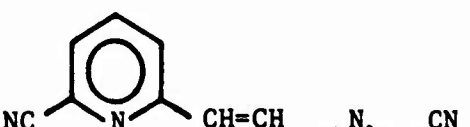


1 (44%) 2 (59%)



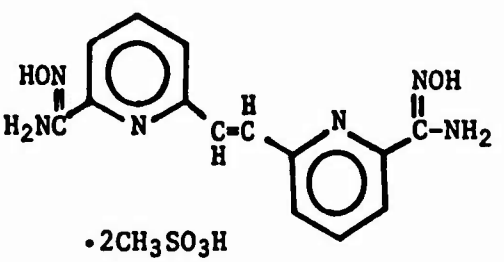
3 (62%)

Compound 2 + Compound 3 → 1) NaOMe, 2) I_2, xylene



4 (74%)

1) NH_2OH
2) CH_3SO_3H



•2CH_3SO_3H

5 (65%) SNL-110, BL00432
WR 254,019

presence of sodium methoxide (Wittig reaction) gave the olefin 4 as a cis-trans mixture. The mixture was refluxed in xylene in the presence of iodine to give the desired trans-pyridylethylene 4. Treatment of 4 with hydroxylamine gave the target compound 5 as a free base which was converted to the target crystalline methanesulfonate salt 5 (SNL-110).

3.3 8-[(6-Diethylaminohexyl-N^1-methyl)amino]-5,6-dimethoxy-4-methylquinoline Citrate (SNL-111, BL03808, WR 254233)

the reaction sequence used for the preparation of the title compound SNL-111 is shown in Chart No. 3.

5,6-Dimethoxy-4-methyl-8-nitroquinoline ((17) p. 52) was hydrogenated to give the required 8-aminoquinoline 1 using a procedure developed in these laboratories ((17) p. 53). Intermediate 1 was condensed with N,N-diethyl-6-chlorohexylamine (12) to give the 8-[(6-diethylaminohexyl)amino]quinoline 2 (WR 226,292, (17) p. 54). This was methylated with sodium cyanoborohydride in the same manner as described above (14) to give the free base 3 as an oil. Treatment of the free base with citric acid afforded the crystalline citrate salt 3 (SNL-111) in 51% yield.

3.4 8-[(6-Cyclobutylaminohexyl)amino]-5,6-dimethoxy-4-methyl-quinoline Monohydrochloride (SNL-112, BL05571, WR 254391)

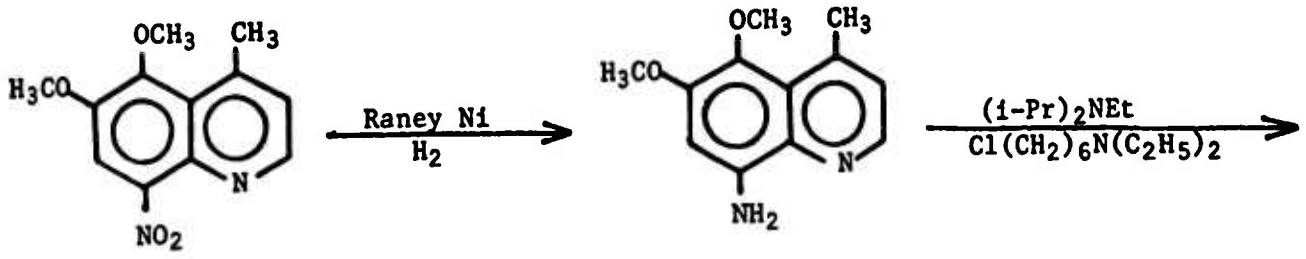
the sequence to the title 8-aminoquinoline with a cyclobutyl-aminohexyl side chain is shown in Chart No. 4. The side chain reagent was prepared as described earlier (13). The intermediate starting 5,6-dimethoxy-4-methyl-8-nitroquinoline, available from earlier work, was prepared by well developed procedures (15). This was hydrogenated with Raney nickel catalyst to give the requisite 8-aminoquinoline 2 (87%). Intermediate 2 was condensed with the side chain reagent 1, hydrochloride salt, to give the target compound 3 (29%).

3.5 2,6-Bis(4-hydrazidophenyl)-4-methylpyridine (SNL-113, BL07691) WR 254588,

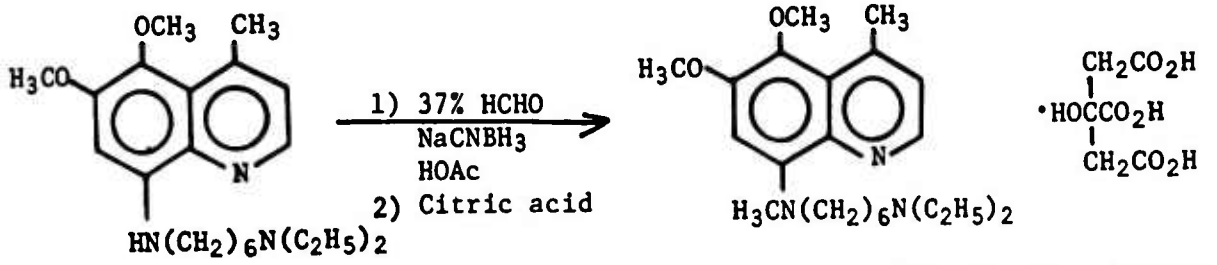
The sequence to the title bis(hydrazide) is shown in Chart No. 5. the starting bis(nitrile), prepared as described earlier ((16) p. 14) was hydrolyzed in a mixture of concentrated hydrochloric acid and acetic acid. The hydrochloride salt was converted with base to the sodium salt and the latter was treated with acetic acid to afford the dibasic acid 1 (65%). Intermediate 1 was esterified with ethanol and sulfuric acid catalyst to give, after workup and recrystallization of the crude diester, pure intermediate 2 (73%). The diester in ethanol containing hydrazine hydrate was refluxed for 48 h to give crude bis(hydrazide) which was recrystallized from DMF to give pure target title compound 3 (85%).

CHART NO. 3

8-[(6-DIETHYLAMINOHEXYL-N^1-METHYL)AMINO]-5,6-DIMETHOXY-4-METHYLQUINOLINE CITRATE (SNL-111, BL03808)



1 (84%)

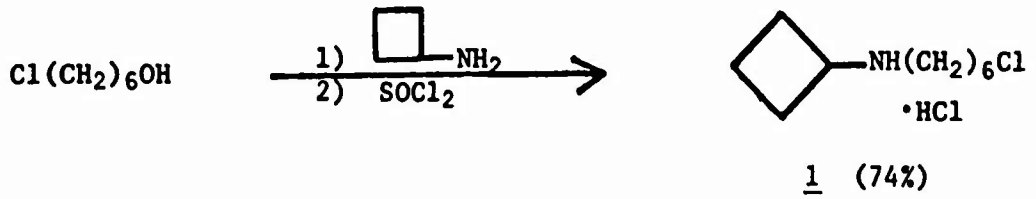


2 WR 226,292 (51%)

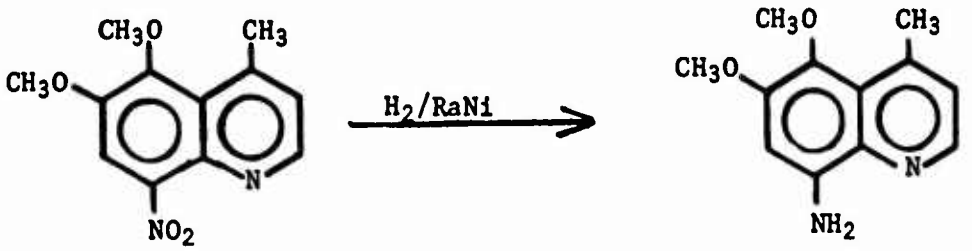
3 (51%) SNL-111, BL03808
WR 254,233

CHART NO. 4

SYNTHESIS OF 8-[(6-CYCLOBUTYLAMINO-1-HEXYL)AMINO]-5,6-DIMETHOXY-4-METHYLQUINOLINE (SNL-112, WR 254,391)

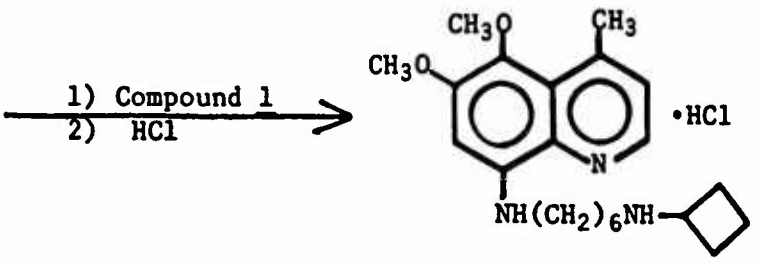


1 (74%)



Ref. 16, p. 52

2 (87%)



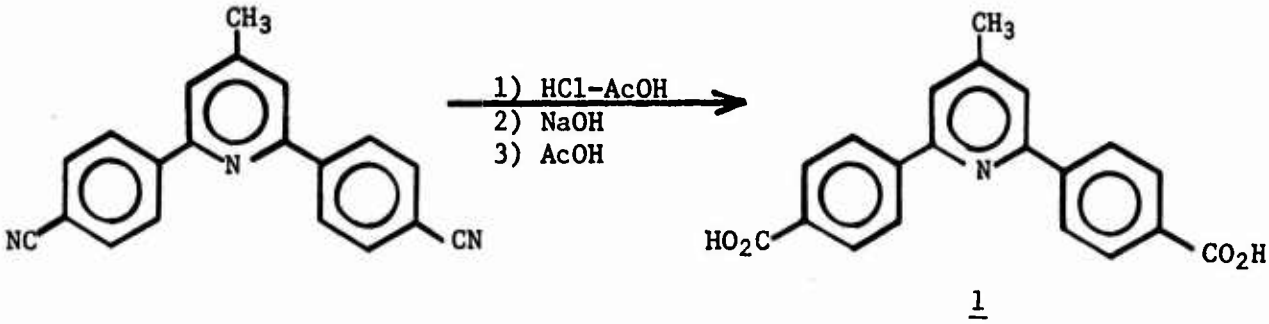
3 (29%)

WR 254,391, BL05571, SNL-112

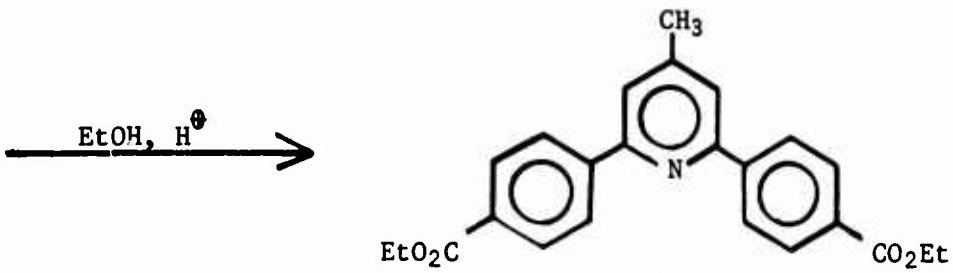
CHART NO. 5

2,6-BIS(4-HYDRAZIDOPHENYL)-4-METHYLPYRIDINE

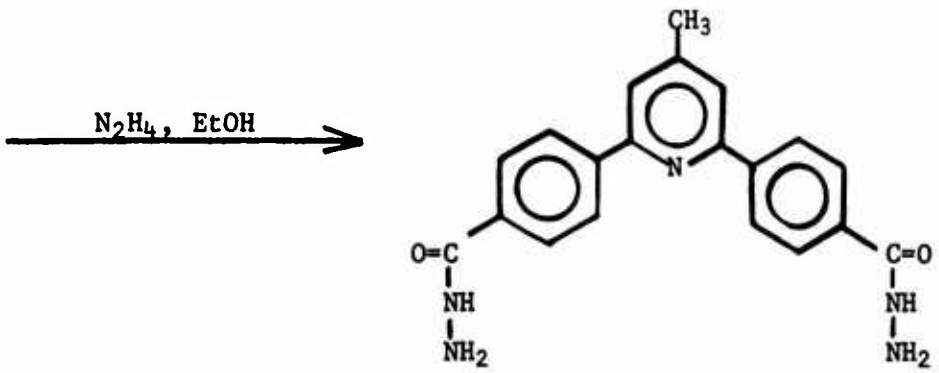
(SNL-113, BL07691)



1



2



3, SNL-113, BL07691

3.6 8-[(6-Cyclobutylaminohexyl)amino]-2,5,6-trimethoxy-4-methylquinoline Monohydrochloride (SNL-114, BL07682, WR 254589)

The sequence to the title target compound is shown in Chart No. 6. As stated earlier, the 2-methoxy derivative of highly active WR 225,448 had a salutary effect both on the activity as well as methemoglobinemia toxicity. Accordingly, seven of the eight steps had been well-developed in the antimalarial program ((17) 1976 and (18) 1984) and had also been used earlier in the preceding leishmaniasis-trypanosomiasis drug development program (1).

Thus, the process and yields shown in Chart No. 6 through precursor 7 quite closely duplicated the earlier work discussed above and need not be discussed further. However, in the final step, the neat condensation of 1-cyclobutylamino-6-chlorohexane hydrochloride with the preecursor 8-aminoquinoline 7 at 95°C (steam bath) resulted in extensive decomposition and the yield was but 14% after extensive purification. The more conventional use of ethoxyethanol in probe runs was also not promising. However, sufficient sample (7 g) was made available for evaluation.

3.7 1-(4-Amidoximinophenyl)-3-[4-(4-amidoximinophenoxy)-phenyl]-triazene Maleate (SNL-115, BL08401, WR 254642)

The sequence to the title amidoxime is shown in Chart No. 7.

4-Aminophenoxy-4-benzonitrile 1, prepared using a known procedure (19), was treated with diazonium salt prepared from 4-aminobenzonitrile to give the triazene intermediate 2. Compound 2 was allowed to react with hydroxylamine under standard conditions to afford the bis(amidoxime) 3 free base. Treatment of the free base with maleic acid gave the target title dimaleate salt 3, SNL-115.

3.8 1-(4-Amidinophenyl)-3-[4-(4-amidinophenoxy)-phenyl]triazene (SNL-116, BL09533, WR 254731)

The reaction sequence used for the preparation of the target compound, SNL-116, is shown in Chart No. 8.

The starting material 4-aminophenoxy-4-benzonitrile, the same as that used for the preparation of SNL-115 above (19), was treated with hydrogen chloride gas in methoxyethanol (Pinner reaction) to give the intermediate imino ether (not shown). The imino ether was mixed immediately with ammonia in ethanol to give 4-aminophenoxybenzamidine (1). Diazotization of compound 1 gave a homogeneous solution of the intermediate diazonium salt (20). This solution was treated at once with a solution of 4-aminobenzamidine dihydrochloride in water to give the free base (40%). The free base was converted to the dimaleate salt which crystallized as the monohydrate 2, SNL-116.

CHART NO. 6

8-[(6-CYCLOBUTYLAMINOHEXYL)AMINO]-2,5,6-TRIMETHOXY-4-METHYLQUINOLINE MONOHYDROCHLORIDE (SNL-114, BL07682)

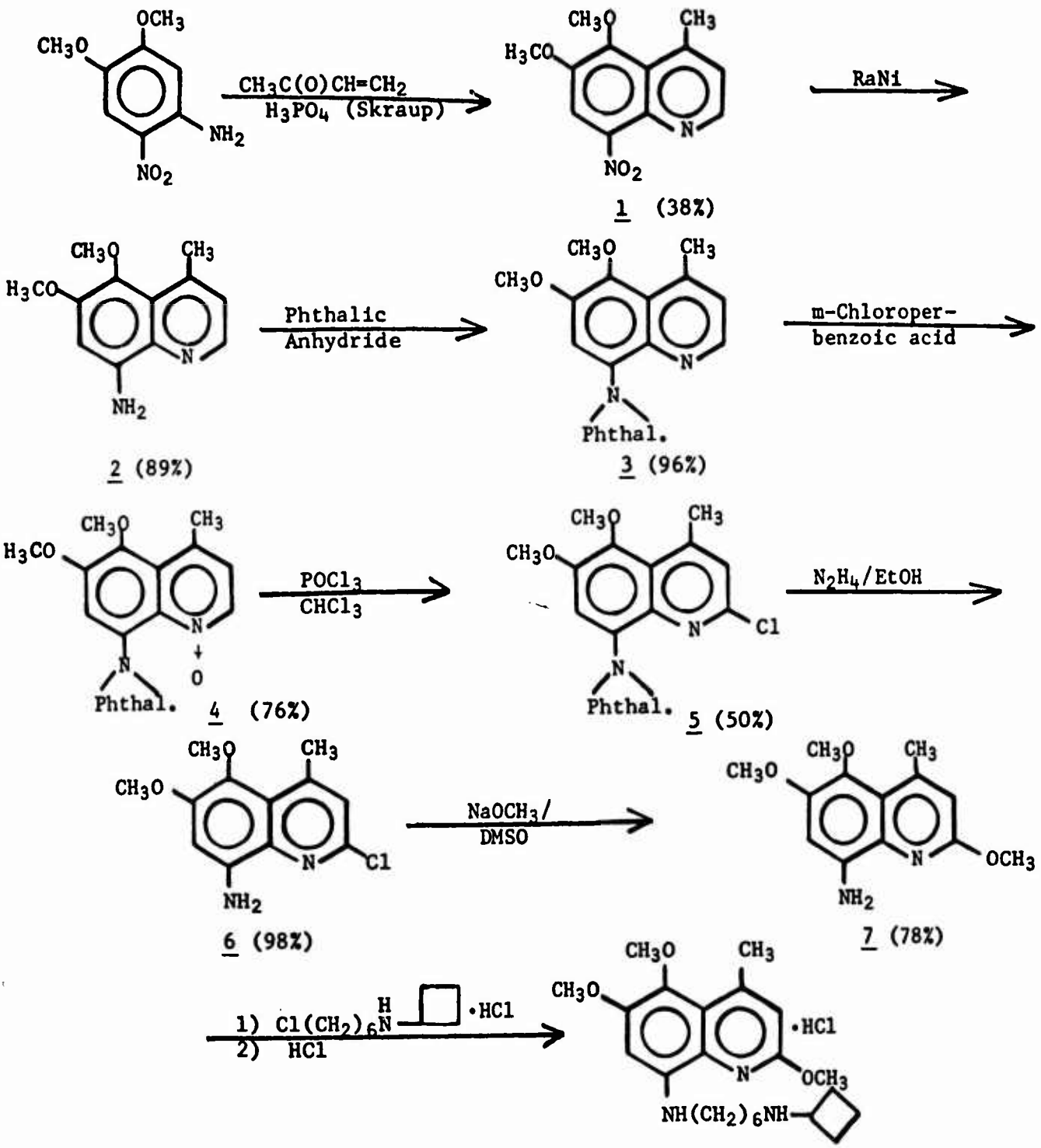
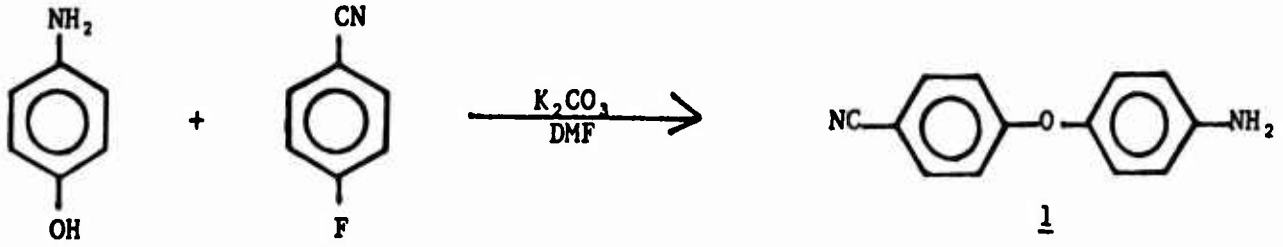
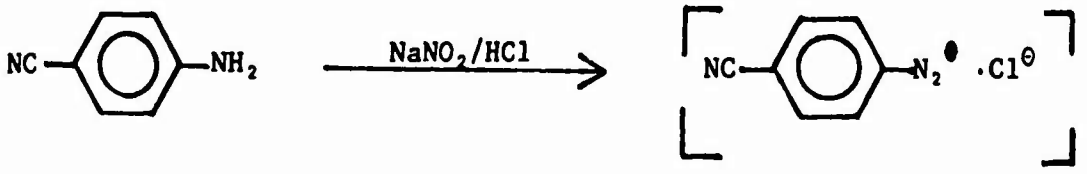


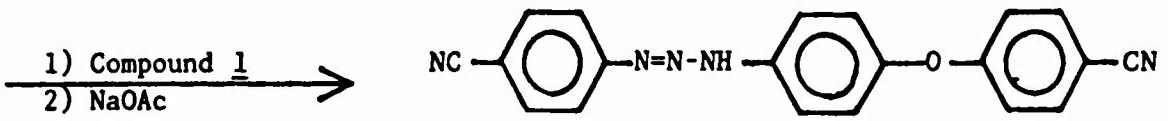
CHART NO. 7

1-(4-AMIDOXIMINOPHENYL)-3-[4-(4-AMIDOXIMINOPHENOXY)-PHENYL]TRIAZENE DIMALEATE (SNL-115, BL08401)

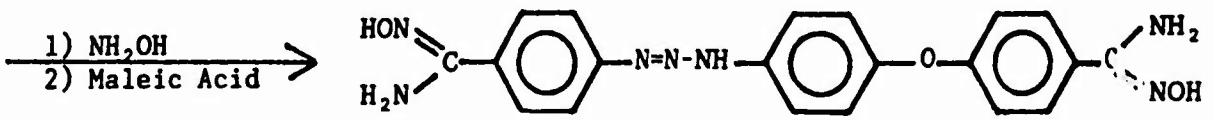


1





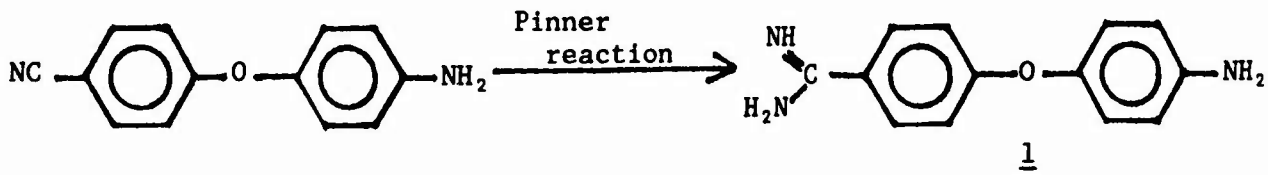
2



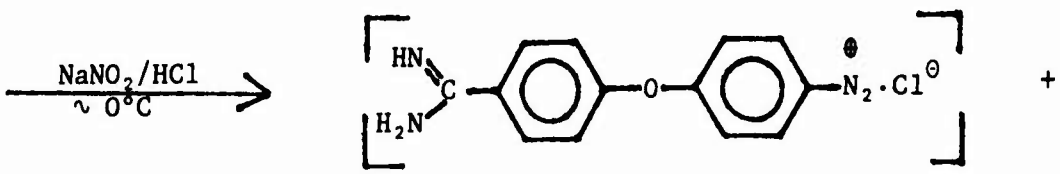
3, SNL-115, BL08401

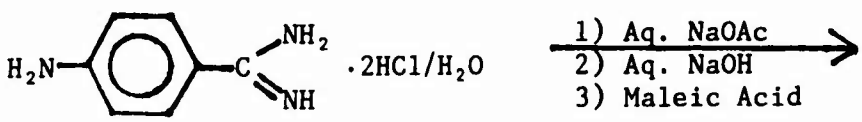
CHART NO. 8

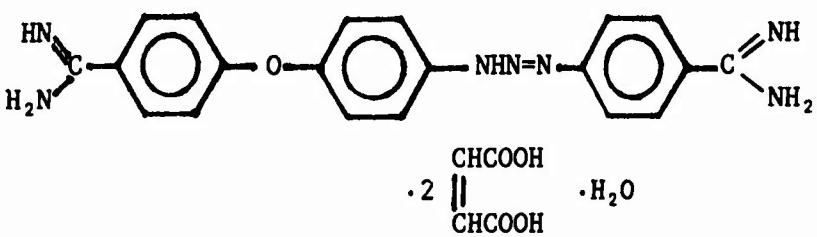
1-(4-AMIDINOPHENYL)-3-[4-(4-AMIDINOPHENOXY)-PHENYL]TRIAZENE DIMALEATE MONOHYDRATE (SNL-116, BL09533)



1







2, SNL-116, BL09533

Alternative Procedure

Initially, SNL-116 was prepared by coupling the diazonium salt of commercially-available 4-aminobenzamidine with aminophenoxy-benzamidine (1, Chart No. 8). However, due to thelow solubility of compound 1, the yield of the target triazenoamidine 2 was very low and the procedure shown in Chart No. 8 proved to be clearly superior. the products obtained by both procedures were identical (21).

3.9 1-(4-Methoxyphenoxy-4-phenyl)-1-(4-methoxyphenyl)-3-amidoxime-prop-1-ene Maleate (SNL-117, BL09524, WR 254729)

The reaction sequence used for the preparation of the title target compound is shown in Chart No. 9. This compound is directed primarily at the refractory T. cruzi (Chagas disease).

4-Cyano-4'-methoxydiphenyl ether (1) was prepared from 4-methoxyphenol and 4-fluorobenzonitrile using a known procedure (22). The Grignard reagent prepared from 4-bromoanisole was allowed to react with the nitrile 1. The intermediate adduct (not shown) was treated with sulfuric acid to give the benzophenone 2. Treatment of the latter with acetonitrile in the presence of sodium amide gave the cyanohydrin 3, an oily intermediate which was used directly in the next step.

Dehydration of the cyanohydrin 3 (P_2O_5), followed by isomerization (xylene, iodine) gave pure cis (E) isomer 4. This was treated with hydroxylamine andd gave the crystalline amidoxime free base which was converted to the maleate salt 5 (SNL-117).

3.10 8-[(6-Amidoximinohexyl)amino]-6-methoxy-4-methylquinoline Succinate (SNL-118, BL12503, 254959)

3.11 8-[(6-Amidinohexyl)amino]-6-methoxy-4-methylquinoline Succinate (SNL-119, BL12790, WR 254985)

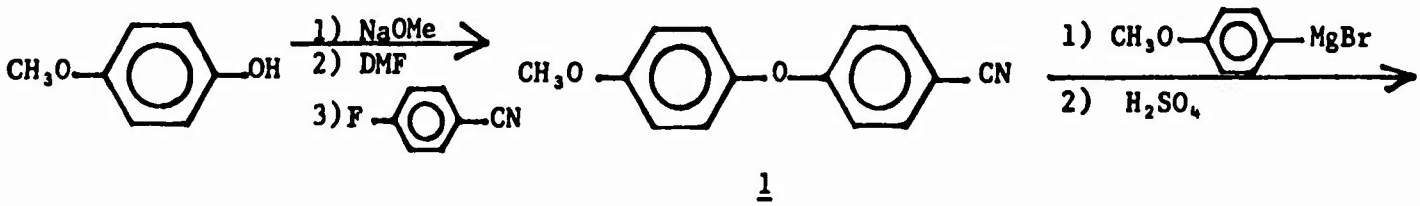
The two target compounds were prepared by the three-step sequence shown in Chart No. 10.

8-Amino-6-methoxy-4-methylquinoline, available in-house from Walter Reed antimalarial preparative work, was treated with 7-bromo-heptanonitrile in the presence of diisopropyl ethylamine to give the intermediate 8-(6-cyanohexyl)aminoquinoline 1 (75%). The nitrile 1 was converted to the amidoxime 2 (64%), isolated as the succinate salt. A 5.0 g sample was shipped to Walter Reed on December 2, 1985 as Code No. KW-08-188, BN BL12503.

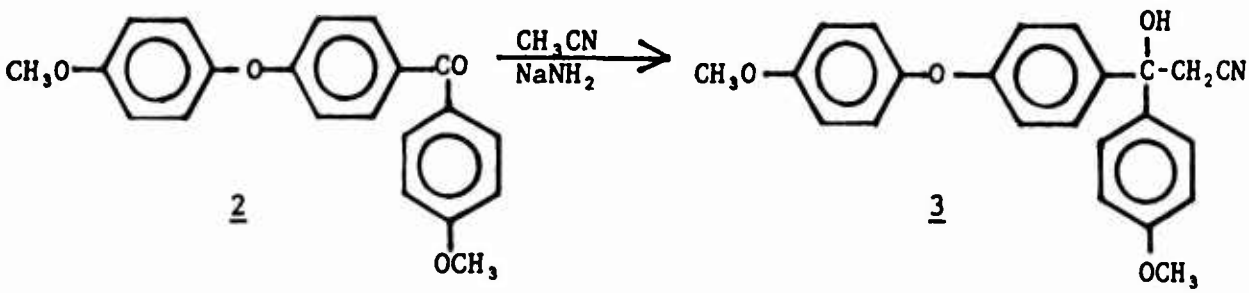
The amidoxime 2 was reduced with hydrogen and Raney nickel catalyst to afford the amidine 3 (65%), also isolated as the succinate salt. A 6.0 g sample was shipped to Walter Reed on January 8, 1986 as Code No. KW-08-211B, BN BL12790.

CHART NO. 9

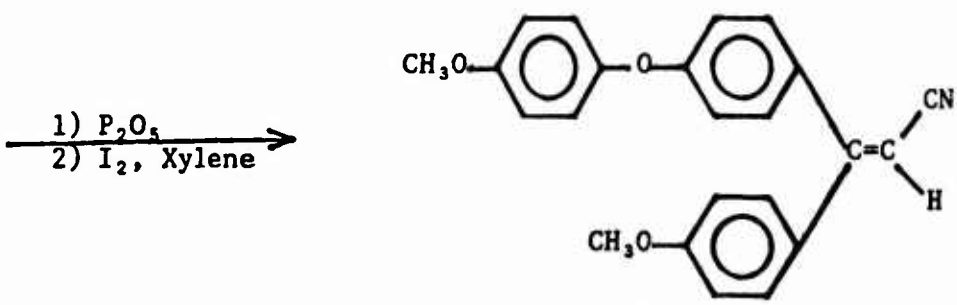
1-(4-METHOXYPHENOXY-4-PHENYL)-1-(4-METHOXYPHENYL)-3-AMIDOXIME-PROP-1-ENE MALEATE (SNL-117, BL09524)



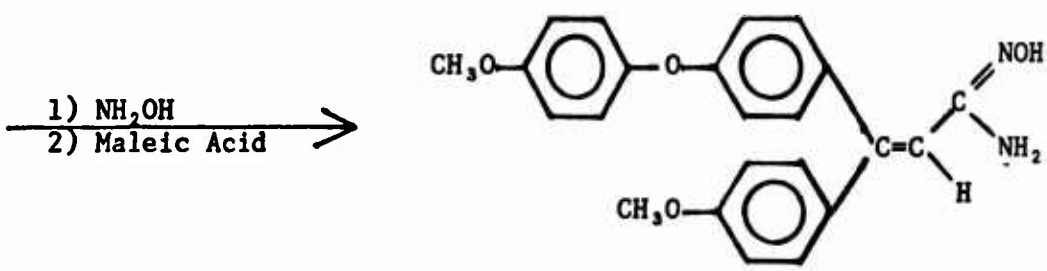
1



2 3



4

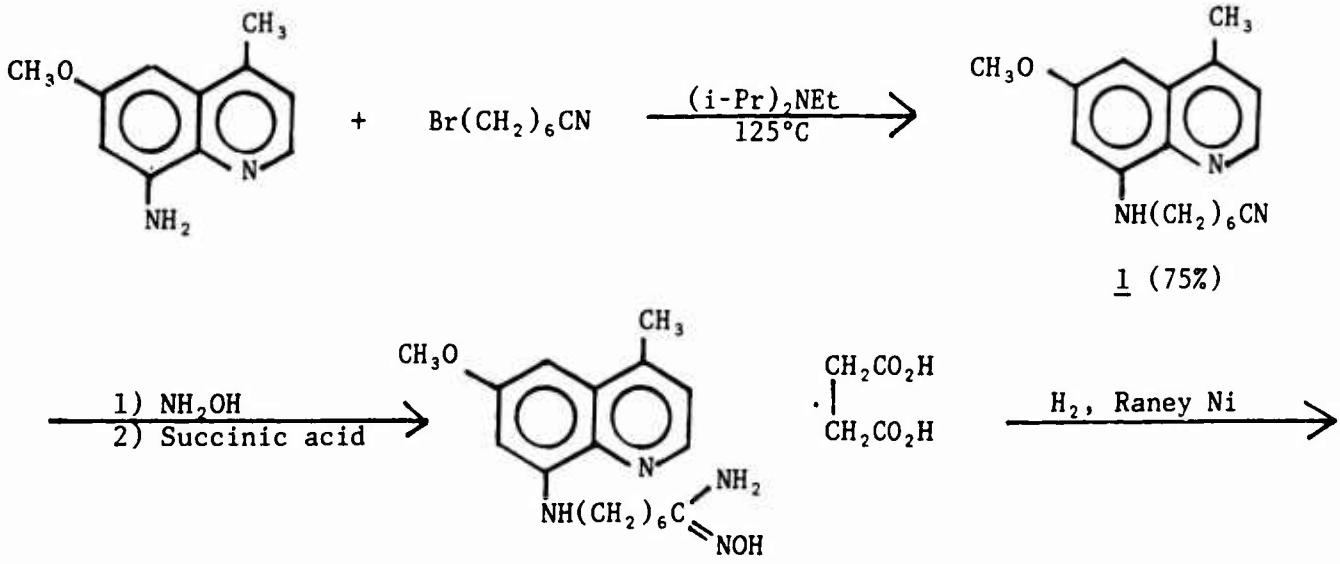


5, SNL-117

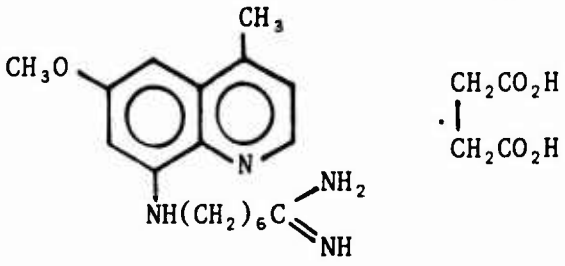
CHART NO. 10

8-[(6-AMIDOXIMINOHEXYL)AMINO]-6-METHOXY-4-METHYLQUINOLINE SUCCINATE (SNL-118; BN BL12503)

8-[(6-AMIDINOHEXYL)AMINO]-6-METHOXY-4-METHYLQUINOLINE SUCCINATE (SNL-119; BN BL12790)



2, SNL-118 (64%); BN BL12503
KW-08-188



3, SNL-119 (65%); BN BL12790
KW-08-211B

3.12 1-(4-Methoxyphenyl)-1-(4'-methoxy-4-biphenylyl)-3-dimethylaminoprop-1-ene Hydrochloride (SNL-120, BL18247, WR 255426)

The five-step sequence to the title compound is shown in Chart No. 11. While the Wellcome Laboratory workers prepared some 130 analogs (3), this 4'-methoxybiphenyl-4-methoxyphenyl analog SNL-120 was selected, in part, because it was not reported by them.

In general, the sequence followed the procedures used by Wellcome workers (8). The first step is a fairly conventional Friedel Craft reaction except that the alkylation of 4-methoxybiphenyl with 4-methoxybenzoyl chloride gave various by-products. This complicated the workup and led to a low yield of the intermediate diaryl ketone 1 (17-19%). [Even in the case where benzene was acylated with 4-methoxybiphenoyl chloride the yields were low (23), although Johnson et al. (24) in a related reaction reported a 62% yield of pure product in the treatment of 4-methoxybiphenyl with acetyl chloride to form 4-(4-methoxyphenyl)acetophenone].

Treatment of intermediate 1 with acetonitrile in the presence of sodamide gave an acceptable yield of the 3-hydroxypropionitrile 2 (82%) as described earlier for a diphenyl ether analog ((13) p. 44). Reduction of intermediate 2 with lithium aluminum hydride gave the 3-hydroxypropyl amine 3 (84%) which was dehydrated readily with mixed acids to the allylic amine 4 (80%). Dimethylation of the allylic amine by the Eschweiler-Clark method failed. The newer formaldehyde-cyanoborohydride procedure of Borch and Hassid (14) gave a crude product which required extensive purification to give the target diaryl dimethylaminomethyl ethylene 5 (23%). A 4.5 g sample was shipped January 23, 1986 as Code No. DJD-06-210, BL18247.

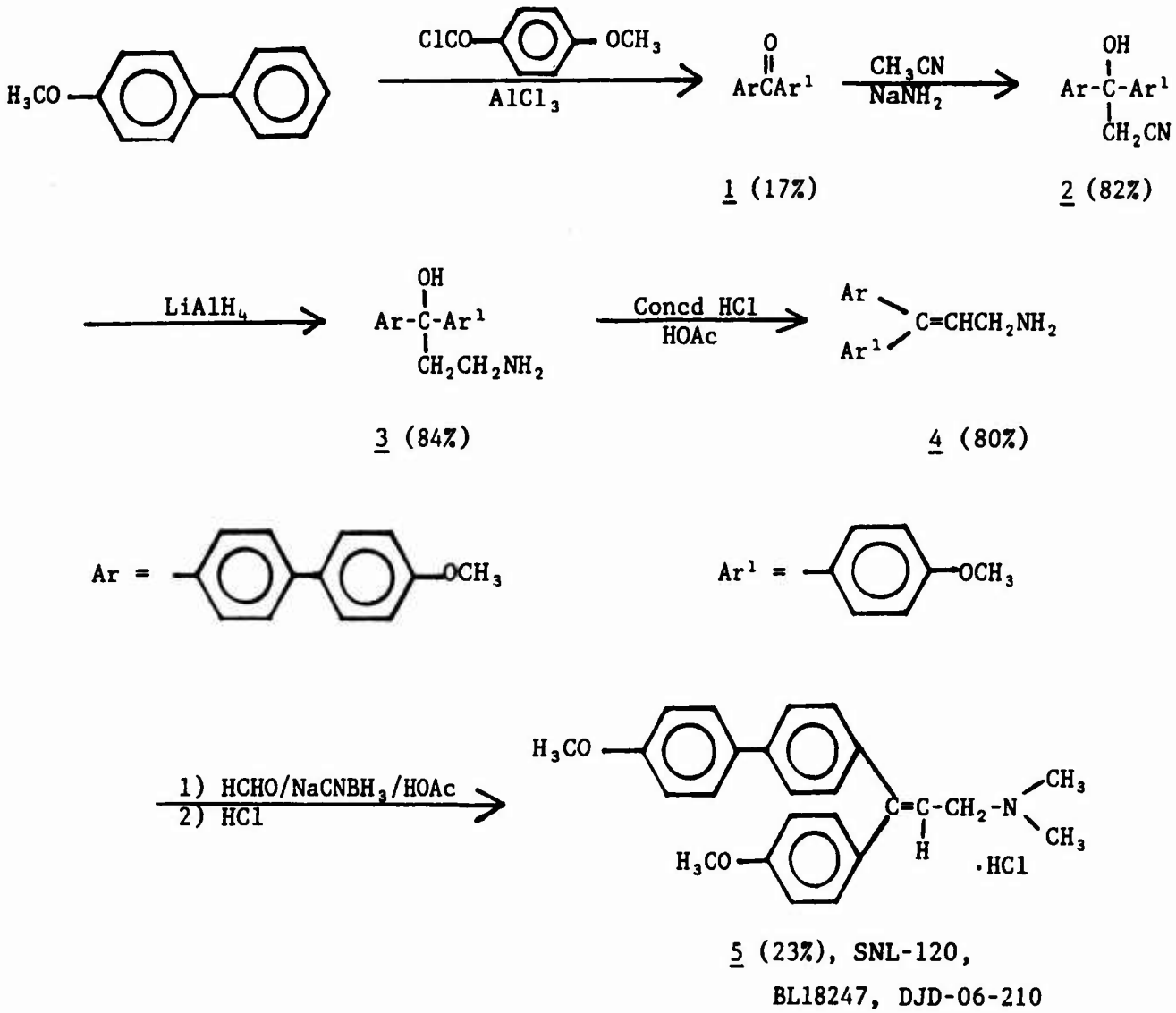
3.13 1-(4'-Methoxy-4-biphenylyl)-1-(4-methoxyphenyl)-2-amidoximinoethylene Maleate (SNL-121, BK40799, WR 255566)

The three-step reaction sequence used for the preparation of the title compound is shown in Chart No. 12.

3-Hydroxy-3-(4'-methoxy-4-biphenylyl)-3-(4-methoxyphenyl)-propionitrile, available from the synthesis of SNL-120, was dehydrated using phosphorous pentoxide to give the acrylonitrile 1. This was treated with hydroxylamine using the standard procedure to afford the amidoxime 2 as a free base. Treatment of the free base with maleic acid gave the target maleate salt 2. A 5.0 g sample was shipped to WRAIR March 31, 1986 as Code No. AM-04-28.

CHART NO. 11

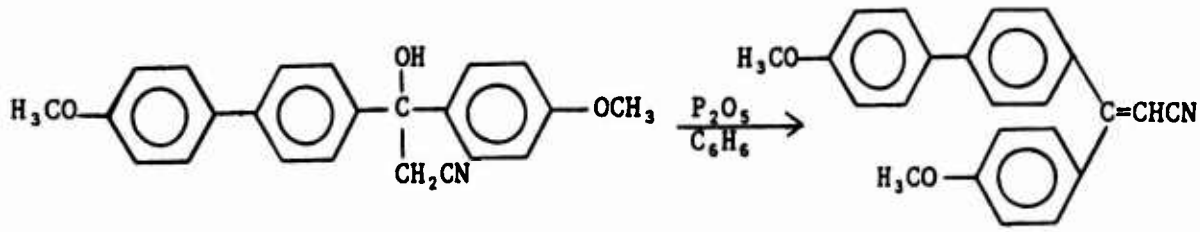
1-(4-METHOXYPHENYL)-1-(4'-METHOXY-4-BIPHENYLYL)-
3-DIMETHYLAMINOPROP-1-ENE HYDROCHLORIDE (SNL-120, BN BL18247)



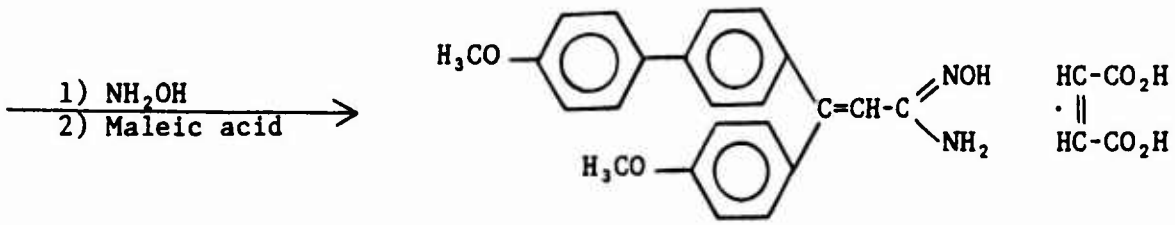
5 (23%), SNL-120,
BL18247, DJD-06-210

CHART NO. 12

1-(4'-METHOXY-4-BIPHENYLYL)-1-(4-METHOXYPHENYL)-2-AMIDOXIMINOETHYLENE MALEATE (SNL-121, BK40799)



(Compound 2, Chart No. 2) 1 (80%)



2, SNL-121, BK40799,
AM-04-28

Yields: Free base: 37% from 1
Maleate salt 2: 69% from 2, free base

3.14 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethyl-phenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-122, BL19333, WR 255593)

3.15 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethyl-phenyl)-3-aminoprop-1-ene Maleate (SNL-123, BL19324, WR 255594)

The six-step sequence to both of the title compounds is shown in Chart No. 13.

3-Trifluoromethylphenol potassium salt was treated with 4-fluorobenzaldehyde to afford intermediate benzaldehyde 1. The aldehyde 1 was treated with 4-trifluoromethylphenyl magnesium bromide to give the corresponding carbinol as a thick oil. The carbinol was oxidized with sodium dichromate to the corresponding benzophenone 2.

Using the procedure developed earlier ((13) p. 44) in this laboratory, intermediate 2 was condensed with acetonitrile to give the hydroxypropionitrile 3. The latter was reduced with lithium aluminum hydride to give the 3-hydroxypropylamine 4 which was dehydrated with mixed acids to the allylic amine 5. A portion of this was converted to the maleate salt 5a, SNL-123 and submitted as Code No. DJD-06-270, BL19324, 5.0 g. The balance of the allylic amine 5 was dimethylated using the formaldehyde-cyanoborohydride procedure ((1) p. 24) to give the target dimethylamine 6 as a free base. This was treated with maleic acid to yield the target maleate 6, SNL-122, submitted as Code No. DJD-06-270, BL19333, 7.5 g. Both of the targets were submitted April 14, 1986.

3.16 1-(3'-Trifluoromethylphenoxy-4-phenyl)-1-(4-trifluoromethyl-phenyl)-2-amidoximinoethylene Maleate (SNL-124, BL19315, WR 255595)

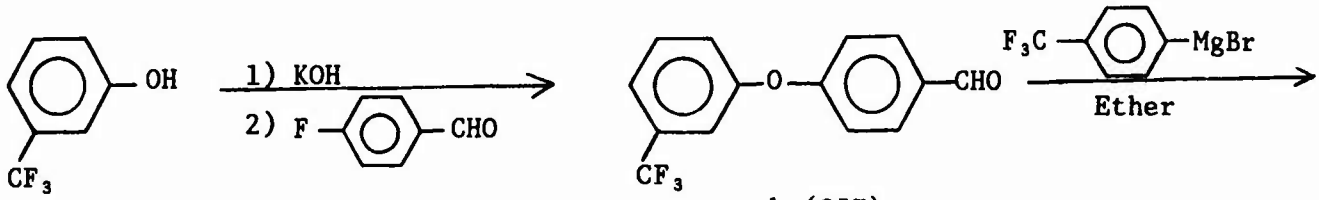
The target compound SNL-124 was prepared using the sequence shown in Chart No. 14.

Hydroxypropionitrile (compound 3, Chart No. 4), prepared according to the procedures described above in sections 3.14 and 3.15, was dehydrated using phosphorus pentoxide to give the acrylonitrile 1. Treatment of 1 with hydroxylamine afforded the amidoxime free base which was converted to the target maleate salt 2, SNL-124, BL19315. A 5.0 g sample was submitted April 14, 1986 as Code No. RK-04-154

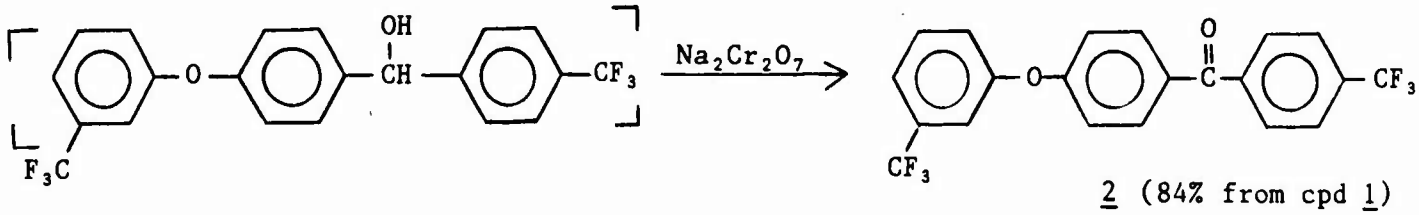
CHART NO. 13

1-(3'-TRIFLUOROMETHYLPHENOXY-4-PHENYL)-1-(4-TRIFLUOROMETHYLPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (6, SNL-122, BL19333)

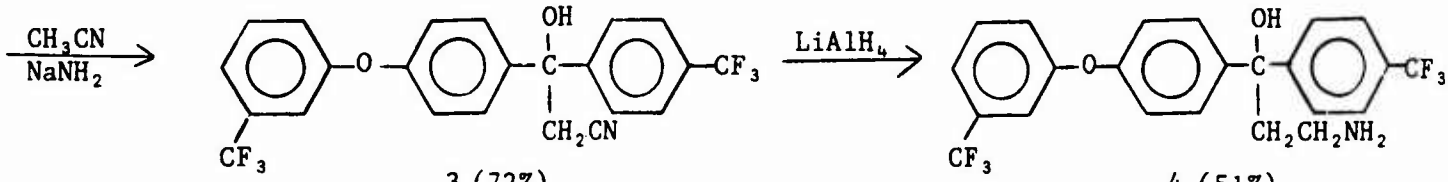
1-(3'-TRIFLUOROMETHYLPHENOXY-4-PHENYL)-1-(4-TRIFLUOROMETHYLPHENYL)-3-AMINOPROP-1-ENE MALEATE (5a, SNL-123, BL19324)



1 (85%)

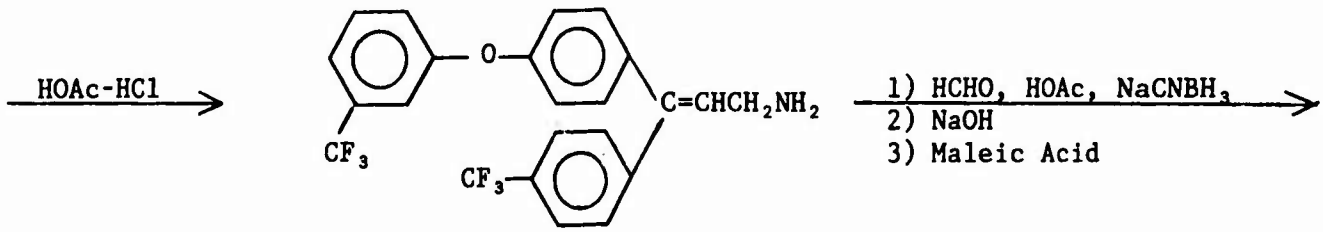


2 (84% from cpd 1)

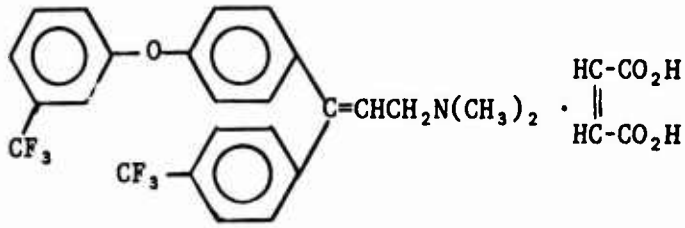


3 (72%)

4 (51%)



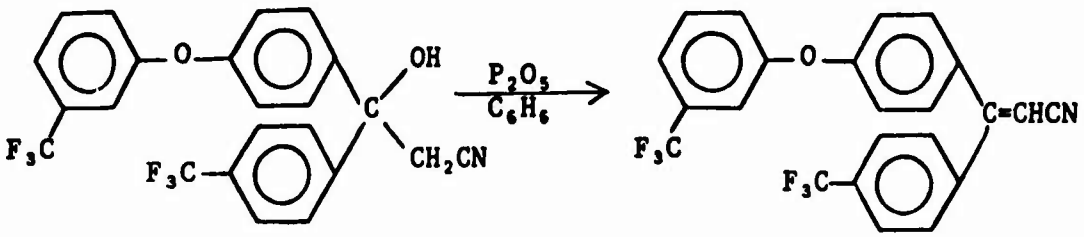
5 Free Base, 79% from 4
5a Maleate Salt, SNL-123
BL19324, DJD-06-270, Yield: 93% from 5 free base.



6 SNL-122, BL19333, DJD-06-268
Yields: 44% from 5, free base; 88% from 6 free base.

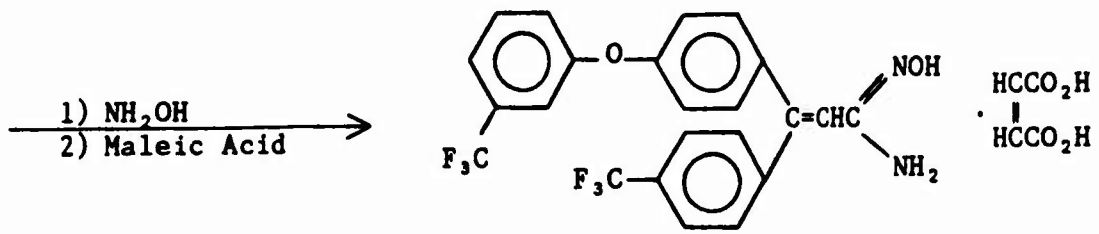
CHART NO. 14

1-(3'-TRIFLUOROMETHYLPHENOXY-4-PHENYL)-1-(4-TRIFLUOROMETHYLPHENYL)-2-AMIDOXIMINOETHYLENE MALEATE (SNL-124, BL19315)



Compound 3 from Chart No. 4

1 (syrup)



2, SNL-124, BL19315, RK-04-154
Yield: 44% from the starting propionitrile.

3.17 Bis(4-methylthiophenyl)-3-dimethylaminoprop-1-ene Maleate (6, SNL-125, BL20336, WR 255664)

3.18 1-Bis(4-Methylthiophenyl)-3-aminoprop-1-ene Maleate (5a, SNL-126, BL20345, WR 255665)

The six-step reaction sequence to the above target compounds is shown in Chart No. 15.

4-Methylthiobenzoic acid was reacted with phosphorous pentachloride to give the corresponding acid chloride 1. The latter was condensed with thioanisole (Friedel Crafts) to yield bis(4-methylthiophenyl)ketone 2. Condensation of 2 with acetonitrile gave the intermediate hydroxypropionitrile 3 which was reduced ($LiAlH_4$) to the hydroxypropyl amine 4. This intermediate was dehydrated with mixed acids to give the allylic amine 5. A portion of 5 was treated with maleic acid to yield the target maleate salt 5a, SNL-126, BL20345. A 4.0 g sample was submitted May 28, 1986 as Code No. DJD-06-293.

In the final step compound 5, free base, was dimethylated using the standard formaldehyde cyanoborohydride procedure to give the target dimethylamine 6, free base. Treatment of the free base with maleic acid gave the above target maleate salt 6, SNL-125, BL20336, 5 g submitted May 28, 1986 as Code No. DJD-06-288.

3.19 1-Bis(4-methylthiophenyl)-2-amidoximinoethylene Maleate (SNL-127, BL20354, WR 255662)

The two-step reaction sequence is shown in Chart No. 16.

The starting hydroxypropionitrile (compound 3, Chart No. 15) was dehydrated with mixed acids to give the acrylonitrile 1. Using the standard procedure, the nitrile 1 was treated with hydroxylamine to give the amidoxime free base which was converted to the target maleate salt 2, SNL-127, BL20354. A 4.0 g sample was submitted May 28, 1986 ad Code No. DJD-06-295.

3.20 1-(4'-Bromophenoxy-4-phenyl)-1-(4-chlorophenyl)-2-amidoximinoethylene Maleate (SNL-128, BK21780, WR 255784)

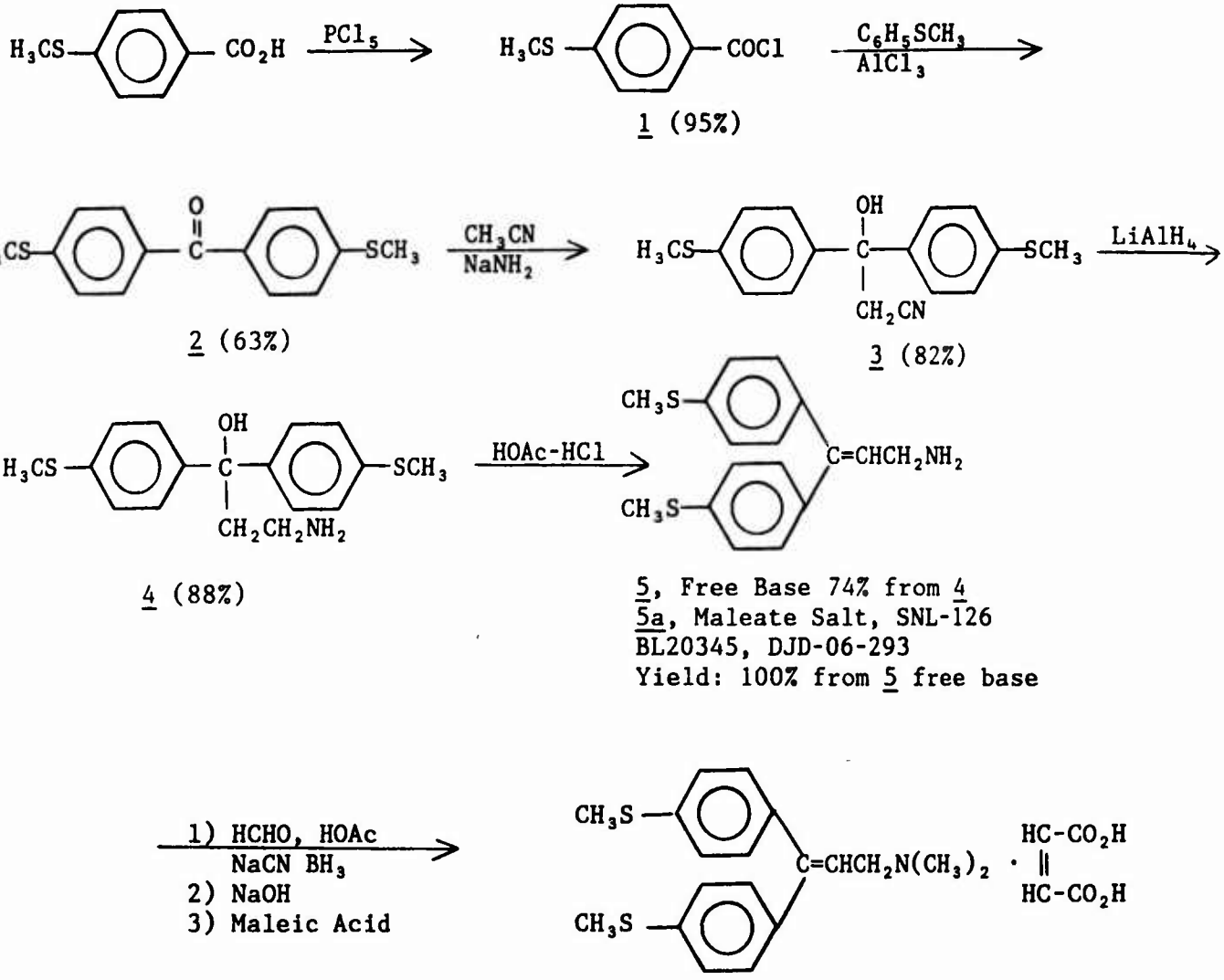
The above target was prepared using the multistep synthesis shown in Chart No. 17. The first three steps are similar to those described above in Sections 3.14 and 3.15 and shown in Chart No. 13.

4'-Bromophenoxy-4-benzaldehyde (1) was prepared by condensing 4-bromophenol with 4-fluorobenzaldehyde. The aldehyde 1 was treated with 4-chlorophenylmagnesium bromide to give the corresponding carbinol (not shown) which was oxidized to give the benzophenone 2. Compound 2 was condensed with acetonitrile to give hydroxypropioni-

CHART NO. 15

1-BIS(4-METHYLTHIOPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (5, SNL-125, BL20336)

1-BIS(4-METHYLTHIOPHENYL)-3-AMINOPROP-1-ENE MALEATE (5a, SNL-126, BL20345)

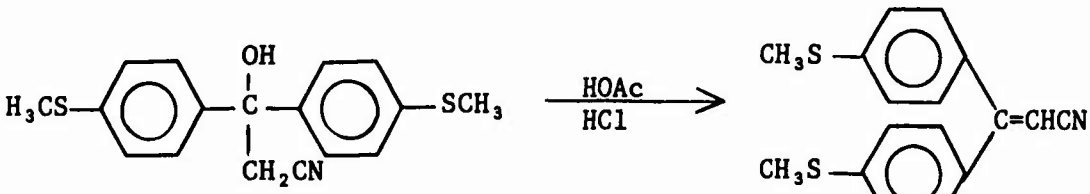


6, Free Base, 56% from 5 free base.
6 Maleate Salt, SNL-125, BL20336
DJD-06-288, Yield: 52% from 5 free base;
93% from 6 free base.

CHART NO. 16

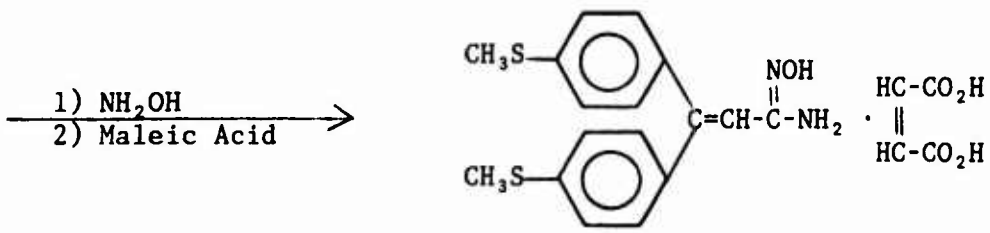
1-BIS(4-METHYLTHIOPHENYL)-2-AMIDOXIMINOETHYLENE

MALEATE (SNL-127, BL20354)



(Compound 3, Chart No. 6)

1 (oil)

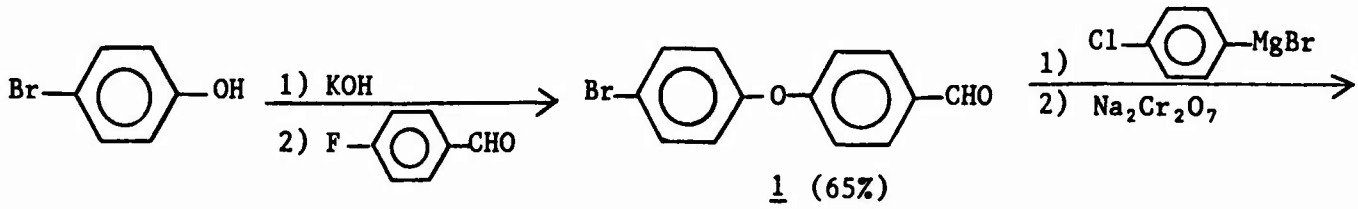


2, Free Base (54% from propionitrile)
2, Maleate salt, SNL-127, BL20354,
DJD-06-295, Yields: 35% from pripionitrile;
64% from 2, free base.

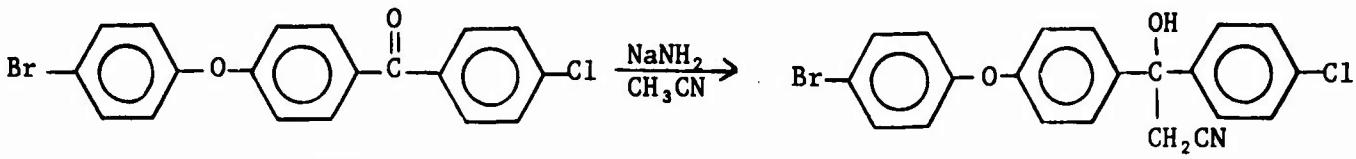
CHART NO. 17

1-(4'-BROMOPHENOXY-4-PHENYL)-1-(4-CHLOROPHENYL)-2-

AMIDOXIMINOETHYLENE MALEATE (SNL-128, BL21780)

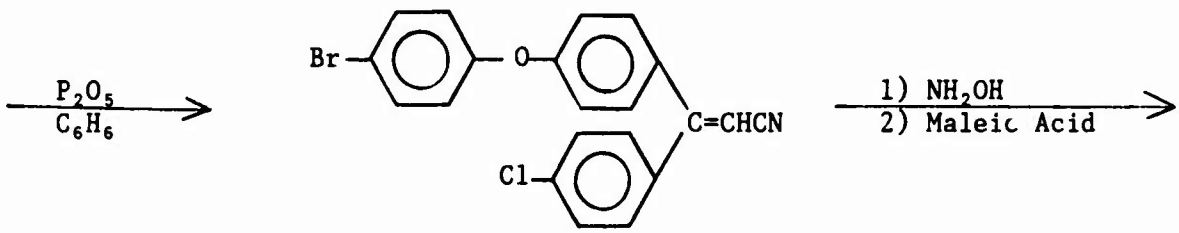


1 (65%)

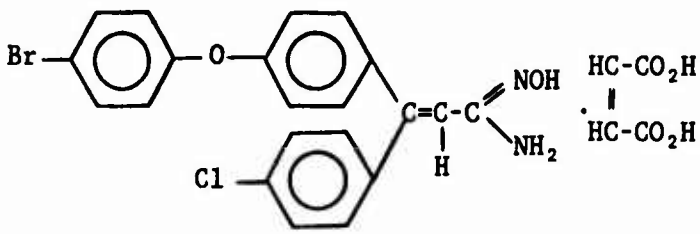


2 (49%)
Intermediate carbinol, 54%
Ketone 2, from carbinol, 91%

3 (61%)



4 (96%, syrup)



5, Free Base, ca. 100% oil.
5, Maleate Salt, 26%, SNL-128, BK21780, DJD-07-27.

trile 3 which was dehydrated readily to afford the diarylacrylo nitrile 4. In the final step, the nitrile 4 was converted to the amidoxime free base which was treated with maleic acid to yield the target amidoxime maleate 5, SNL-128, BK21780. A 7.5 g sample was submitted July 26, 1986 as Code No. DJD-07-27.

3.21 1-(4'-Bromophenoxy-4-phenyl)-1-(4-chlorophenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-129, BL22205, WR 255810)

The two-step reaction sequence is shown in Chart No. 18.

The starting material for the above target was the benzophenone (compound 2, Chart No. 17) which was condensed (Wittig reaction) with(2-dimethylaminoethyl)triphenylphosphonium bromide (Aldrich) to give the corresponding crude dimethylamine derivative 1, free base. This was treated with maleic acid to give the target maleate salt 2, SNL-129, BL22205. A 6.5 g sample was submitted August 7, 1986 as Code No. DJD-07-32.

3.22 1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-3-dimethylaminoprop-1-ene Maleate (2, SNL-130, BL24003, WR 255931)

The target compound, SNL-130, is the maleate salt of compound 353C reported by the Wellcome Research Laboratories to be a powerful trypanocide effective orally against Peruvian strains of T. cruzi (8a).

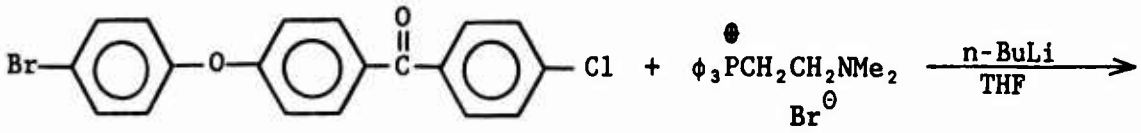
The synthesis route shown in Chart No. 19 is essentially the same as that reported in the literature (8b). The benzophenone 1, obtained by the Friedel Crafts condensation of 4-bromobiphenyl and 4-chlorobenzoyl chloride, was condensed with commercially-available (2-dimethylaminoethyl)triphenylphosphonium bromide (Wittig reaction) to give the target compound 2 as a free base. After extensive purification to remove unreacted benzophenone 1 and other by-products, the free base was converted to the title maleate salt 2 (SNL-130, BL2003). A 4.5 g sample was submitted August 31, 1986 as Code No. DJD-07-44.

3.23 1-(4'-Bromo-4-biphenylyl)-1-(4-chlorophenyl)-2-amidoximinoethylene Maleate (SNL-131, WR 255934)

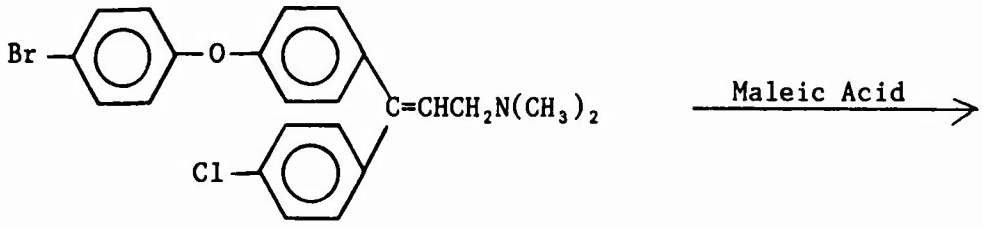
The reaction sequence for the preparation of the title compound is shown in Chart No. 20. 1-(4'-Bromo-4-biphenylyl)-4-chlorobenzophenone (3, p. 48) was treated with acetonitrile in the presence of sodium amide to give the 3-diaryl-3-hydroxypropionitrile 1. This was dehydrated using phosphorus pentoxide to give the corresponding unsaturated nitrile 2. The acrylonitrile 2 was allowed to react with hydroxylamine using the standard procedure to afford the title target amidoxime 3 as a free base which was converted to the target maleate salt 3, SNL-131. A 4.5 g sample of this was shipped to WRAIR on September 12, 1986 as Code No. DJD-07-51, Bottle No. BL24012.

CHART NO. 18

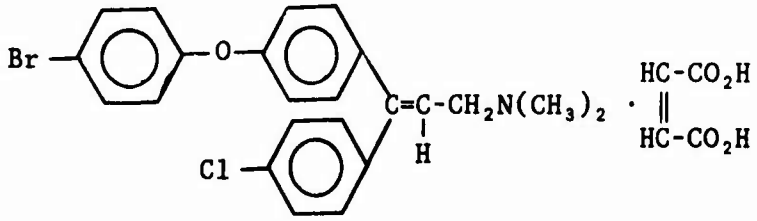
1-(4'-BROMOPHENOXY-4-PHENYL)-1-(4-CHLOROPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (SNL-129, BL22205)



(Compound 2, Chart No. 8)



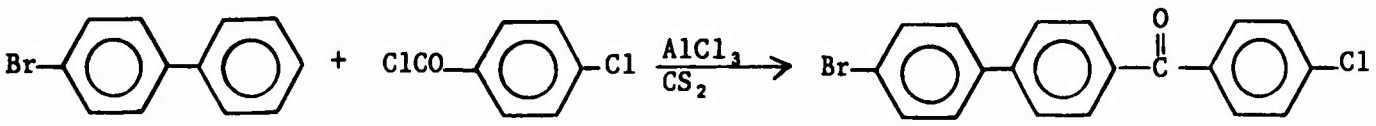
1 Free Base (42%)



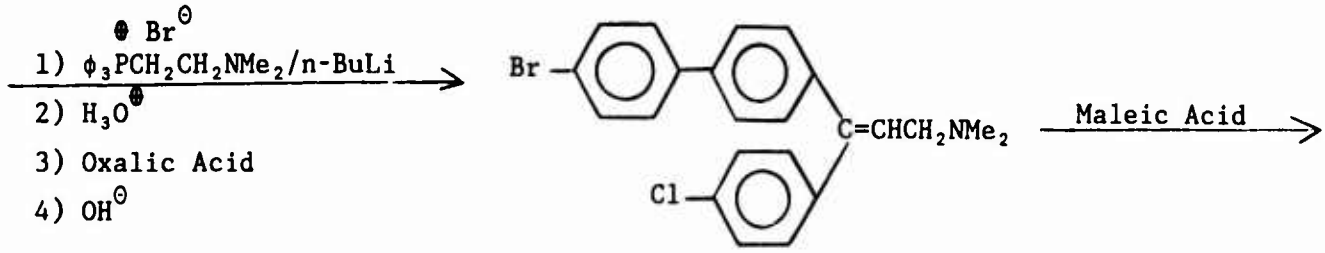
2 Maleate Salt (87%), SNL-129, BL22205, DJD-07-32

CHART NO. 19

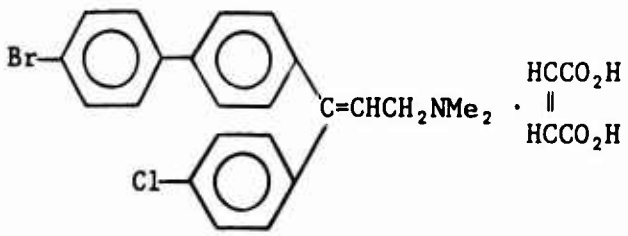
1-(4'-BROMO-4-BIPHENYLYL)-1-(4-CHLOROPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (SNL-130)



1 (58%)



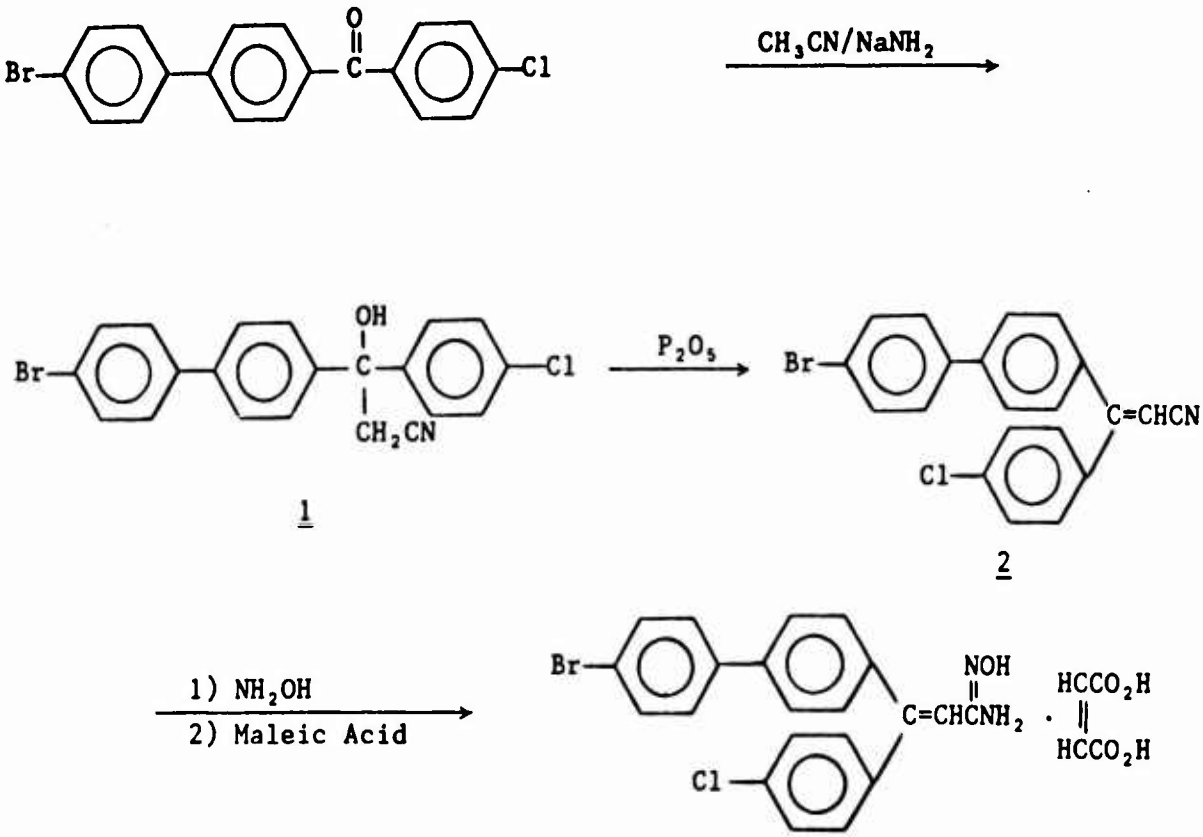
2 (79%), Free base (oil).



2 (97%), SNL-130, BL24003, DJD-07-44.
Wellcome Research Laboratories
Compound 353C as the tartrate salt.

CHART NO. 20

1-(4'-BROMO-4-BIPHENYLYL)-1-(4-CHLOROPHENYL)-2-AMIDOXIMINOETHYLENE MALEATE (SNL-131, WR 255934)



1

2

3 SNL-131, DJD-07-51, WR 255934

3.24 1,1,2-Tris(4-methoxyphenyl)-3-aminoprop-1-ene Maleate (SNL-133, WR 256123)

3.25 1,1,2-Tris(4-methoxyphenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-132, WR 256122)

The four-step sequence to the two title compounds is shown in Chart No. 21. 4-Methoxyphenylacetonitrile was treated with isopropyl magnesium chloride followed by 4,4'-dimethoxybenzophenone to give3-hydroxy-2,3,3-triarylpropionitrile 1 as reported by Kaiser and Hauser for phenylacetonitrile (25). The nitrile group was reduced using a borane-tetrahydrofuran complex to give the 3-hydroxy-2,3,3-triarylpropyl amine 2. Intermediate 2 was dehydrated by heating (steam bath) the compound in an concentrated hydrochloric acid-acetic acid mixture to afford the 2,3,3-triarylallyl amine 3 as a free base. A portion of this free amine was converted to the maleate salt, SNL-133, and a 5.8 g sample was shipped to WRAIR as Code No. DJD-07-66, Bottle No. BL27853, on October 27, 1986.

The balance of the amine 3, free base, was dimethylated using our standard formaldehyde-cyanoborohydride procedure to give the target N,N-dimethylallyl amine 4 as a free base. This was converted to the target maleate salt 4, SNL-132, and a 5 g sample was shipped to WRAIR as Code No. DJD-07-65, Bottle No. BL27862, on October 27, 1986.

3.26 3-Hydroxy-2,3,3-tris(3-trifluoromethylphenyl)propylamine Maleate (SNL-134, WR 256541)

3.27 1,1,2-Tris(3-trifluoromethylphenyl)-3-aminoprop-1-ene Maleate (SNL-136, WR 256540)

3.28 1,1,2-Tris(3-trifluoromethylphenyl)-3-dimethylaminoprop-1-ene Maleate (SNL-135, WR 256539)

The reaction sequence used for the preparation of the above three title compounds is shown in Chart No. 22.

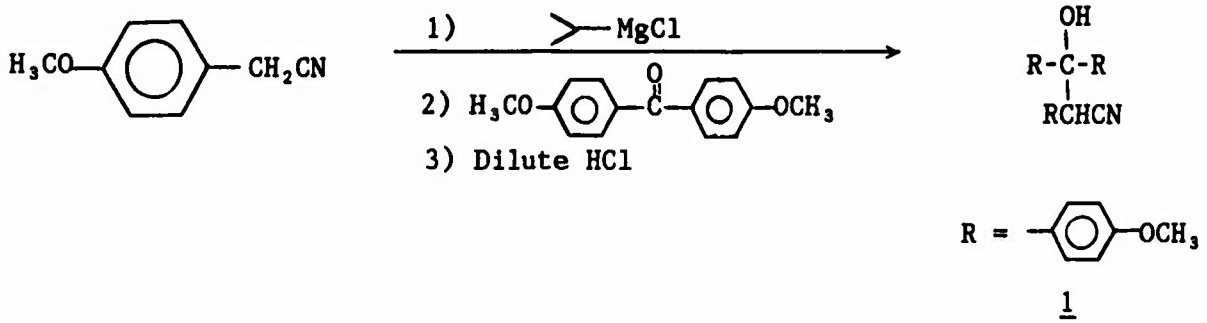
3-Trifluoromethylphenylacetonitrile was treated with isopropyl magnesium chloride followed by the addition of 3,3'-bis(trifluoromethyl)benzophenone to give the 3-hydroxy-2,3,3-triarylpropionitrile 1. The nitrile group was reduced with borane-tetrahydrofuran complex to give the corresponding propyl amine 2 as a free base. A portion of this was treated with maleic acid to afford the target maleate salt SNL-134, and a 3.5 g sample was submitted to WRAIR as Code No. DJD-07-89, Bottle No. BL31768.

The balance of the free base 2 was dehydrated with mixed acids to give the corresponding triarylallyl amine 3 which, after workup, was isolated as the free base. A portion of the free base 3 was converted to the maleate salt, SNL-136. A 4.5 g sample was shipped to WRAIR as Code No. DJD-07-97, Bottle No. BL31759.

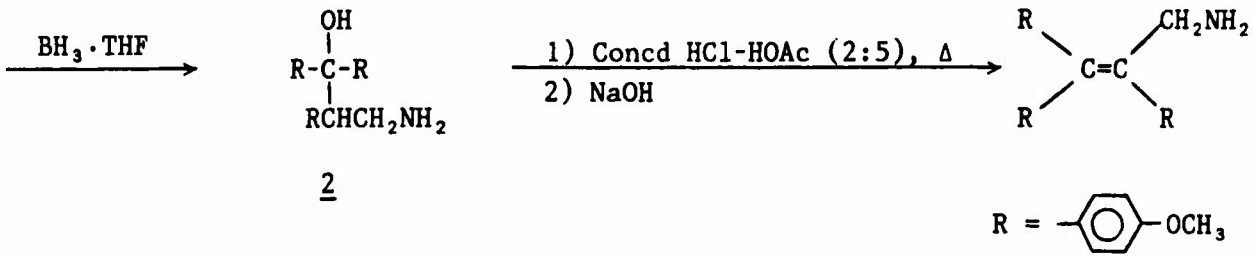
CHART NO. 21

1,1,2-TRIS(4-METHOXYPHENYL)-3-AMINOPROP-1-ENE MALEATE (SNL-133, WR 256123)

1,1,2-TRIS(4-METHOXYPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (SNL-132, WR 256122)



1

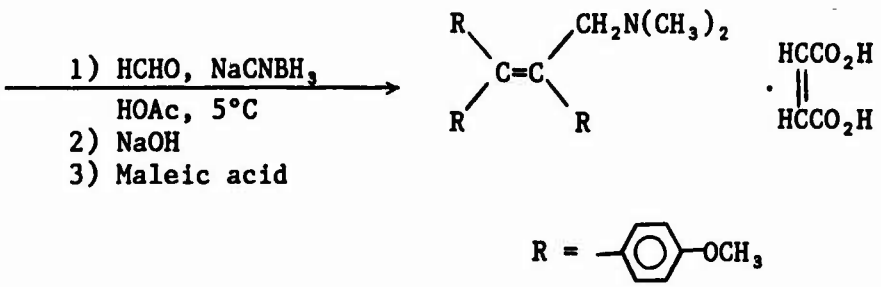


2

3 Free Base

SNL-133, Maleate salt

DJD-07-66, WR 256123



4 Maleate salt

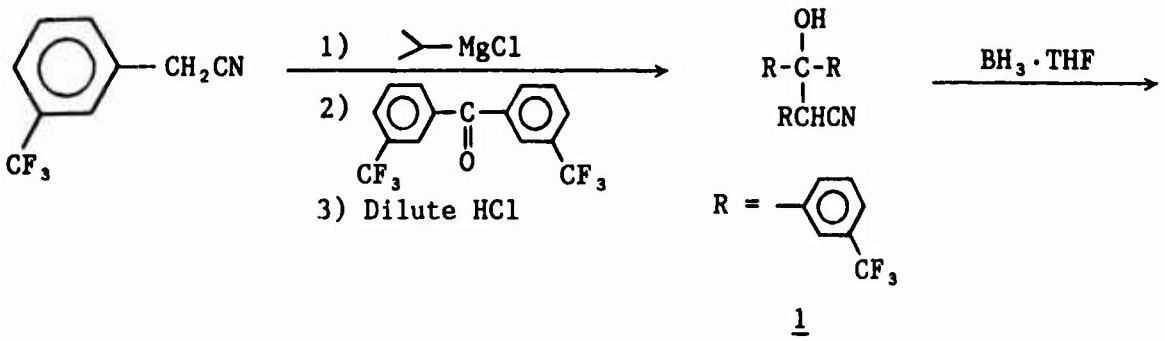
SNL-132, DJD-07-65, WR 256122

CHART NO. 22

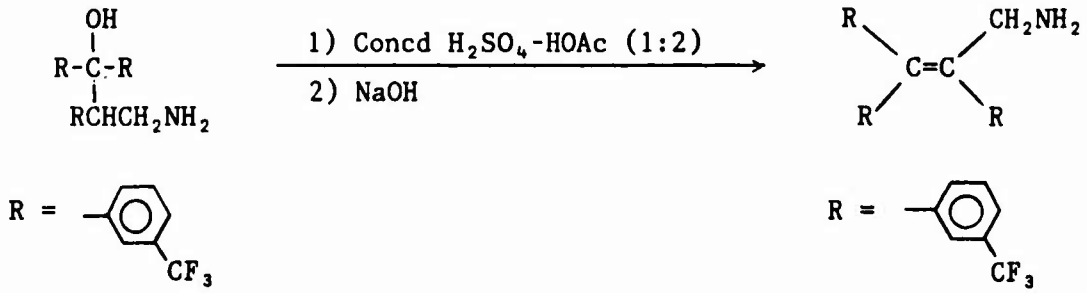
3-HYDROXY-2,3,3-TRIS(3-TRIFLUOROMETHYLPHENYL)PROPYLAMINE MALEATE (SNL-134, WR 256541

1,1,2-TRIS(3-TRIFLUOROMETHYLPHENYL)-3-AMINOPROP-1-ENE MALEATE (SNL-136, WR 256540

1,1,2-TRIS(3-TRIFLUOROMETHYLPHENYL)-3-DIMETHYLAMINOPROP-1-ENE MALEATE (SNL-135, WR 256539)



1



2 Free Base

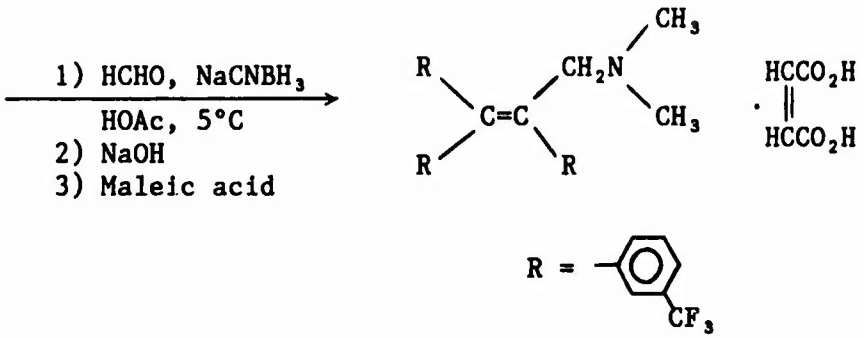
SNL-134, Maleate salt

DJD-07-89, WR 256541

3 Free Base

SNL-136, Maleate salt

DJD-07-97, WR 256540



4 SNL-135, DJD-07-94, WR 256539

The remaining free amine 3 was dimethylated with formaldehyde-cyanoborohydride in the usual manner to afford the target triaryl-dimethylaminomethyl ethylene 4 as a free base. This was treated with maleic acid to yield the title target maleate salt 4, SNL-135. Of this a 6.5 g sample was submitted to WRAIR as Code NO. DJD-07-94, Bottle No. BL31777.

The above three target compounds, SNL-134, SNL-136 and SNL-135 were shipped to WRAIR on December 29, 1986.

1-(2-Pyridyl)-1-[6-(4-trifluoromethylphenyl)-2-trifluoro-methyl-4-pyridyl]-3-dimethylaminoprop-1-ene Maleate

3.29 SNL-137; Isomer A, WR 256599

3.30 SNL-138; Isomer B, WR 256600

The reaction sequence used for the preparation of both isomers is shown in Chart No. 23.

Using the Wittig reaction, 2-pyridyl-4-[6-(trifluoromethyl-phenyl)-2-trifluoromethyl]pyridyl ketone (available from an earlier antimalarial contract (26) was condensed with 2-dimethylamino-ethyltriphenylphosphonium bromide to give a mixture of the isomers A and B, SNL-137 and SNL-138 respectively. After purification (chromatography) the oily mixture in anhyd ether was treated with maleic acid in methanol. Isomer A, being less-soluble, was separated by filtration. A 4.5 g sample of isomer A maleate salt, SNL-137, was shipped to WRAIR on January 20, 1987 as Code No. DJD-07-107, Bottle No. BL33137.

After the separation of isomer A, the mother liquors were evaporated to near dryness. The residue was triturate with ether to afford crystalline isomer B, SNL-138. An 8.5 g sample was shipped to WRAIR on January 20, 1987 as Code No. DJD-07-107A, Bottle No. BL33146.

3.31 1-(2-Pyridyl)-1-[6-(4-trifluoromethylphenyl)-2-trifluoromethyl-4-pyridyl]-2-amidoximinoethylene Maleate (SNL-139, WR 256782)

The sequence to the title amidoxime is shown in Chart No. 24.

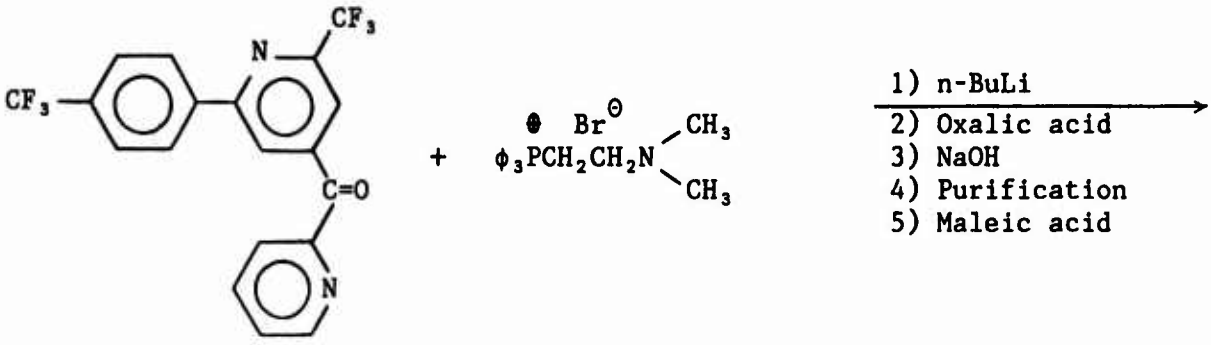
Commercially-available cyanomethyltriphenylphosphonium chloride in dichloromethane was treated with 2 N aq. sodium hydroxide to provide the starting Wittig reagent, triphenylphosphoranylidene-acetonitrile (1). The phosphorane 1 in dichloromethane was allowed to react with the dipyridyl ketone (26; p. 57; purified as described in combined sections 5.7 and 5.8). The resulting acrylonitrile 2 was purified (chromatography) to give an oil which was treated with hydroxylamine hydrochloride and sodium bicarbonate. Workup gave the crude title amidoxime 3 as a free base which was purified via the

CHART NO. 23

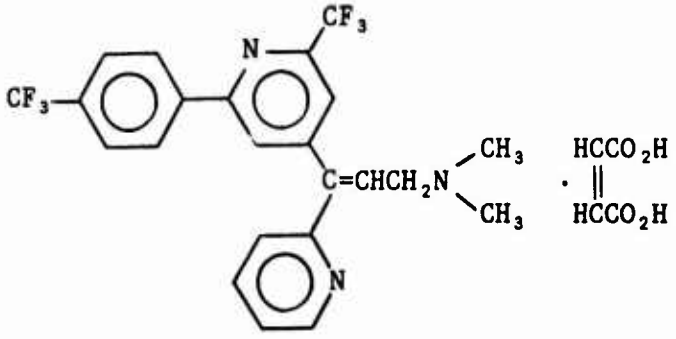
1-(2-PYRIDYL)-1-[6-(4-TRIFLUOROMETHYLPHENYL)-2-TRIFLUOROMETHYL-4-PYRIDYL]-3-DIMETHYLAMINOPROP-1-ENE MALEATE

SNL-137, Isomer A, WR 256599

SNL-138, Isomer B, WR 256600



Ref. 8, p. 57

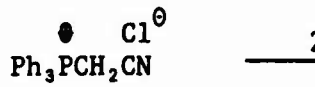


SNL-137, Isomer A, DJD-07-107, WR 256599

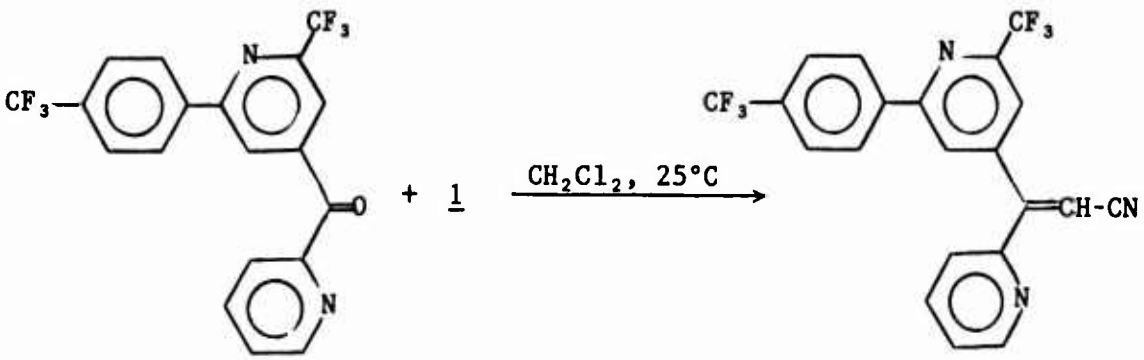
SNL-138, Isomer B, DJD-07-107A, WR 256600

CHART NO. 24

1-(2-PYRIDYL)-1-[6-(4-TRIFLUOROMETHYLPHENYL)-2-TRIFLUOROMETHYL-4-PYRIDYL]-2-AMIDOXIMINOETHYLENE MALEATE (SNL-139, WR 256782)

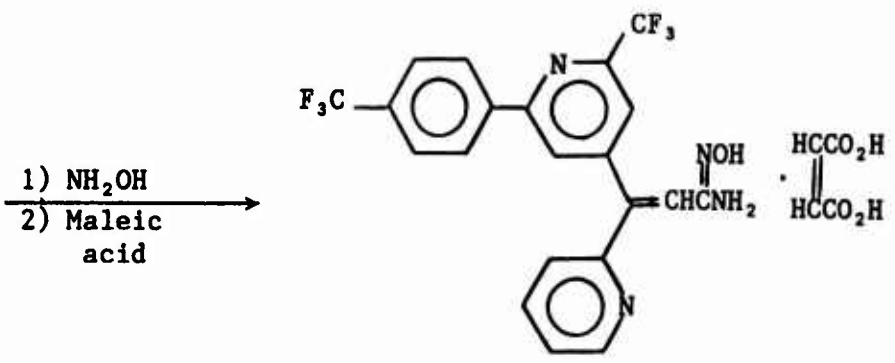


1, Ref. 9



Ref. 8, p. 57

2



3, SNL-139, DJD-07-117, WR 256782

oxalate salt. The free base was regenerated from the oxalate salt and converted to the title target maleate salt 3, SNL-139. A 10 g sample was shipped to WRAIR on March 4, 1987 as Code No. DJD-07-117, Bottle No. BL35828.

3.32 3-Hydroxy-3-[4-(4'-methoxyphenoxy)phenyl]-3-(4-methoxyphenyl)-propylamine Maleate (SNL-140, WR 256780)

3.33 1-[4-(4'-Methoxyphenoxy)phenyl]-1-(4-methoxyphenyl)-3-amino-prop-1-ene Maleate (SNL-142, WR 256779)

3.34 1-[4-(4'-Methoxyphenoxy)phenyl]-1-(4-methoxyphenyl)-3-dimethyl-amino-prop-1-ene Maleate (SNL-141, WR 256781)

The reaction sequence used for the preparation of the above three compounds is shown in Chart No. 25.

The starting 3,3-diaryl-3-hydroxypropionitrile (ref. 2, p. 44) was reduced with LAH to give the 3,3-diaryl-3-hydroxypropyl amine 1 as the free base. A portion of this intermediate was converted to the title maleate salt, SNL-140, a 3.5 g sample of which was shipped to WRAIR on March 4, 1987 as DJD-07-118, Bottle No. BL35837.

The remaining hydroxypropyl amine 1 was dehydrated with mixed acids to give, after workup, the corresponding 3,3-diarylallyl amine 2 as the free base. A portion of this was converted to the maleate salt, SNL-142, and a 5.0 g sample was shipped to WRAIR as Code No. DJD-07-128, Bottle No. BL35855.

The remaining allyl amine 2 free base was dimethylated using the standard formaldehyde-cyanoborohydride method to afford the dimethyl amino derivative 3 as a free base. Treatment with maleic acid afforded the maleate salt 3, SNL-141. A 6.0 g sample of SNL-141 was shipped to WRAIR as Code No. DJD-07-123, Bottle No. BL35846. All three maleate salts, SNL-140, 142 and 141, were shipped on March 4, 1987.

3.35 8-[(4-Amino-1-methylbutyl)amino]-4-methyl-2,5,6-trimethoxy-quinoline Hemisuccinate (SNL-143, WR 257305)

The sequence to the title 2,5-dimethoxy-4-methylprimaquine is shown in Chart No. 26.

The starting 8-amino-4-methyl-2,5,6-trimethoxyquinoline in crude form was available from an earlier program (1). This material was purified to give pure product with acceptable analysis and melting point (1, p. 38).

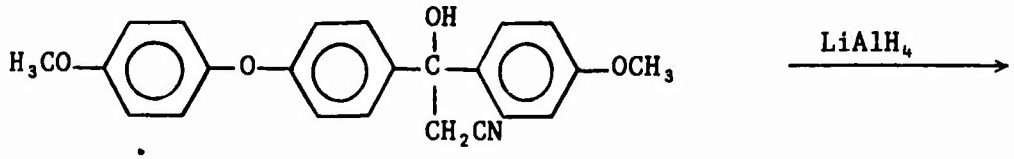
The pure product was condensed with the side-chain reagent 4-iodophthalimidopentane in acetonitrile to give the blocked

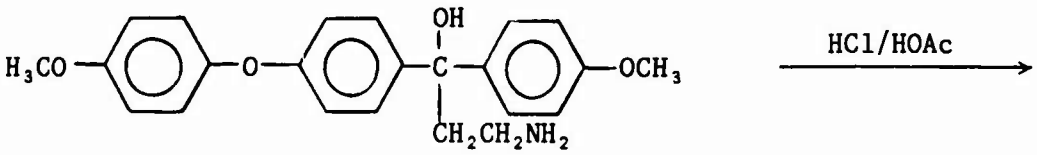
CHART NO. 25

3-HYDROXY-3-[4-(4'-METHOXYPHENOXY)PHENYL]-3-(4-METHOXYPHENYL) PROPYLAMINE MALEATE 1 (SNL-140, WR 256780)

1-[4-(4'-METHOXYPHENOXY)PHENYL]-1-(4-METHOXYPHENYL)-3-AMINOPROP-1-ENE MALEATE 2 (SNL-142, WR 256779)

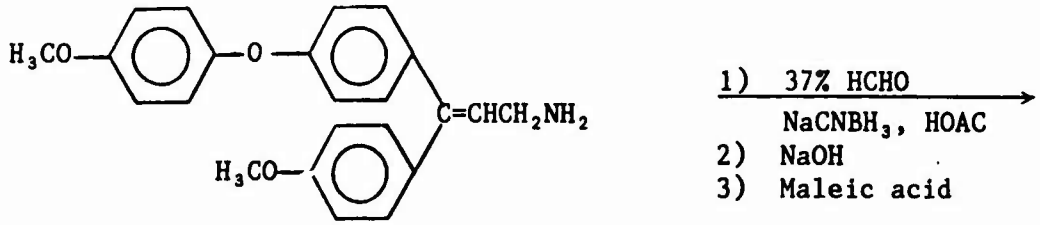
1-[4-(4'-METHOXYPHENOXY)PHENYL]-1-(4-METHOXYPHENYL)-3-DIMETHYL-AMINOPROP-1-ENE MALEATE 3 (SNL-141, WR 256781)





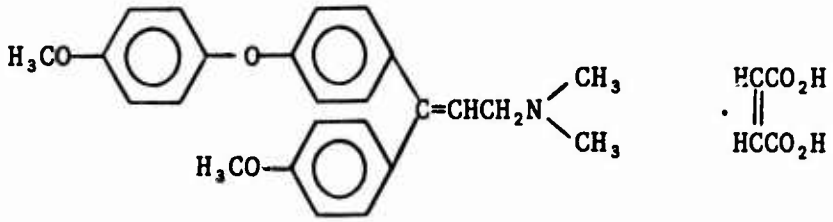
1, Free base

SNL-140, Maleate salt, DJD-07-118, WR 256780



2, Free base

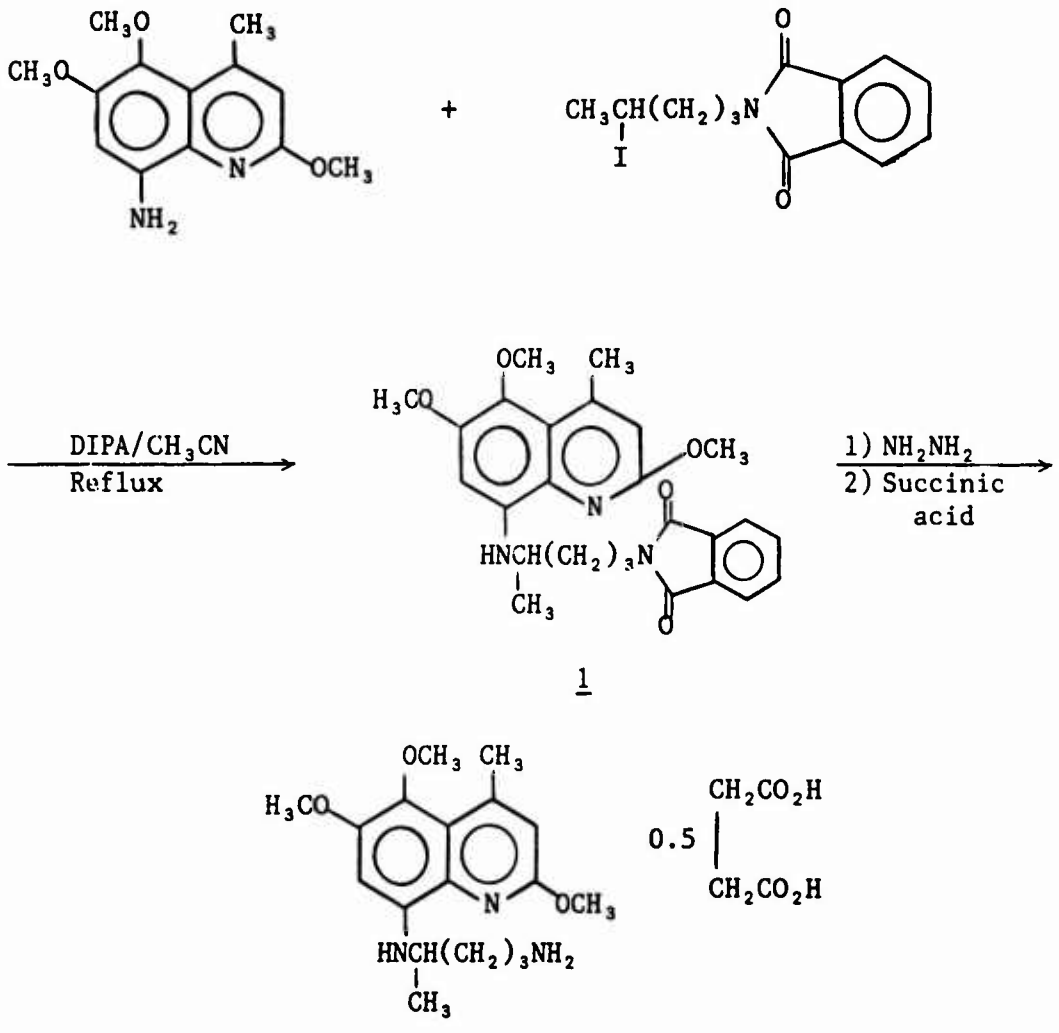
SNL-142, Maleate salt, DJD-07-128, WR 256779



3, SNL-141, Maleate salt, DJD-07-123, WR 256781

CHART NO. 26

8-[(4-AMINO-1-METHYLBUTYL)AMINO]-4-METHYL-2,5,6-TRIMETHOXY-QUINOLINE HEMISUCCINATE (SNL-143, WR 257305)



1

2, Hemisuccinate salt

SNL-143, DJD-07-153, WR 257305

side-chain 8-amiloquinoline 1 (62%). The phthalimido group was removed with hydrazine to give, after chromatography, pure title free base (82%). Attempts to prepare a monosuccinate salt in pure form was unsuccessful but the hemisuccinate salt was isolated in pure form in 71% yield from the free base or 58% from the precursor 3. A 5.5 g sample was shipped to WRAIR as Code No. DJD-07-153, on May 21, 1987.

3.36 6-Methoxy-4-methyl-8-[(6-pyrrolidinohexyl)amino]quinoline Dihydrochloride (SNL-144, WR 257566)

The sequence to the title compound is shown in Chart No. 27.

6-Methoxy-4-methyl-8-nitroquinoline was hydrogenated using Raney nickel catalyst to give the corresponding 8-aminoquinoline 1 in 84% yield as described under an earlier contract (27). The 8-aminoquinoline 1 was condensed with 6-bromohexanoyl chloride following a literature procedure (28, Johnson and Werbel, 1983) to give the 8-bromohexanoylaminoquinoline 2 (79%). Intermediate 2 was then condensed with pyrrolidine to give the corresponding 8-(N-pyrrolohexanoylamide 3 (62%). The amide 3 was reduced with LAH to give the title compound free base which was purified and converted to the title dihydrochloride salt 4 (42%). A 5.0 g sample was shipped to WRAIR as Code No. DJD-07-161 on July 14, 1987.

3.37 6-Methoxy-4-methyl-8-[(6-morpholinohexyl)amino]quinoline Dihydrochloride (SNL-145, WR 257680)

As shown in Chart No. 28, 8-(6-bromohexanamido)-6-methoxy-4-methylquinoline (1) was prepared in 79% yield as reported in the literature (28). Intermediate 1 was treated with morpholine to give the corresponding 8-(6-morpholino)hexanamidoquinoline 2 (84%). The amide 2 was reduced with lithium aluminum hydride to give the title compound as a free base. The free base was purified and converted to the title target dihydrochloride salt 3 (45%). A 3.5 g sample was shipped to WRAIR on November 5, 1987 as Code No. DJD-07-214, Bottle No. BL49993.

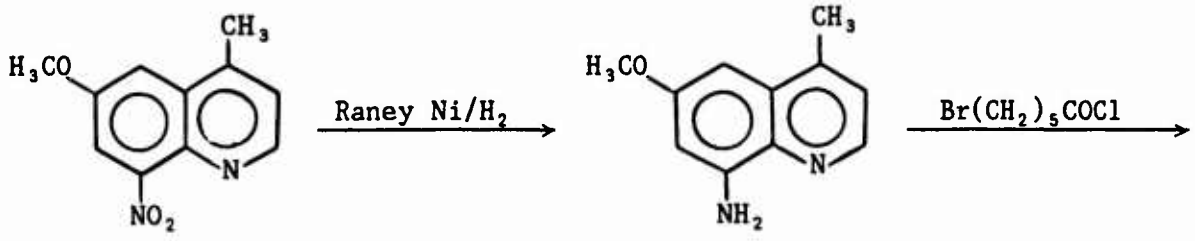
3.38 8-[(6-Diethylaminohexyl)amino]-6-methoxy-4-methoxymethylquinoline Dihydrochloride Monohydrate (SNL-146, WR 257683)

The five-step sequence to the title compound is shown in Chart No. 29.

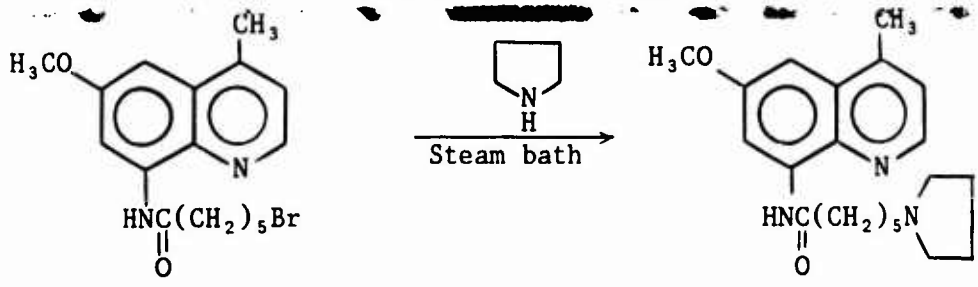
6-Methoxy-4-methyl-8-nitroquinoline was oxidized using selenium dioxide (29) to give the 4-carboxaldehyde 1 (75%) which was reduced with sodium borohydride to afford the carbinol 2 (73%). The carbinol 2 was treated with dimethyl sulfate (phase transfer catalyst) to give the 4-methoxymethyl-8-nitroquinoline 3 (80%). The latter was hydrogenated (using platinum oxide catalyst) to give the corresponding 8-aminoquinoline 4 (ca. 100%). The amine 4 was treated with

CHART NO. 27

6-METHOXY-4-METHYL-8-[(6-PYRROLIDINOHEXYL)AMINO]QUINOLINE DIHYDROCHLORIDE (SNL-144, WR 257566)

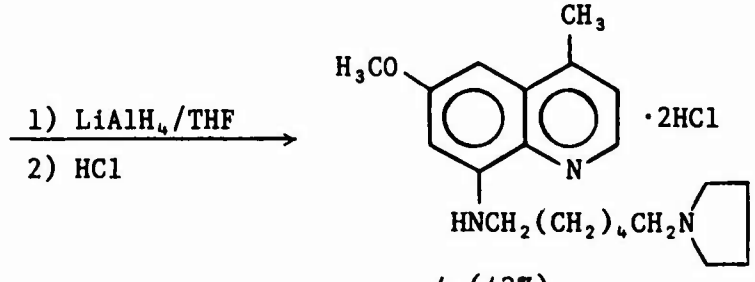


1 (84%)



2 (79%)

3 (62%)

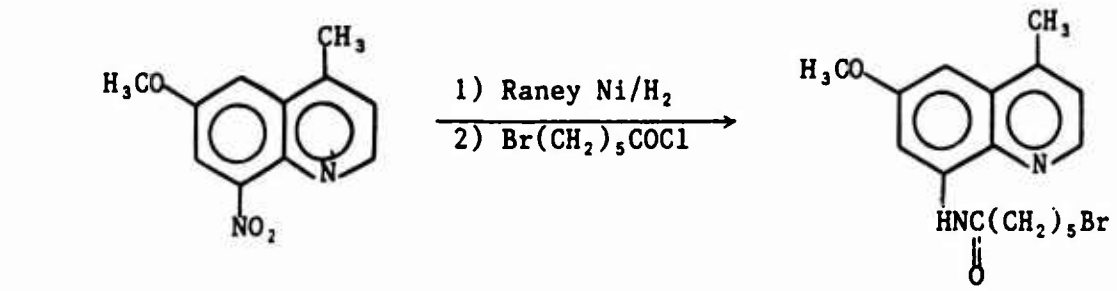


4 (42%)

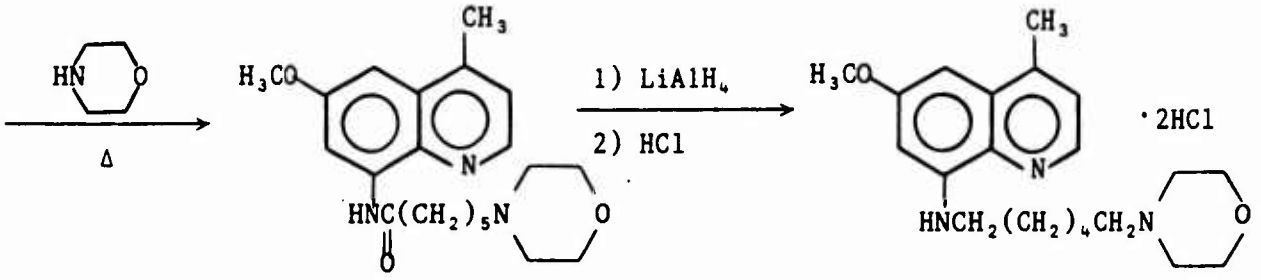
SNL-144, DJD-07-161, WR 257566

CHART NO. 28

6-Methoxy-4-methyl-8-[(6-morpholinohexyl)amino]quinoline Dihydrochloride (SNL 145, WR 257680):



1 (79%)

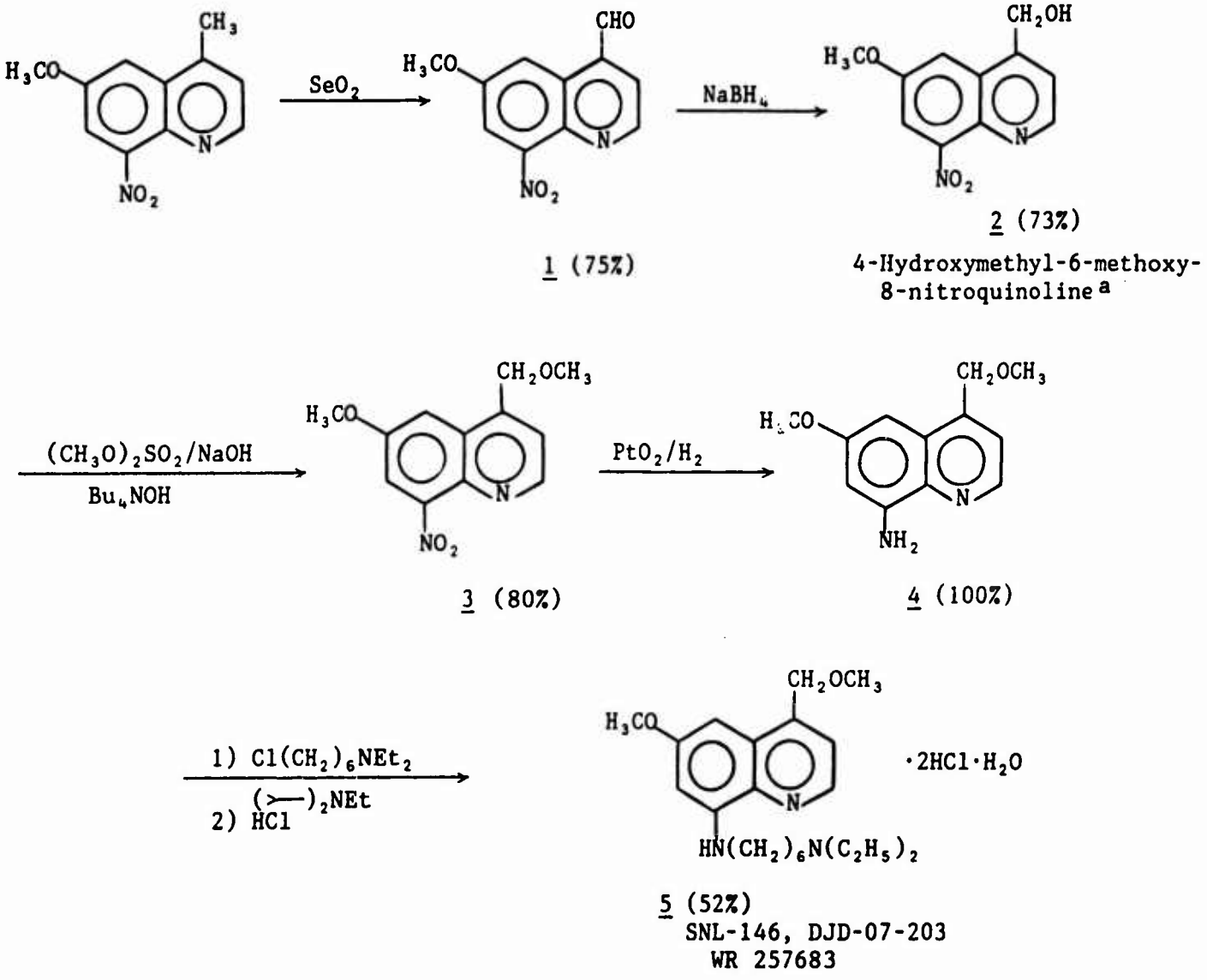


2 (84%)

3 (45%),
SNL-145, DJD-07-214
WR 257680

CHART NO. 29

8-[(6-Diethylaminohexyl)amino]-6-methoxy-4-methoxymethylquinoline Dihydrochloride Monohydrate (SNL 146, WR 257683):



(a) Used also as starting material for target compounds in Chart No. 3.

6-diethylaminohexyl chloride to give the title compound, free base. The latter was purified and converted to the title dihydrochloride salt monohydrate 5 (52%).

A 10.3 g sample was shipped to WRAIR on November 11, 1987 as Code No. DJD-07-203, Bottle No. BL50021.

3.39 8-[(6-Diethylaminohexyl)amino]-4-hydroxymethyl-6-methoxyquinoline Dihydrochloride (SNL-147, WR 254421)

Two routes were developed to prepare the title compound. The first route is shown below.

8-Amino-4-hydroxymethyl-6-methoxyquinoline $\xrightarrow{6\text{-Br}(CH_2)_5COCl}$

8-(6-Bromohexanamido)quinoline 1 (73%) $\xrightarrow{Et_2NH}$

8-(6-$Et_2N(CH_2)_5C(O)NH$ Q 2 (100%) $\xrightarrow{BH_3/H_2SO_4/HCl}$

8-[(6-Et_2N(hexyl)amino]quionoline 3, (13%, WR 254421)

The three-step sequence is fairly conventional but the yield in the last step was low (13%). Attempts to improve the yield were unsuccessful and the four-step sequence shown in Chart No. 30 was used successfully.

4-Hydroxymethyl-6-methoxy-8-nitroquinoline was converted to the t-butyldimethylsilyl ether 1 (91%) which was reduced catalytically to give the corresponding 8-aminoquindine 2 (94%). This was followed by side chain introduction to afford intermediate 3. The protecting silyl group was removed using tetrabutylammonuium fluoride to afford the target compound 5 as the free base. The latter was treated with hydrogen chloride to give title dihydrochloride salt 4 (42%).

A 6.0 g sample was submitted on December 18, 1987 as Code No. DJD-07-239, Bottle No. BL51297.

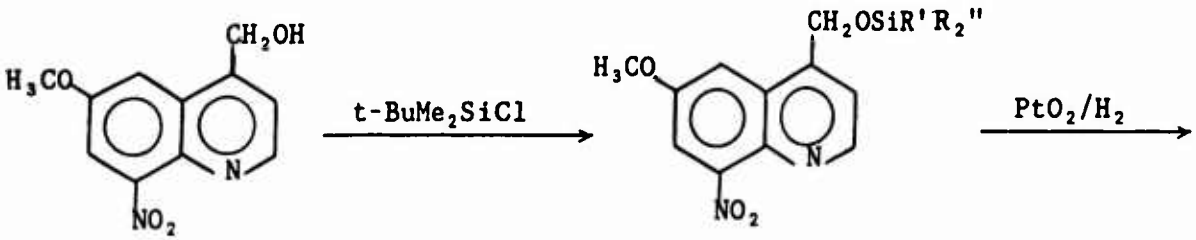
3.40 8-[(6-Ethylaminohexyl)amino]-4-hydroxymethyl-6-methoxyquinoline Dihydrochloride (SNL 148, WR 257767)

The reaction sequence to prepare the title compound is shown in Chart No. 31.

The side chain was prepared by the procedure developed in these laboratories (13). Anhydrous ethylamine was treated with 6-chlorohexanol to give the aminoalcohol 1 which was treated with thionyl chloride to give 6-ethylaminohexylchloride hydrochloride 2. Intermediate 2 was allowed to react with the protected 4-hydroxymethyl amine 3, prepared as described in Section 3.39 (Chart No. 30). The alkylated product was deprotected using tetrabutylammonium fluoride and purified by column chromatography. The purified title free base

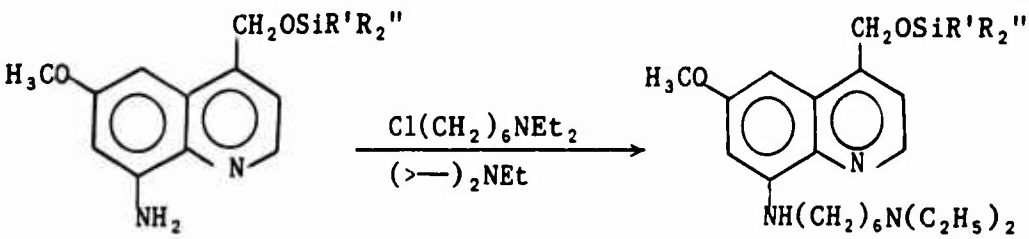
CHART NO. 30

8-[(6-Diethylaminohexyl)amino]-4-hydroxymethyl-6-methoxyquinoline Dihydrochloride (SNL-147, WR 254421)



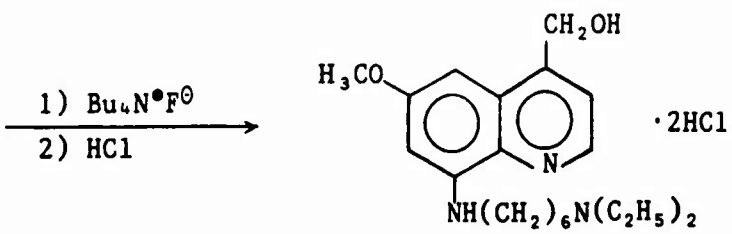
From Section 3.2, Chart No. 2

1 (91%)
R'-t-Bu, R"=Me



2 (94%)

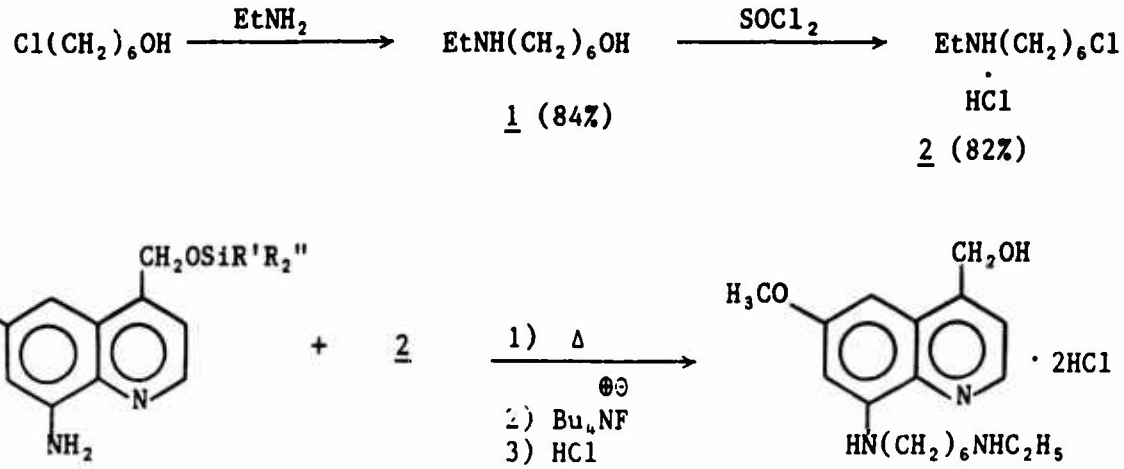
3



4 (42%) SNL-147,
WR 254421
DJD-07-239

CHART NO. 31

8-[(6-Ethylaminohexyl)amino]-4-hydroxymethyl-6-methoxyquinoline Dihydrochloride (SNL-148, WR 257767)



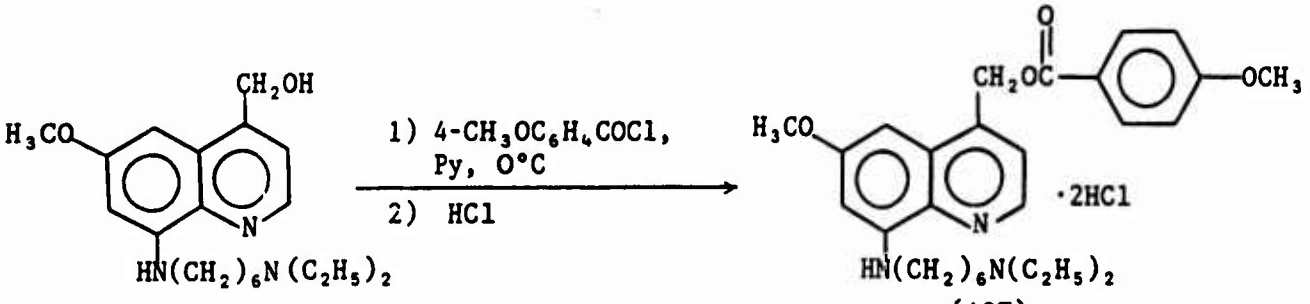
3 R'=tBu, R"=Me

From Section 3.3
Chart No. 3

4 (39%)
SNL-148, DJD-07-248,
WR 257767

CHART NO. 32

8-[(6-Diethylaminohexyl)amino]-6-methoxy-4-[(4-methoxybenzoyloxy)methyl]quinoline Dihydrochloride (SNL-149, WR 258444)



WR 254441, free base
Section 3.3, Chart No. 3

(40%)
SNL-149, DJD-07-283
WR 258444

was treated with hydrogen chloride to give title dihydrochloride 4 (39%).

A 7 g sample was shipped to WRAIR on May 10, 1988 as Code No. DJD-07-248, Bottle No. BL51304.

3.41 8-[(6-Diethylaminohexyl)amino]-6-methoxy-4-[(4-methoxybenzoyloxy)methyl]quinoline Dihydrochloride (SNL-149, WR 258444)

The two-step sequence to prepare the title compound is shown in Chart No. 32.

The starting material, 8-[(6-diethylaminohexyl)amino]-4-hydroxymethyl-6-methoxyquinoline, WR 254221 (a metabolite of WR 6026), was prepared by the procedure discussed in Section 3.39, Chart No. 30. Referring to Chart No. 32, 4-methoxybenzoyl chloride was added to a cold soln of WR 254221 in pyridine (30) to produce the crude target 4-ester. The mixture was purified by chromatography and the title compound (free base) was converted to the target dihydrochloride salt (40%).

A 3.8 g sample was shipped to WRAIR on March 29, 1988 as Code No. DJD-07-283, Bottle No. BL52196.

3.42 8-[(6-Diethylaminohexyl)amino]-6-methoxy-4-trimethylacetyloxymethylquinoline Dihydrochloride (SNL 150, WR 258651)

The reaction sequence to prepare the title compound is shown in Chart No. 33.

The title quinolinediamine ester was prepared according to a literature procedure (30), by the addition of trimethylacetyl chloride to a cold solution of WR 254421 in pyridine. The mixture was purified by column chromatography and the purified free base was converted to the title dihydrochloride salt (54%).

A 5 g sample was shipped to WRAIR on April 21, 1988 as Code No. DJD-07-289, Bottle No. BL52749.

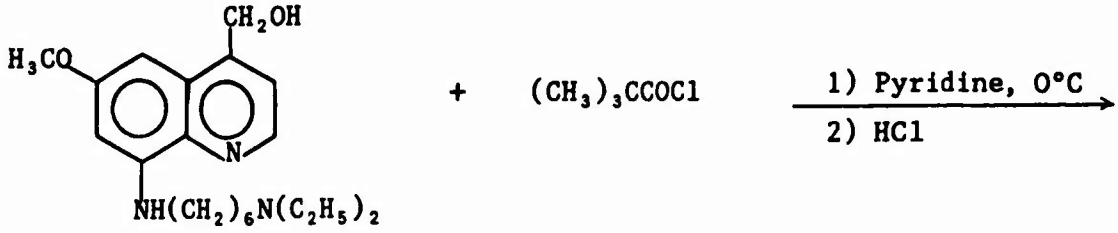
3.43 8-[(6-Ethylaminohexyl)amino]-6-methoxy-4-methoxymethylquinoline Dihydrochloride (SNL-151, WR 258820)

The reaction sequence to prepare the title compound is shown in Chart No. 34.

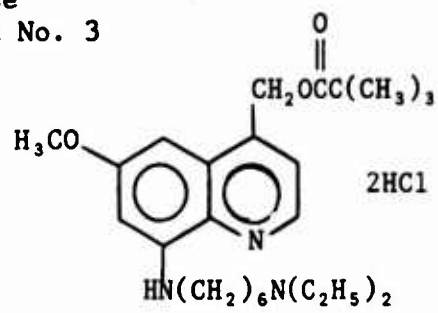
The title compound was prepared by condensing 8-amino-6-methoxy-4-methoxymethylquinoline with 6-ethylaminohexyl chloride hydrochloride. The alkylation product was purified by column chromatography and the pure free base, upon treatment with hydrogen chloride, gave pure title compound (51%).

CHART NO. 33

8-[(6-Diethylaminohexyl)amino]-6-methoxy-4-trimethylacetyloxy-methylquinoline Dihydrochloride 2 (SNL 150, WR 258651)



WR 254441, Free Base
Section 3,3, Chart No. 3

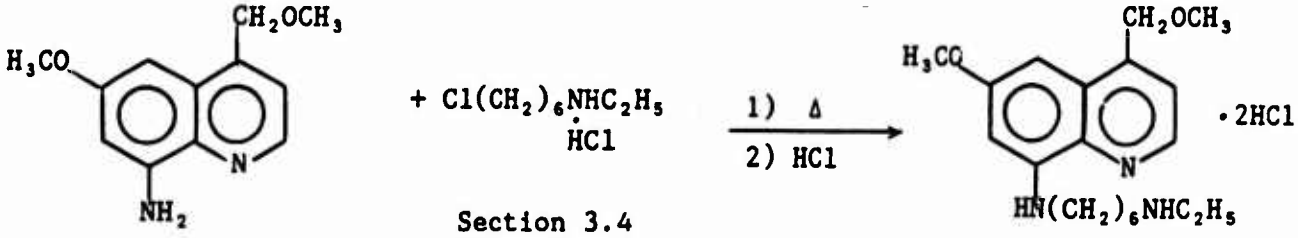


SNL-150, DJD-07-289

WR 258651

CHART NO. 34

8-[(6-Ethylaminohexyl)amino]-6-methoxy-4-methoxymethylquinoline Dihydrochloride (SNL 151, WR 258820):



Section 3.2
Chart No. 2

Section 3.4
Chart No. 4

(51%)

SNL 151, DJD-07-299

WR 258820

A 5.8 g sample was shipped to WRAIR on January 27, 1988 as Code No. DJD-07-299, Bottle No. BL52954.

3.44 8-[(6-Diethylaminohexyl)amino]-6-methoxy-4-[(3-trifluoromethylbenzoyloxy)methyl]quinoline Dihydrochloride (SNL-152 WR 259036)

The reaction sequence to prepare the title compound is shown in Chart No. 35.

The title aromatic ester of the metabolite of WR 6026, was prepared following a known procedure (30). 3-Trifluoromethylbenzoyl chloride was added to a cold solution of WR 254421 in pyridine. The mixture was purified by column chromatography and the free base of the title compound was converted to the dihydrochloride salt (29%).

A 4.5 g was sample was shipped to WRAIR on May 24, 1988 as Code No. DJD-07-301, Bottle No. BL53308.

3.45 8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-4-methoxymethylquinoline Hemisuccinate (SNL-153, WR 259219)

The reaction sequence to prepare the title compound is shown in Chart No. 36.

The starting 8-amino-6-methoxy-4-methoxymethylquinoline was prepared as described in Section 3.38. 8-Amino quinoline was condensed with 4-iodo-1-phthalimidopentane in acetonitrile to give intermediate 1 (70%). The phthalimido group was removed with hydrazine to give, after chromatography, pure title free base (80%). The free base was treated with one-half equivalent of succinic acid to give the pure title compound 2, (65%).

A 6 g sample was shipped to WRAIR on June 15, 1988 as Code No. DJD-08-68, Bottle No. BL53602.

3.46 8-[(4-Amino-1-methylbutyl)amino]-4-hydroxymethyl-6-methoxyquinoline Fumarate (SNL-154, WR 215300)

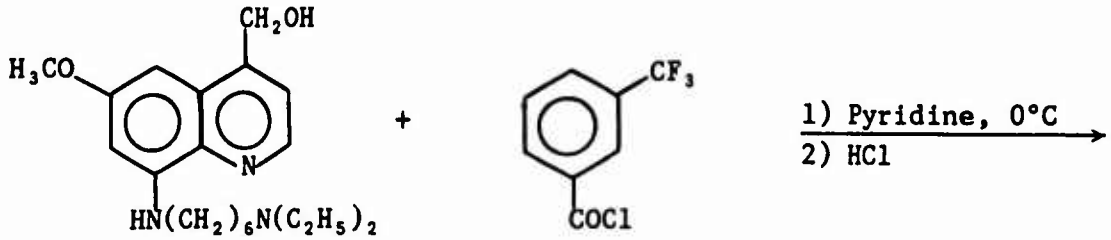
The reation sequence to prepare the title 4-hydroxymethylprimaquine, is shown in Chart No. 37.

8-Amino-4-t-butyldimethylsilyloxymethyl-6-methoxyquinoline, prepared as described earlier in section 3.39, was alkylated with 4-iodo-1-phthalimidopentane to give intermediate 1 (74%). The latter was deprotected using tetrabutylammonium fluoride to afford the 4-hydroxymethyl intermediate 2 (45%). The phthalimide group was removed with hydrazine to give the title free base which was purified by column chromatography and treated with fumaric acid gave the title compound 6 (61%).

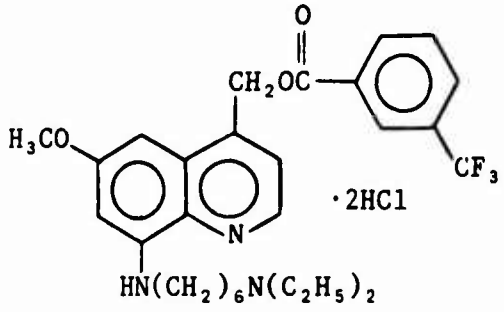
A 5.0 g sample was shipped to WRAIR on July 12, 1988 as Code No. DJD-08-77, Bottle No. BL54207.

CHART NO. 35

8-[(6-Diethylaminohexyl)amino]-6-methoxy-4-[(3-trifluoromethyl-benzoyloxy)methyl]quinoline Dihydrochloride (SNL 152, WR 259036)



Free Base
WR 254441
Section 3.3, Chart No. 3



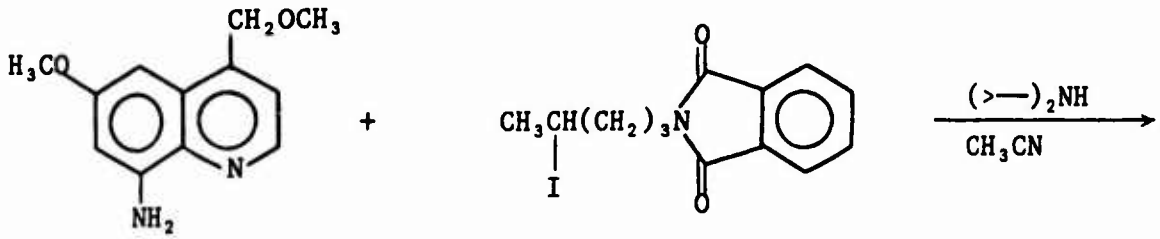
(39%)

SNL-152, DJD-07-301

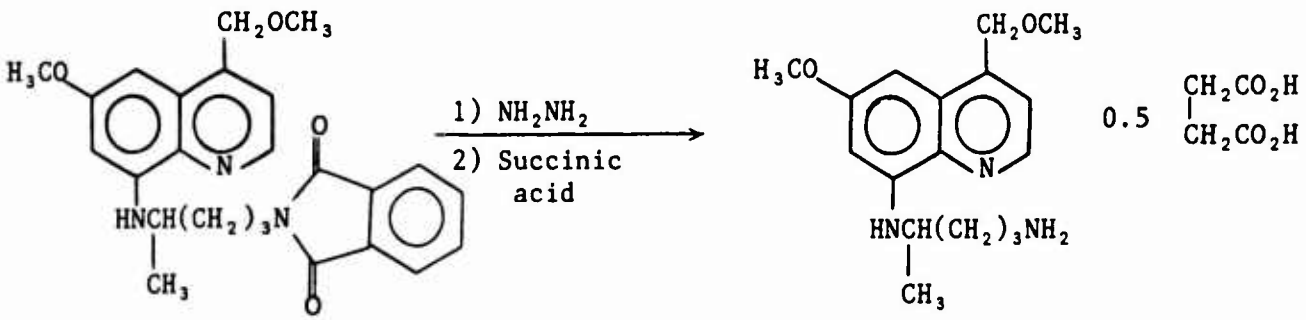
WR 259036

CHART NO. 36

8-[(4-Amino-1-methylbutyl)amino]-6-methoxy-4-methoxymethyl-quinoline Hemisuccinate (SNL 153, WR 259219):



Section 3.2
Chart No. 2



1 (70%)

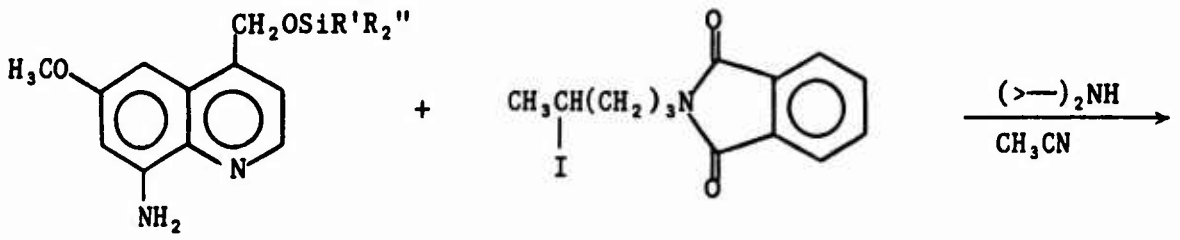
2 (65%)

SNL 153, DJD-08-68

WR 259219

CHART NO. 37

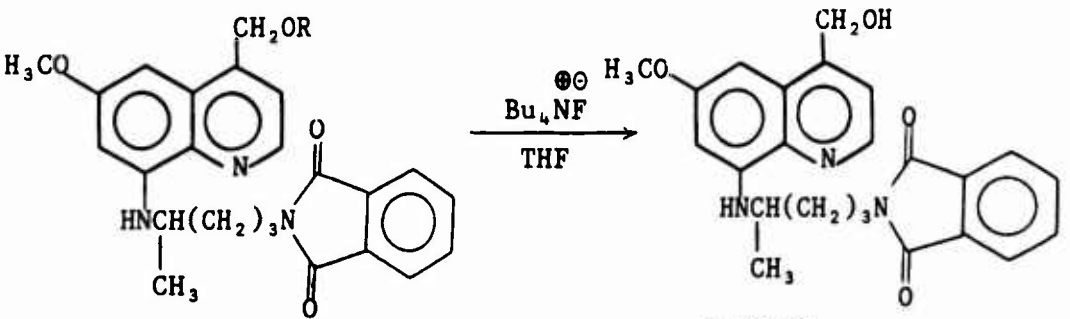
8-[(4-Amino-1-methylbutyl)amino]-4-hydroxymethyl-6-methoxy-quinoline Fumarate (SNL 154, WR 215300)



R'=t Bu, R"=Me

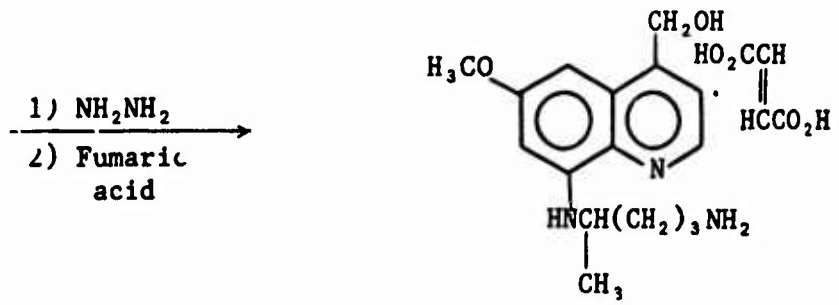
Section 3.3

Chart No. 3



1 (74%)

2 (45%)



3 (61%)

SNL-154, DJD-08-77

WR 215300

4. REFERENCES CITED

1) "Synthesis of Improved Antileishmanial and Antitrypanosomal Drugs", Final Summary Report, U.S. Army Medical Research and Development Command, Contract No. DAMD17-78-C-8001, dated August, 1984, Ash Stevens Inc., Detroit, Michigan.

2) "Synthesis of Improved Antileishmanial and Antitrypanosomal Drugs", Annual Progress Report, U.S. Army Medical Research and Development Command, Contract No. DAMD17-84-C-4210, dated November 1985, Ash Stevens Inc., Detroit, Michigan.

3) "Synthesis of improved Antileishmanial and Antitrypanosomal Drugs", Annual Report, U.S. Army Medical Research and Development Command, Contract No. DAMD17-84-C-4210, dated November 1986, Ash Stevens Inc., Detroit, Michigan.

4) "Synthesis of Improved Antileishmanial and Antitrypanosomal Drugs, Treatment and Prophylaxis", Annual Report, U.S. Army Medical Research and Development Command, Contract No. DAMD17-84-C-4210, dated March, 1988, Ash Stevens Inc., Detroit, Michigan.

5) "Synthesis of Improved Antileishmanial and Antitrypanosomal Drugs, Treatment and Prophylaxis", Annual Report, U.S. Army Medical Research and Development Command, Contract No. DAMD17-84-C-4210, dated March, 1989, Ash Stevens Inc., Detroit, Michigan.

6) a. "Potentiating Action of Rifampicin and Isoniazid Against Leishmania mexican amazonensis", Peters, W. et.al., The Lancet, p. 1122, May 23, 1981.

   b. "Antituberculous Drugs and Kala-azar", The Lancet, p. 304, August 8, 1981 (two communications).

7) "Ketoconazole Protects Against Infection with Trypanosoma cruzi in a Murine Model", McCabe, R.E., Araujo, F.G. and Remington, J.S., Am. J. Trop. Med. Hyg., 1983, 32(5), 960.

8) a. "The Efficacy of a Novel Compound, (E)-1-(4'-bromo-4-biphenyl)-1-(4-chlorophenyl)-3-dimethylaminoprop-1-ene against trypanosoma cruzi in mice", P.A. Barrett et.al., Experientia 38 (1982), Birkhauser Verlag. CH 4010 Basel Switzerland, p. 339.

   b. "Certain 3-Aminoprop-1-enes for Testing T. cruzi Infection", U.S. 3,932,663 (Jan. 13, 1976), P. Barrett, Burroughs Wellcome Co., Research Triangle Park, N.C.

   c. "1-(Halobiphenyl)-1-(halophenyl)-3-aminoprop-1-enes", U.S. 3,954,869 (May 4, 1969), ibid.

REFERENCES CITED (Continued)

9) "Activity of 8-Aminoquinolines against, L. tropica within human macorophages in vitro", Berman, J.D., and Lee, L.S., Am. J. Tropical Med. Hyg., 1983, 32, 753.

10) "Metabolism of a Potential 8-Aminoquinoline Antileishmanial Drug in Rat Liver Microsomes", Theoharides, A.D., Chung, Ho, and Velaquez, H., Biochemical Pharmacology, 1985, 34, 181.

11) K.N. Campbell, et.al., J. Amer. Chem. Soc., 68, 1556 (1946).

12) T.S. Worth, J. Chem. Soc. 426 (1942).

13) "Synthesis of Improved Antileishmanial Drugs, First Annual Progress Report, October 1978, U.S. Army Medical Research and Development Command, Contract No. DAMD17-78-C-8001, covering work performed 1 October 1977 to 30 Spetember 1978 by Ash Stevens Inc., Detroit, Michigan.

14) R.F. Borch and A.I. Hassid, J. Org. Chem., 37, 1673 (1972).

15) K. Eichinger, H. Berbalk and H. Kronberger, Synthesis, 1094 (1982).

16) "Synthesis of Improved Antileishmanial Drugs, Third Annual Progress Report, January 1981, U.S. Army Medical Research and Development Command, Contract No. DAMD17-78-C-8001, covering work performed 1 January 1980 to 31 December 1980 by Ash Stevens Inc., Detroit, Michigan.

17) "Preparation of Bulk Chemicals and Drugs for Use in the Antimalarial Program", Third Annual Progress Report, August 1976, U.S. Army Medical Research and Development Command, Contract No. DADA17-73-C-3158, covering work performed 1 July 1975 to 30 June 1976 by Ash Stevens Inc., Detroit, Michigan.

18) "Preparation of Bulk Chemicals and Drugs for Use in the Antimalarial Program", First Annual Progress Report, February 1985, U.S. Army Medical Research and Development Command, Contract No. DAMD17-83-C-3208, covering work performed 15 September 1983 to 30 September 1984 by Ash Stevens Inc., Detroit, Michigan, p. 57.

19) German Patent, 1,241,832 (1967) assigned to Hoechst AG, CA 68, 49639h (1968).

20) U.S. 2,83,485 (1958), assigned to Hoechst AG.

REFERENCES CITED (Continued)

21) a. Dimroth Ber. 1905, 38, 683, 2328.

b. C.K. Ingold and H.A. Piggot, J. Chem. Soc. 1922, 121, 2381.

c. L. Hunter, ibid, 1937, 320.

22) R. Stahr, Z. Physiol. Chem. 1931, 201, 142.

23) "The Orientation of P-Methoxydiphenyl in the Friedel and Crafts Reaction", L.F. Fieser and C.K. Broadsen, J. Am. Chem. Soc., 58, 1738 (1936).

24) "4-(p-Hydroxyphenyl)-cyclohexanecarboxylic Acid and Derivatives", W.S. Johnson et.al., ibid 68, 1648 (1946).

25) "Influence of Metallic Cation in Carbonyl Addition Reactions of Certain Nitriles and Sulfones with Benzophenone, E.M. Kaiser and C.R. Hauser, J. Am. Chem. Soc., 89, 4566 (1967).

26) "Preparation of Bulk Chemicals and Drugs for Use in the Antimalarial Program", Second Annual Progress Report, U.S. Army Medical Research and Development Command, Contract No. DADA17-73-C-3158 dated November 1975, Ash Stevens Inc., Detroit, Michigan, p. 57.

27) "Synthesis of Pyridinemethanols", Fifth Annual Progress Report, U.S. Army Medical Research and Development Command, Contract No.DADA17-69-C-9065 dated December 1973, Ash Stevens Inc., Detroit, Michigan, p. 48.

28) "Synthesis and antileishmanial activity of 6-methoxy-4-methyl-N-[6-(substituted-1-piperazinyl)hexyl]-8-quinolinamines and related compounds", J.L. Johnson and L.M. Werbel, J. Med. Chem. 26, 185 (1983).

29) "Synthesis of 4-Alleyl and 4-(B-Alkyluinyl) derivatives of Primoquine as potential antimalarials", Carroll, F.I., Berang, B.D., and Linn, C.P., J. Med. Chem., 1979, 22, 1363.

30) "Conversion of aryl carbinols to deoxy compounds through catalytes reducton of their esters", Zymalkowski, F., Arch. Oharm., 1954, 287, 505, Chem. Abstr., 1958, 52, 5407e.

SUPPLEMENTARY

INFORMATION

5

DEPARTMENT OF THE ARMY
U S ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
FORT DETRICK, FREDERICK, MD 21702-5012

REPLY TO ATTENTION OF

ERRATA

B145101

SGRD-RMI-S (70-1y)

24 JUL 1992

MEMORANDUM FOR Administrator, Defense Technical Information Center, ATTN: DTIC-HDS/William Bush, Cameron Station, Bldg. 5, Alexandria, VA 22304-6145

SUBJECT: Request Change in Distribution Statement

1. The U.S. Army Medical Research and Development Command (USAMRDC), has reexamined the need for the limited distribution statement on technical reports for Contract No. DAMD17-84-C-4210. Request the limited distribution statement for AD Nos. ADB109535, ADB110976, ADB121621, ADB144742, and **ADB145101**, be changed to "**Approved for public release;** distribution unlimited," and that copies of these reports be released to the National Technical Information Service.

2. Point of contact for this request is Ms. Virginia Miller, DSN 343-7325.

ERRATA

for Carey O. Leverett MAJ, MS

CAREY O. LEVERETT
LTC, MS
Deputy Chief of Staff for
Information Management

CF:
Dr. Ruthann Smejkal/WRAIR

ERRATA: B145101