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Synthesis and Antimalarial Properties of 1-Imino Derivatives of 7-Chloro-3-substituted-3,4-dihydro-1,9(2*H*,10*H*)-acridinediones and Related Structures[1,2]

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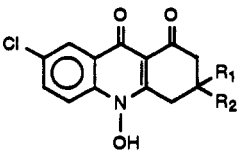
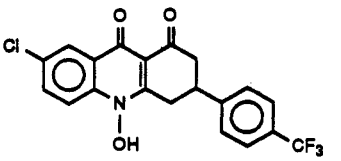
To improve upon the activity and properties of the 3-aryl-7-chloro-3,4-dihydro-1,9(2*H*,10*H*)-acridinediones, a variety of 1-[(alkylamino)alkylene]imino derivatives (**3**) were prepared and shown to be highly active antimalarial agents in both rodents and primates. Among structural modifications prepared, including N_{10}-alkyl and C_2-substituted analogs, removal of the C_9 oxygen, and introduction of an imino side chain at C_9, the imines of the N_{10}-H acridinediones were the most active compounds obtained. The [3-(*N*,*N*-dimethylamino)propyl]imino derivative of 7-chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1,9(2*H*,10*H*)-acridinedione (**9aa**) proved to be highly active in advanced studies in primates.

To the chemotherapist the revelation of a new chemical class with potent activity against an important disease entity, which might portend a unique mechanism of action as well, is always exciting. Thus our interest was piqued some years ago by the report[3] of the activity of acridinedione structure **1** against chloroquine-resistant strains of plasmodia. Later reports[4-7] made it apparent that the structure of primary interest was **2**. Although our early efforts were directed toward the delineation of the structural features required for activity within this system, we turned rapidly to improving the apparent shortcomings of **2**, i.e., limited solubility and a hint of toxic liability. Our initial success was reported in a patent.[8] We continued to refine and extend our work,[9,10] and during this time further work from the Hoechst group also appears.[11-13]



1



2

The exciting activity of our compounds and the time needed for the Walter Reed Army Institute of Research

(1) This is Paper 64 of a series of antimalarial drugs. For Paper 63, see: Werbel, L. M.; Degnan, M. J. Synthesis and Antimalarial and Antitumor Effects of 2-Amino-4-(hydrazino and hydroxyamino)-6-[(aryl)thio] Quinazolines. *J. Med. Chem.* **1987**, *30*, 2151–2154.

(2) This investigation was supported by U.S. Army Medical Research and Development Command COntract DAMD 17-79-C-9115. This is contribution 1886 to the Army Research Program in Malaria.

(3) Belgian Patent 818,048, Hoechst, Feb 13, 1975.

(4) Raether, W.; Fink, E. *Tropenmed. Parasitol.* **1977**, *28*, 268.

(5) Schmidt, L. H. Antimalarial Properties of Floxacrine, a Dihydroacridinedione Derivative. *Antimicrob. Agents Chemother.* **1979**, *16*, 475–485.

(6) Raether, W.; Fink, E. Antimalarial Activity of Floxacrine I. *Ann. Trop. Med. Parasitol.* **1979**, *73*, 505–526.

(7) Joyner, L. P. Chemotherapy of Protozoal Infections of Veterinary Medicine. *J. Protozool.* **1980**, *27*, 31A.

(8) U.S. 4,291,034, Sept 22, 1981; 7-Chloro-3-substituted Aryl-3,4-dihydro-1,9(2H,10H) and 10 Hydroxy Acridinedioneimines Having Antimalarial Activity. *Chem. Abstr.* **1982**, *96*, 66114.

(9) Werbel, L. M.; Hung, J.; McNamara, D.; Ortwine, D. F. 3-Aryl-7-chloro-3,4-dihydro-1,9(2H,10H)acridinedione, 1-Hydrazones as Potent Antimalarial Agents. *Eur. J. Med. Chem.* **1985**, *20*, 363–370.

(10) Hung, J.; McNamara, D. J.; Werbel, L. M. Synthesis of 3,4-Dihydrothioxanthene-1,9-dione Analogs as Potential Antimalarial Agents. *J. Heterocycl. Chem.* **1983**, *20*, 1575–1580.

(11) Durckheimer, W.; Raether, W.; Seliger, H.; Seidenath, H. 10-Hydroxy-3,4-dihydroacridine-1,9(2H,10H)-diones. A New Group of Malaricidal and Coccidiostatic Compounds. *Arzneim.-Forsch./Drug Res.* **1980**, *30*(II), 1041–1046.

(12) Raether, W.; Fink, E. Antimalarial Activity of Floxacrine (HOE 991). II. Studies on Causal Prophylactic and Blood Schizonticidal Action of Floxacrine and Related Dihydroacridinediones Against Plasmodium yoelli and P. berghei. *Ann. Trop. Med. Hyg.* **1982**, *76*, 507–516.

(13) Winkelmann, E.; Raether, W. Antimalarial and Anticoccidial Activity of 3-Aryl-7-chloro-3,4-dihydroacridine-1,9-(2H,10H)-diones, 1-Imines, 1-Amines, 1-Oximes, 1-Hydrazones and Related Compounds. *Arzneim.-Forsch./Drug Res.* **1987**, *37*, 647–661.

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Scheme I

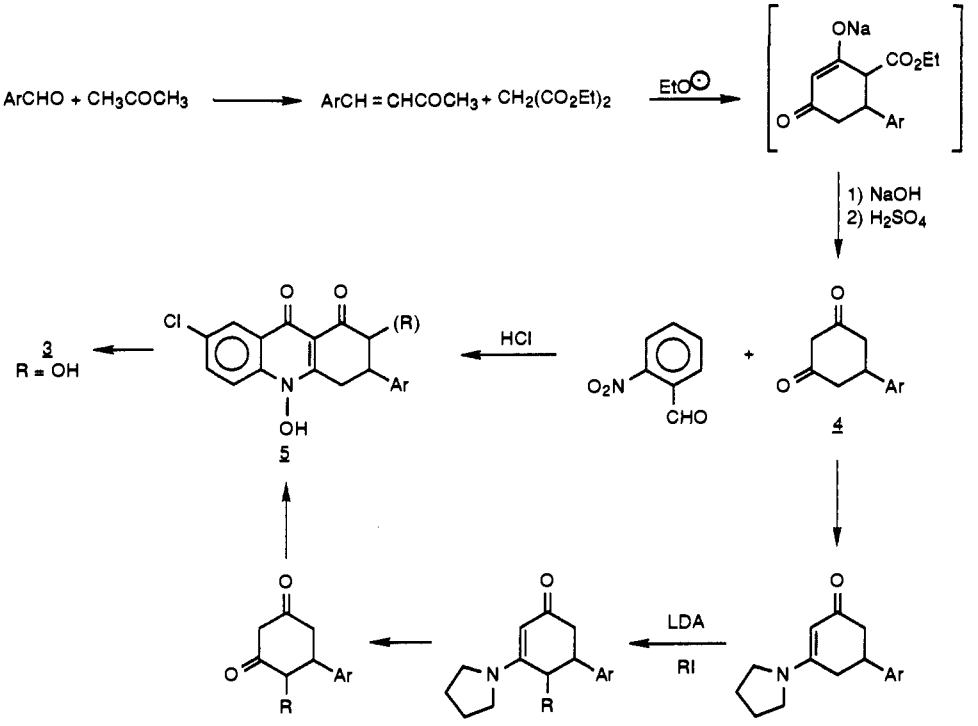
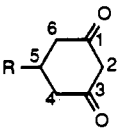


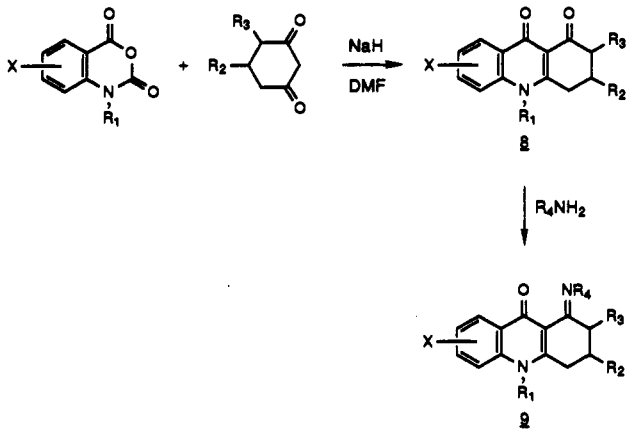
Table I. Preparation of Cyclohexan-1,3-diones



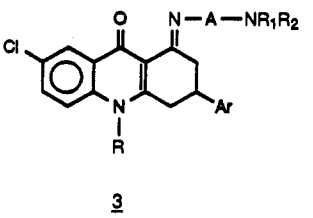
no.	R	mp, °C	(lit. mp, °C)	yield, purified % 1st step	2nd step	3rd step	proc	purification solvent(s)[a]	formula	analysis (±0.40)
4a	3,4-$Cl_2C_6H_3$	198–200	(190–192)[q]	70	40		A	R-2-propanol	$C_{12}H_{10}Cl_2O_2$	C,H,Cl
4b	3-CF_3-C_6H_4	173–176		73	43		A	T-toluene	$C_{13}H_{11}F_3O$	C,H,F
4c	C_6H_{11}	162–163	(154–156)[r]	76	35		A	R-acetone, ether	$C_{12}H_{18}O_2$	C,[b]H
4d	4-CF_3-C_6H_4	164–167		32	43		A	T-toluene	$C_{13}H_{11}O_2F_3$	C,H,F
4e	1-$C_{10}H_7$	157		92	71		A	T-toluene	$C_{16}H_{14}O_2 \cdot 0.7H_2O$	C,H,H_2O
4f	3,4,5-$(OCH_3)_3C_6H_2$	155–159		100	69		A	T-ether	$C_{15}H_{18}O_5 \cdot 1.0H_2O$	C,H,H_2O
4g	4-Me_2N-C_6H_4[c]	207–210		100	63		A	none	$C_{14}H_{16}NO_2Na$	C,H,N
4h	3-Br-C_6H_4	181–183		97			A	T-toluene	$C_{12}H_{11}BrO_2$	C,H,Br
4i	2,6-Cl_2-C_6H_3	205–207		94			A	T-C_6H_6	$C_{12}H_{10}Cl_2O$	C,[d]H,Cl
4j	C_6H_5	192–194	(187–189)[r]	72	45		A	T-toluene	$C_{12}H_{11}O_2 \cdot 0.1H_2O$	C,H
4k	$(CH_2)_5$	166–168	(170.5)[e]	14	39		A	T-ether	$C_{11}H_{16}O_2$	
4l	2-Cl-C_6H_4	150–152	(153–154)[r]	64	26		A	R-CH_2Cl_2, $CH_3CO_2C_2H_5$	$C_{12}H_{11}ClO_2$	C,[f]H,Cl
4m	4-C_6H_{11}-C_6H_4[g]	238–240		85	57		A	T-CH_3OH, ether	$C_{18}H_{22}O_2$	C,[h]H
4n	2-CF_3-C_6H_4	194–197		86	49		A	T-toluene	$C_{13}H_{11}F_3O_2$	
4o	4-CH_3-C_6H_4	180–182	(165–167)[r]	93	77		A	T-toluene	$C_{13}H_{14}O_2$	
4p	2-OCH_3-C_6H_4	145–148	(145)[s]	98	73		A	T-toluene	$C_{13}H_{14}O_3$	
4q	4-OCH_3-C_6H_4	178–181	(177–178.5)[r]	97	40		A	T-toluene	$C_{13}H_{14}O_3$	
4r	2,4-Cl_2-C_6H_3	192–196	(179–181)[r]	78	67		A	R-DMF, $CH_3CO_2C_2H_5$	$C_{12}H_{10}Cl_2O_2$	
4s	4-C_5H_4N	197–198			79	71[i]	A2	R-DMF	$C_{11}H_{11}NO_2$	C,H,N
4t	2,4-Cl_2-C_6H_3(4-CH_3)	182–184		67	40		A3	R-CH_3CN	$C_{13}H_{12}Cl_2O_2$	
4u	3,4-Cl_2-C_6H_3(4-CH_3)	110–136		73	18[j]		A3	R-pet. ether	$C_{13}H_{12}Cl_2O_2$	
4v	4-SCH_3-C_6H_4						A			
4w	4-NO_2-C_6H_4[k]	225 dec			40		A4	R-CH_3CN	$C_{12}H_{11}NO_4$	C,H,N
4x	4-CF_3-C_6H_4(4-C_2H_5)[o]	160–163		90	81	70	A5	R-$CHCl_3$	$C_{15}H_{15}F_3O_2$	C,[l]H
4y	4-CF_3-C_6H_4(4-CH_3)[o]	178–180		90	61	79	A5	R-$CHCl_3$	$C_{14}H_{13}F_3O_2$	
4z	2-C_5H_4N	160–161		78[m]	33		A2	R-CH_2Cl_2, $CH_3CO_2C_2H_5$	$C_{11}H_{11}NO_2$	C,[n]H,N
4aa	3,4-Cl_2-C_6H_3(4-C_6H_5)	85–90		70	56[j]		A6	T-aq. AcOH	$C_{18}H_{14}Cl_2O_2$	
4bb	3-CF_3,4-Cl-C_6H_3[p]	192–194			9		A2	R-CH_3CN	$C_{13}H_{10}ClO_2F_3$	

[a] R = recrystallized, T = triturated. [b] Anal. calcd for C, 74.19; found, 73.57. [c] Isolated as sodium salt. [d] Anal. calcd for C, 56.06; found, 55.64. [e] Lit. mp = 170.5 °C. (Wallach, O. *Annalen* **1912**, *394*, 376. Norris, W.; Thorpe, J. F. *J. Chem. Soc.* **1921**, *119*, 1199.) [f] Anal. calcd for C, 64.73; found, 64.00. [g] Benzaldehyde prepared as described previously.[22] [h] Anal. calcd for C 79.96; found, 79.33. [i] Yield from the cyclohexene–carboxylic acid. [j] Crude yield. [k] 4-Position of NO_2 group assigned from the para splitting pattern in the NMR. [l] Anal. calcd for C, 63.37; found, 62.87. [m] Yield of the cyclohexene carboxylic acid, sodium salt. [n] Anal. calcd for C, 69.82; found, 69.37. [o] Cis, trans mixture. [p] Benzaldehyde prepared as described previously.[23] [q] Schoen, K.; Pachter, I. J., US Patent 3503990, 1970. [r] Tamura, Y.; Yoshimoto, Y.; Kunimoto, K.; Tada, S.; Tomita, T.; Wada, T.; Seto, E.; Murayama, M.; Shibata, Y.; Nomura, A.; Ohata, K. *J. Med. Chem.* **1977**, *20*, 709. [s] Hinkel, L. E.; Ayling, E. E.; Dippy, J. F. J. *J. Chem. Soc.* **1935**, 539. [t] Yields are in enamine steps from cyclohexanedione.

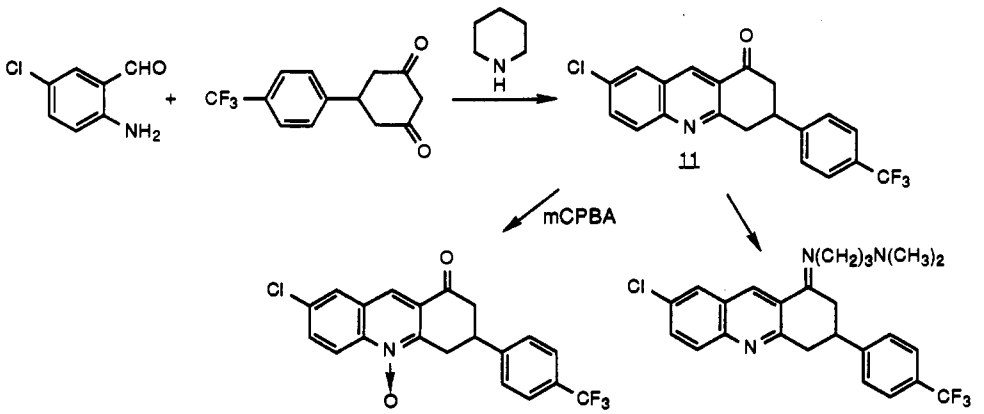
Scheme II



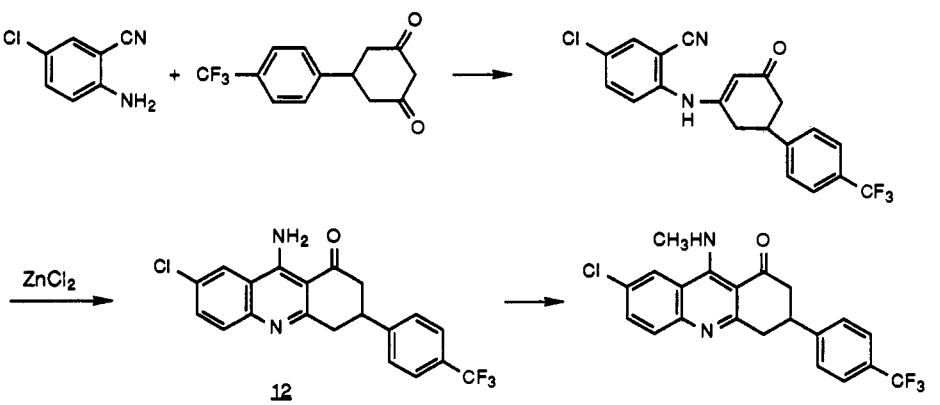
to complete the needed extensive biological studies in their effort to work toward selection of one of these analogs for IND filing has necessitated some delay in the publication of this information. However in this manuscript we are now able to report full chemical and biological details of the development of a series of structures 3 with potent antimalarial properties devoid of the negative manifestations of the acridinediones 2.



Scheme III



Scheme IV



Scheme V

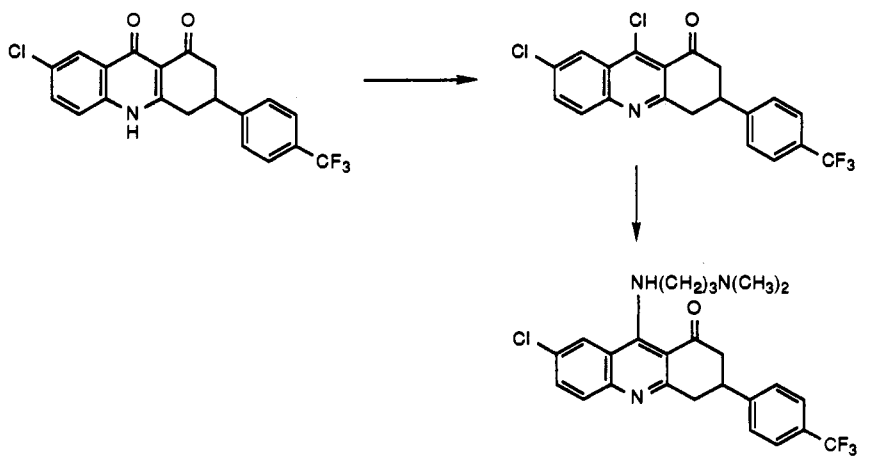
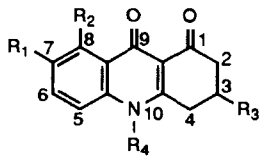


Table II. 3,4-Dihydro-1,9(2*H*,10*H*)-acridinediones



no.	R_1	R_2	R_3	R_4	mp, °C	yield, purified %	proc	purification solvent(s)[a]	formula	analysis (±0.40)
8a	Cl	H	3,4-Cl_2-C_6H_3	OH	268–269 dec	60	B	T-CH_3OH	$C_{19}H_{12}FCl_3NO_3$	C,H,N,Cl
8b	Cl	H	$CH(CH_3)_2$	OH	271–275 dec	45	B	T-C_2H_5OH	$C_{18}H_{14}ClNO_3$	C,H,N,Cl
8c	Cl	H	3-CF_3-C_6H_4	OH	248–250 dec	53	B	T-C_2H_5OH	$C_{20}H_{13}ClF_3NO_3$	C,H,N,Cl
8d	Cl	H	3-CF_3-C_6H_4	ONa	315–320 dec	73	C	T-C_2H_5OH	$C_{20}H_{12}ClF_3NO_3Na{\cdot}H_2O$	C,H,N,Cl,Na,H_2O[b]
8e	Cl	H	3-CF_3-C_6H_4	H	346–350 dec	23	D	T-CH_3OH, aq. NaOH	$C_{20}H_{13}ClF_3NO_2$	C,H,N,Cl[c]
8f	H	H	3,4-Cl_2-C_6H_3	OH	257–260 dec	68	E	T-C_2H_5OH	$C_{19}H_{13}Cl_2NO_3{\cdot}0.1Cl^-$	C,H,N,Cl
8g	Cl	Cl	3,4-Cl_2-C_6H_3	OH	282–283 dec	18	B	T-CH_3OH, DMF	$C_{19}H_{11}Cl_4NO_3{\cdot}0.1C_3H_7NO$	C,H,N,Cl
8h	Cl	H	C_6H_{11}	OH	255–258 dec	68	B	R-DMF	$C_{19}H_{20}ClNO_3$	C,H,N,Cl
8i	Cl	H	3,4-Cl_2-C_6H_3	H	>325	34	D	T-aq. C_2H_5OH	$C_{19}H_{12}Cl_3NO_2{\cdot}0.2H_2O$	C,H,N,Cl,H_2O
8j	Cl	H	4-CF_3-C_6H_4	OH	265–267	55	B	T-C_2H_5OH	$C_{20}H_{13}ClF_3NO_3{\cdot}0.1H_2O$	C,H,N,Cl,F,H_2O
8k	Cl	H	1-$C_{10}H_7$	OH	264	47	B	T-CH_3OH	$C_{22}H_{16}ClNO_3$	C,H,N,Cl
8l	Cl	H	3,4,5-$(OCH_3)_3C_6H_2$	OH	236–238	29	B	T-C_2H_5OH	$C_{22}H_{20}ClNO_6{\cdot}1.1H_2O$	C,H,N,Cl,H_2O
8m	Cl	H	4-$Et_2N(CH_2)_2OC_6H_4$	ONa	277–279	25	B[d]	R-CH_3OH, ether	$C_{25}H_{26}ClN_2NaO_4{\cdot}0.4H_2O$	C,H,N,Cl,H_2O
8n	Cl	H	4-$Me_2NC_6H_4$	OH	244–248	53	B[e]	T-C_2H_5OH	$C_{21}H_{19}ClN_2O_3{\cdot}0.3HCl{\cdot}0.3H_2O$	C,H,N,Cl,Cl^-,H_2O
8o	Cl	H	3-Br-C_6H_4	OH	234–236	57	B	T-C_2H_5OH	$C_{19}H_{13}BrClNO_3$	C,H,N,Br,Cl
8p	Cl	H	2,6-Cl_2-C_6H_3	OH	242–245 dec	70	B	T-C_2H_5OH	$C_{19}H_{12}Cl_3NO_3$	C,H,N,Cl,H_2O
8q	H	H	$CH(CH_3)_2$	CH_3	226–228	36	F	R-CH_3CN	$C_{16}H_{17}NO_2$	C,H,N
8r	Cl	H	C_6H_5	OH	250 dec	72	B	T-C_2H_5OH	$C_{19}H_{14}ClNO_3$	C,H,N,Cl
8s	Cl	H	$(CH_2)_5$	OH	260–261	74	B	R-CH_2Cl_2–C_2H_5OH	$C_{19}H_{18}ClNO_3{\cdot}0.1H_2O$	C,H,N,Cl,H_2O
8t	Cl	H	$CH(CH_3)_2$	H	>280	58	G	T-CH_3OH	$C_{18}H_{14}ClNO_2$	C,H,N
8u	Cl	H	3,4-Cl_2-C_6H_3	CH_3	276 dec	31	F	R-DMF–C_2H_5OH	$C_{20}H_{14}Cl_3NO_2$	C,H,N
8v	Cl	H	4-CF_3-C_6H_4	H	342–346	66	D	T-C_2H_5OH	$C_{20}H_{13}ClF_3NO_2$	C,H,N,Cl,F
8w	Cl	H	2,4-Cl_2-C_6H_3	OH	254–255	65	B	T-C_2H_5OH	$C_{19}H_{12}Cl_3NO_3$	C,H,N,Cl
8x	Cl	H	$(CH_2)_5$	H	>350	38	D	T-CH_3OH–aq NaOH (tr)	$C_{18}H_{18}ClNO_2$	C,H,N,Cl
8y	Cl	H	3,4-Cl_2-C_6H_3	OH (2-CH_3)	236 dec	30	B	T-DMF	$C_{20}H_{14}Cl_3NO_3{\cdot}0.3C_3H_7NO$	C,H,N
8z	Cl	H	4-CF_3-C_6H_4	OH (6-F)	239–242 dec	46	B	T-C_2H_5OH	$C_{20}H_{12}ClF_4NO_3$	C,H,N
8aa	Cl	Cl	4-CF_3-C_6H_4	OH	244 dec	37	B	T-C_2H_5OH	$C_{20}H_{12}Cl_2F_3NO_3$	C,H,N
8bb	Cl	H	4-CF_3-C_6H_4	C_2H_5	262–266	43	F	R-CH_2Cl_2–CH_3CO_2Et	$C_{22}H_{17}ClF_3NO_2$	C,H,N,Cl,F
8cc	Cl	H	4-CF_3-C_6H_4	*n*-C_4H_9	271–275	26	F	R-CH_2Cl_2–CH_3CO_2Et	$C_{24}H_{21}ClF_3NO_2$	C,H,N,Cl,F
8dd	Cl	H	4-CF_3-C_6H_4	$CH_2C_6H_5$	270–274	28	F	R-CH_2Cl_2–CH_3CO_2Et	$C_{27}H_{19}ClF_3NO_2$	C,H,N,Cl,F
8ee	Cl	H	2-Cl-C_6H_4	OH	243–245	44	B	T-DMF–CH_3OH	$C_{19}H_{13}Cl_2NO_3$	C,H,N,Cl
8ff	I	H	4-CF_3-C_6H_4	H	315–316	50	F	T-DMF–CH_3OH	$C_{20}H_{13}F_3INO_2$	C,H,N,F,I
8gg	Cl	H	4-CF_3-C_6H_4	$CH_2CH{=}CH_2$	273–275	42	F	R-CH_2Cl_2–CH_3CO_2Et	$C_{23}H_{17}ClF_3NO_2$	C,H,N,Cl,F
8hh	Cl	H	4-CF_3-C_6H_4	*n*-C_6H_{13}	215–218	30	F	R-$CH_3CO_2C_2H_5$	$C_{26}H_{25}ClF_3NO_2$	C,H,N,Cl,F
8ii	Cl	H	2-Cl-C_6H_4	H	353–355	51	F	T-DMF–CH_3OH–ether	$C_{19}H_{13}Cl_2NO_2$	C,H,N,Cl
8jj	O_2N	H	4-CF_3-C_6H_4	H	310–312	54	F	R-DMF–CH_3OH	$C_{20}H_{13}F_3N_2O_4$	C,H,N,Cl
8kk	Cl	H	4-(C_6H_{11})-C_6H_4	OH	327–330	59	B	T-DMF–CH_3OH	$C_{25}H_{24}ClNO_3$	C,H,N,Cl
8ll	Cl	H	2-CF_3-C_6H_4	OH	269–271	38	B	R-DMF	$C_{20}H_{13}ClF_3NO_3$	C,H,N
8mm	Cl	H	4-CH_3-C_6H_4	OH	267–268	65	B	T-C_2H_5OH	$C_{20}H_{16}ClNO_3$	C,H,N
8nn	Cl	H	2-OCH_3-C_6H_4	OH	230 dec	47	B	R-CH_3OH	$C_{20}H_{16}ClNO_4$	C,H,N
8oo	Cl	H	4-OCH_3-C_6H_4	OH	255 dec	83	B	T-C_2H_5OH	$C_{20}H_{16}ClNO_4$	C,H,N
8pp	C_2H_5	H	4-CF_3-C_6H_4	H	>360	50	F	T-DMF–CH_3OH–ether	$C_{22}H_{18}F_3NO_2$	C,H,N,F
8qq	Cl	H	4-(C_6H_{11})-C_6H_4	H	>360	50	F[f]	T-DMF–CH_3OH–ether	$C_{25}H_{24}ClNO_2$	C,H,N,Cl
8rr	Cl	H	4-F-C_6H_4	OH	229–240	78	B	T-C_2H_5OH	$C_{19}H_{13}ClFNO_3$	C,H,N
8ss	Br	H	4-CF_3-C_6H_4	H (5-Br)	263–265	50	F	R-DMF–CH_3OH	$C_{20}H_{12}Br_2F_3NO_2$	C,H,N,Br,F
8tt	H	H	$CH(CH_3)_2$	H	347–348	13	I	R-DMF–CH_3OH	$C_{18}H_{15}NO_2$	C,H,N
8uu	Br	H	4-CF_3-C_6H_4	H	326–329	45	F	R-DMF–CH_3OH	$C_{20}H_{13}BrF_3NO_2$	C,H,N,Br,F
8vv	H	H	4-CF_3-C_6H_4	H	330	58	F	T-DMF–CH_3OH–ether	$C_{20}H_{14}F_3NO_2$	C,H,N,F
8ww	Cl	H	2-CF_3-C_6H_4	H	>300	54	D	T-aq. NH_4OH (dilute)	$C_{20}H_{13}ClF_3NO_2$	C,H,N
8xx	Cl	H	4-CH_3-C_6H_4	H	>300	74	D	T-aq. NH_4OH (dilute)	$C_{20}H_{16}ClNO_2$	C,H,N
8yy	Cl	H	2-OCH_3-C_6H_4	H	>300	89	D	T-aq. NH_4OH (dilute)	$C_{20}H_{16}ClNO_3$	C,H,N
8zz	OCH_3	H	4-CF_3-C_6H_4	H	>360	60	F	R-CH_3OH–DMF	$C_{21}H_{16}F_3NO_3$	C,H,N,F

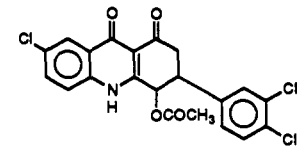
8aaa	Cl	H	4-CF_3-C_6H_4	H (5-Cl)	296–298	37	F	R·DMF–C_2H_5OH–ether	$C_{20}H_{12}Cl_2F_3NO_2$	C,H,Cl,F,N
8bbb	H	Cl	4-CF_3-C_6H_4	H	308–312	24[d]	F	R·DMF	$C_{20}H_{13}ClF_3NO_2$	C,H,N,Cl,F
8ccc	F	H	4-CF_3-C_6H_4	H	>330	46	F	T·DMF–CH_3OH–ether	$C_{20}H_{13}F_4NO_2$	C,H,N,F
8ddd	Cl	H	2,4-Cl_2-C_6H_3	H	308–310	48	F	T·CH_3OH–ether	$C_{19}H_{12}Cl_3NO_2$	C,H,N,Cl
8eee	Cl	H	3,4-Cl_2-C_6H_3	H (2·CH_3)	>260	16	F	R·DMF	$C_{20}H_{14}Cl_2NO_2$	C,H,N
8fff	H	Cl	2,4-Cl_2-C_6H_3	H (5-Cl)	240–242	42	F	R·DMF	$C_{19}H_{11}Cl_3NO_2$	C,H,N,Cl[a]
8ggg	H	H	2,4-Cl_2-C_6H_3	H (5-Cl)	242–245	51	F	R·DMF	$C_{19}H_{12}Cl_2NO_2$	C,H,N,Cl
8hhh	CF_3	H	4-CF_3-C_6H_4	H	>330	57	F	R·DMF	$C_{21}H_{12}F_6NO_2$	C,H,N,F
8iii	Cl	H	4-CO_2H-C_6H_4	OH	>260	65	B	T·C_2H_5OH	$C_{20}H_{14}ClNO_5$	C,H,N
8jjj	Cl	H	4-OCH_3-C_6H_4	H	>300	81	D	R·DMF	$C_{20}H_{16}ClNO_3$	C,H,N,Cl
8kkk	Cl	H	4-C_5H_4N	OH	231	54	B	T·DMF–CH_3OH	$C_{19}H_{13}ClN_2O_3$	C,H,N,Cl
8lll	Cl	H	4-C_5H_4N	H	329–330	57	F	R·DMF	$C_{19}H_{13}ClN_2O_2$	C,H,N,Cl
8mmm	Cl	H	4-SCH_3-C_6H_4	H	>260	53	F	T·DMF	$C_{20}H_{16}ClNO_2S$	C,H,N
8nnn	Cl	H	4-NO_2-C_6H_4	H	>260	70	F	T·C_2H_5OH	$C_{19}H_{13}ClN_2O_4$	C,H,N
8ooo	Cl	H	4-CF_3-C_6H_4	H (2-C_2H_5)	310 dec	42	F	R·DMF	$C_{23}H_{17}ClF_3NO_2$	C,H,N,Cl
8ppp	Cl	H	4-CF_3-C_6H_4	H (2-CH_3)	320 dec	53	F	R·DMF	$C_{21}H_{15}ClF_3NO_2$	C,H,N,Cl
8qqq	Cl	H	2-C_5H_4N	H (2-C_6H_5)[f]	336–338	50	F	T·DMF–CH_3OH	$C_{18}H_{13}ClN_2O_2$	C,H,N,Cl
8rrr	Cl	H	3,4-Cl_2-C_6H_3	H (2-C_6H_5)[f]	>260	37	F	T·C_2H_5OH	$C_{25}H_{16}Cl_3NO_4$·0.2H_2O	C,H,N,H$_2$O
8sss	Cl	H	4-Cl,3-CF_3-C_6H_3	H	317 dec	59	F	R·DMF	$C_{20}H_{12}Cl_2F_3NO_2$	C,H,N,Cl
8ttt	Cl	H	2,4-Cl_2-C_6H_3	OH (2·CH_3)	230	45	B	R·DMF	$C_{20}H_{14}Cl_3NO_3$	C,H,N,Cl
8uuu	H	H	2,4-Cl_2-C_6H_3	H (6-Cl)	342–344	63	F	R·DMF, C_2H_5OH	$C_{19}H_{12}Cl_3NO_2$	C,H,N,Cl
8vvv	Cl	H	2,4-Cl_2-C_6H_3	H (2·CH_3)	>330	49	F	T·C_2H_5OH	$C_{20}H_{14}Cl_3NO_2$	C,H,N,Cl
8www	Cl	H	4-CF_3-C_6H_4	OH (2·CH_3)	265 dec	33	B	R·DMF	$C_{21}H_{15}ClF_3NO_3$	C,H,N,Cl
8xxx	Cl	H	H	H (2-C_6H_5)[f]	>260	8	F	R·DMF	$C_{19}H_{14}ClNO_2$·0.1C_5H_7NO	C,H,N
8yyy	H	H	4-CF_3-C_6H_4	H (6-Cl)	>320	60	F	R·DMF, CH_3OH	$C_{20}H_{13}ClF_3NO_2$	C,H,N,Cl,F

[a] R = recrystallized, T = triturated. [b] Anal. calcd for H_2O, 4.02; found, 3.31. [c] Anal. calcd for C, 61.31; N, 3.58; found C, 60.86; N, 4.07. [d] Aqueous sulfuric acid suspension neutralized to pH 7.2 with 50% aqueous sodium hydroxide after completion of reaction. [e] Sodium salt of cyclohexanedione used as starting compound. [f] A suspension of the cyclohexanedione in DMF was added all at once to the suspension of sodium hydride in DMF. [g] Crude yield. [h] Anal. calcd for C, 67.89; N, 3.96; found C, 67.47; N, 4.41. [i] Phenyl group may be on C_4 rather than the C_2 structure is assigned based on analogy with other compounds in the series.

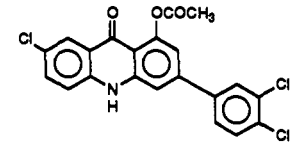
Chemistry

The general synthetic[3] approach utilized in preparing the 7-chloro-10-hydroxy-3-arylacridinedione precursors is outlined in Scheme I. The requisite benzaldehyde was allowed to react with acetone in the presence of base (procedure A) or with 1-(triphenylphosphoranylidene)-2-propanone in toluene (procedure A2) to provide the corresponding 1-aryl-1-buten-3-one. The arylaldehyde could also be allowed to react with 2-butanone under acidic conditions to provide exclusively the 4-aryl-3-methyl-3-buten-2-one (procedure A3). The unsaturated ketones were treated with the sodium salt of diethyl malonate and the intermediate 6-aryl-2-hydroxy-4-oxo-2-cyclohexene-1-carboxylic ester was hydrolyzed and decarboxylated to give 5-aryl-1,3-cyclohexanediones (**4**) (Table I). Several 5-alkyl-1,3-cyclohexanediones were also prepared similarly. Additional substitution of the 1,3-cyclohexanediones could be achieved by reaction of their pyrrolidinyl enamines with LDA and methyl or ethyl iodide followed by acid hydrolysis (procedure A5).[14-17] The 5-substituted 1,3-cyclohexanediones were treated with *o*-nitrobenzaldehyde to furnish 7-chloro-3-aryl-3,4-dihydro-10-hydroxy-1,9-(2*H*,10*H*)-acridinediones (**5**). An unusual, somewhat limiting, but well-documented, feature of the latter reaction is the simultaneous introduction of a chlorine atom into the 7-position. The importance of this halogen for biological activity is addressed later.

An early effort was made at acylation of the N–OH function of the acridinediones with the thought that this might aid in solubilization of the system as well as providing extended duration of action. Despite the report in the original patent,[3] several attempts provided instead C_1- or C_4-substituted products such as **6** or **7** (see Experimental Section).



6



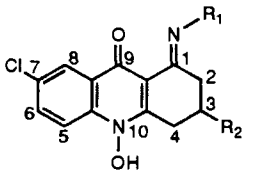
7

We then sought to increase solubility by derivatizing the ketone at the 1-position with a nitrogen containing functionality, **9**. We learned early on that this approach not only improved the physical properties of the series but led to improved biological activity and eliminated the requirement for the N_{10}-hydroxy function. Therefore an extensive exploration was undertaken.

The 7-chloro-3-aryl-3,4-dihydro-1,9(2*H*,10*H*)-acridinediones (**8**, R_1 = H) (the deshydroxy analogs) could be prepared by treating the parent N_{10}-hydroxy compounds with PCl_3. However this procedure limited analog synthesis to those with a chlorine at C_7. This shortcoming was circumvented by development of a much more flexible route involving (Scheme II) the reaction of an appropriately substituted isatoic anhydride with a 5-aryl-1,3-cyclohexanedione. The conversion of anilines to isatoic

(14) Szmuszkovicz, J. Enamines. In *Adv. Org. Chem. Methods and Results*. Raphael, R. A., Taylor, E. C., Wynberg, H., Eds.; Interscience: New York, 1963; Vol. 4, p 98.
(15) Bryson, T. A.; Gammill, R. B. Enamine Chemistry I. Carbanion Alkylations. *Tetrahedron Lett.* **1974**, 3963–3966.
(16) After Telschow, J. E.; Reusch, W. A Study of the Enamino Ketone Variant of the Robinson Annelation. *J. Org. Chem.* **1975**, *40*, 862–865.
(17) Stork, G.; et al. The Enamine Alkylation and Acylation of Carbonyl Compounds. *J. Am. Chem. Soc.* **1963**, *85*, 207–222.

Table III. Imines of 7-Chloro-3,4-dihydro-10-hydroxy-1,9(2*H*,10*H*)-acridinediones



no.	R_1	R_2	mp, °C	yield, purified %	proc.	purification solvent(s)[a]	formula	analysis (±0.40)
3a	$(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	208–210	73	H[b]	R-C_2H_5OH	$C_{24}H_{24}Cl_3N_3O_2$	C,H,N
3b	$(CH_2)_3CH_3$	3,4-Cl_2-C_6H_3	185–187	52	H[b]	R-$CH_3CO_2C_2H_5$	$C_{23}H_{21}N_2O_2$	C,H,N
3c	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	130–135	79	H	R-C_6H_6, C_6H_{12}	$C_{25}H_{25}ClF_3N_3O_2 \cdot 0.4H_2O$	C,H,N,Cl,F,H_2O
3d	$(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	212–213	61	H	R-C_2H_5OH	$C_{25}H_{26}Cl_3N_3O_2$	C,H,N
3e	$O(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	178–180	87	H	R-$CH_3CO_2C_2H_5$	$C_{25}H_{26}Cl_3N_3O_3$	C,H,N
3f	$(CH_2)_3N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	182–184	74	H	R-$CH_3CO_2C_2H_5$	$C_{26}H_{28}Cl_3N_3O_2$	C,H,N
3g	$(CH_2)_3N(CH_3)_2$	1-naphthyl	205–206	72	H	T-$CH_3CO_2C_2H_5$	$C_{26}H_{28}ClN_3O_2$	C,H,N,Cl
3h	$(CH_2)_3N(CH_3)_2$	3,4,5-$(OCH_3)_3$-C_6H_2	171–174	91	H	T-C_6H_{12}	$C_{27}H_{32}ClN_3O_5 \cdot 0.15H_2O$	C,H,N,Cl,H_2O
3i	$(CH_2)_3N(CH_3)_2$	3-CF_3-C_6H_4	134–136	91	H	R-C_6H_6, C_6H_{12}	$C_{25}H_{25}ClF_3N_3O_2$	C,H,N,Cl,F
3j	$(CH_2)_6CH_3$	3-CF_3-C_6H_4	111–113	90	H	T-C_6H_6, pet. ether	$C_{27}H_{28}ClF_3N_2O_2$	C,H,N,Cl,F
3k	$(CH_2)_3OCH_3$	3-CF_3-C_6H_4	135–137	83	H	R-C_6H_6, C_6H_{12}	$C_{24}H_{22}ClF_3N_2O_3 \cdot 0.5H_2O$	C,H,N,Cl,F,H_2O
3l	CH_2-C_6H_3-3,4-Cl_2	3-CF_3-C_6H_4	84–88	54	H	T-C_6H_{12}	$C_{27}H_{16}Cl_3F_3N_2O_2$	C,H,N,Cl
3m	$(CH_2)_7N(CH_3)_2$	3,4-Cl_2-C_6H_3	155	95	H	T-ether	$C_{26}H_{32}Cl_3N_3O_2$	C,H,N,Cl
3n	$(CH_2)_3N(CH_2)_5$	3,4-Cl_2-C_6H_3	195–197	87	H	T-$CH_3CO_2C_2H_5$	$C_{27}H_{28}Cl_3N_3O_2$	C,H,N
3o	$CH(CH_3)(CH_2)_3N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	150–154	98	H[c]	R-ether	$C_{28}H_{32}Cl_3N_3O_2 \cdot 2HCl \cdot 1.2H_2O$	C,H,N,Cl,Cl^-,H_2O
3p	$(CH_2)_3N(CH_3)_2$	4-Me_2N-C_6H_4	184–185	61	H	none	$C_{28}H_{31}ClN_4O_2 \cdot 0.4H_2O$	C,H,N,Cl,H_2O
3q	$(CH_2)_3SCH_3$	3,4-Cl_2-C_6H_3	190–192	75	H	R-C_2H_5OH	$C_{23}H_{21}Cl_3N_2O_2S$	C,H,N
3r	$(CH_2)_3N(CH_3)_2$	2,6-Cl_2-C_6H_3	100–105	65	H	T-C_6H_{12}	$C_{24}H_{24}Cl_3N_2O_2 \cdot 0.7H_2O$	C,H,N,Cl,H_2O
3s	$(CH_2)_3N(CH_3)_2$	3-Br-C_6H_4	158–161	83	H	R-C_6H_6, C_6H_{12}	$C_{24}H_{25}BrClN_3O_2 \cdot 0.3H_2O$	C,H,N,Br,Cl,H_2O
3t	CH_3	3,4-Cl_2-C_6H_3	231 dec	80	H[d]	T-C_2H_5OH	$C_{20}H_{15}Cl_3N_2O_2$	C,H,N
3u		3,4-Cl_2-C_6H_3	163–179	48	H[b]	R-$CH_3CO_2C_2H_5$, C_6H_{12}	$C_{26}H_{26}Cl_3N_3O_2$	C,H,N
3v	$(CH_2)_3N(CH_3)_2$	C_6H_5	122–126 p.s.	98	H	T-C_6H_6, C_6H_{12}	$C_{24}H_{26}ClN_3O_2 \cdot H_2O$	C,H,N,Cl,H_2O
3w	$(CH_2)_2N(C_2H_5)CH_2$-C(OH)$(CH_3)_2$	3,4-Cl_2-C_6H_3	175–179	96	H	T-C_6H_{12}	$C_{27}H_{30}Cl_3N_3O_3$	C,H,N
3x	$(CH_2)_2N[CH_2CH(CH_3)_2]_2$	3,4-Cl_2-C_6H_3	196–197	62	H	none	$C_{29}H_{34}Cl_3N_3O_2$	C,H,N
3y	$(CH_2)_3N(CH_2CH_2OH)_2$	3,4-Cl_2-C_6H_3	112–115	68	H	T-CH_3CN	$C_{26}H_{28}Cl_3N_3O_4 \cdot 0.8H_2O$	C,H,N,Cl,H_2O
3z	$(CH_2)_3NHCH_2CH_2OH$	3,4-Cl_2-C_6H_3	187–188	83	H	R-C_2H_5OH	$C_{24}H_{24}Cl_3N_3O_3$	C,H,N,Cl
3aa	4-C_6H_{12}-$N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	144–149	97	H	T-n-C_7H_{16}	$C_{28}H_{32}Cl_3N_3O_2 \cdot 0.4H_2O$	C,H,N,Cl,H_2O
3bb	H	3-CF_3-C_6H_4	248 dec	90	H[e]	T-C_2H_5OH	$C_{20}H_{14}ClF_3N_2O_2$	C,H,N
3cc	$(CH_2)_2NHCH_2CH{=}CH_2$	3-CF_3-C_6H_4	198–200	73	H	R-ether	$C_{25}H_{23}ClF_3N_3O_2$	C,H,N,Cl,F
3dd	3-C_6H_4-$CH_2N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	100–105	32	H[f]	R-$CHCl_3$	$C_{30}H_{28}Cl_3N_3O_2 \cdot 1.1H_2O$	C,H,N,Cl,H_2O
3ee	$(CH_2)_3N(CH_3)_2$	$(CH_2)_5$	185–187	88	H	T-C_6H_{12}	$C_{23}H_{30}ClN_3O_2$	C,H,N,Cl
3ff	$CH_2CH(C_2H_5)NH$-*n*-C_4H_9	3-CF_3-C_6H_4	167–168	100	H	T-n-C_7H_{16}	$C_{26}H_{31}ClF_3N_3O_2$	C,H,N,Cl,F
3gg	$(CH_2)_2N(n\text{-}C_4H_9)_2$	3-CF_3-C_6H_4	169.5–170.5	88	H	T-n-C_7H_{16}	$C_{30}H_{35}ClF_3N_3O_2$	C,H,N,Cl,F
3hh	$(CH_2)_3N(CH_3)_2$	$CH(CH_3)_2$	106–113	74	H	R-CH_3CN	$C_{20}H_{26}ClN_3O_2 \cdot 0.5H_2O$	C,H,N,H_2O
3ii	$(CH_2)_3NH$-*n*-C_4H_9	3,4-Cl_2-C_6H_3	142–144	36	H	R-$CH_3CO_2C_2H_5$	$C_{28}H_{28}Cl_3N_3O_2 \cdot 0.3H_2O$	C,H,N,H_2O
3jj	$(CH_2)_3N(C_2H_5)CH_2CH_2OH$	3,4-Cl_2-C_6H_3	87–90	79	H	R-CH_3CN	$C_{26}H_{28}Cl_3N_3O_3 \cdot 0.5H_2O$	C,H,N,H_2O
3kk	$(CH_2)_3N(CH_2CH_2)_2N(CH_3)$	3,4-Cl_2-C_6H_3	200–202	90	H	T-$CH_3CO_2C_2H_5$	$C_{27}H_{29}Cl_3N_4O_2$	C,H,N
3ll	$(CH_2)_4N(CH_2)_4$	3-CF_3-C_6H_4	144–148	88	H	T-n-C_7H_{16}	$C_{28}H_{29}ClF_3N_3O_2$	C,H,N,Cl,F
3mm	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	197–199	70	H	R-$CH_3CO_2C_2H_5$	$C_{28}H_{32}Cl_3N_3O_2$	C,H,N
3nn	$(CH_2)_5N(CH_2)_4$	3-CF_3-C_6H_4	120–124	95	H	T-n-C_7H_{16}	$C_{29}H_{31}ClF_3N_3O_2$	C,H,N,Cl,^9F
3oo	$CH_2CH(CH_3)N(CH_3)_2$	3-CF_3-C_6H_4	168–171	81	H	R-C_6H_6	$C_{27}H_{29}ClF_3N_3O_2$	C,H,N
3pp	$(CH_2)_3N(CH_2)_4$	3-CF_3-C_6H_4	165–166	83	H	T-n-C_7H_{16}	$C_{27}H_{27}ClF_3N_3O_2 \cdot 0.25H_2O$	C,H,N,H_2O
3qq	$(CH_2)_2N(CH_2)_4$	3-CF_3-C_6H_4	191–192	52	H	R-toluene	$C_{28}H_{25}ClF_3N_3O_2$	C,H,N,Cl,F
3rr	$(CH_2)_6N(CH_2)_5$	3-CF_3-C_6H_4	167–170 dec	38	H[c]	T-$CH_3CO_2C_2H_5$	$C_{31}H_{36}ClF_3N_3O_2 \cdot 1.5HCl \cdot 1.1H_2O$	C,H,N,Cl,F,H_2O
3ss	$CH(CH_2CH_2)_2N$-$CH_2C_6H_5$	3-CF_3-C_6H_4	133–140	75	H[h]	R-toluene, C_6H_{12}	$C_{32}H_{29}ClF_3N_3O_2 \cdot 0.1HCl \cdot 0.5H_2O$	C,H,N,Cl,Cl^-,F,H_2O
3tt	$(CH_2)_3N(C_2H_5)_2$	4-CF_3-C_6H_4	182–183	90	H	R-CH_2Cl_2:tol.:C_6H_{14}	$C_{26}H_{27}ClF_3N_3O_2$	C,H,N,Cl,F
3uu	$(CH_2)_3N(CH_2)_4$	4-CF_3-C_6H_4	182–183	80	H	R-CH_2Cl_2:tol.:C_6H_{14}	$C_{27}H_{27}ClF_3N_3O_2$	C,H,N,Cl,F
3vv	$(CH_2)_3N(C_2H_5)_2$	4-CF_3-C_6H_4	155–157	88	H	R-CH_2Cl_2:tol.:C_6H_{14}	$C_{27}H_{29}ClF_3N_3O_2$	C,H,N,Cl,F
3ww	$(CH_2)_4N(C_2H_5)_2$	4-CF_3-C_6H_4	122–125	40	H	R-CH_2Cl_2:C_6H_{12}	$C_{26}H_{31}ClF_3N_3O_2$	C,H,N,Cl,F
3xx	$(CH_2)_3N(CH_2CH_2OH)_2$	4-CF_3-C_6H_4	87–90	77	H	R-CH_2Cl_2–ether	$C_{27}H_{29}ClF_3N_3O_4$	C,H,N,Cl,F

3yy	$(CH_2)_3N(CH_2)_5$	4-CF_3-C_6H_4	194–195	95	H	R-CH_2Cl_2–ether	$C_{28}H_{33}ClF_3N_3O_2$	C,H,N,Cl,F
3zz	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	4-CF_3-C_6H_4	172–173	59	H	R-CH_2Cl_2–ether	$C_{28}H_{33}ClF_3N_3O_2$	C,H,N,Cl,F
3aaa	$(CH_2)_3N(C_2H_5)_2$	3,4,5-$(OCH_3)_3$-C_6H_2	142–145	51	H′	R-CH_2Cl_2–ether	$C_{28}H_{36}ClN_3O_5$	C,H,N,Cl
3bbb	$(CH_2)_2CH_3$	4-CF_3-C_6H_4	199–201	71	H	R-$CH_3CO_2C_2H_5$	$C_{24}H_{22}ClF_3N_2O_2$	C,H,N
3ccc	$(CH_2)_6CH_3$	4-CF_3-C_6H_4	99–101	83	H	R-C_2H_5–C_6H_{12}	$C_{27}H_{28}ClF_3N_2O_2$	C,H,N
3ddd	$(CH_2)_3N(CH_2)_4$	3,4,5-$(OCH_3)_3$-C_6H_2	152–154	24	H′	R-CH_2Cl_2–ether	$C_{28}H_{34}ClN_3O_6$	C,H,N,Cl
3eee	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	3,4,5-$(OCH_3)_3$-C_6H_2	152–154	51	H	R-$CH_2CO_2C_2H_5$–ether	$C_{31}H_{40}ClN_3O_6$	C,H,N,Cl
3fff	$(CH_2)_2NHCH_2CH{=}CH_2$	4-CF_3-C_6H_4	116–119	78	J	R-$CH_2CO_2C_2H_5$–ether	$C_{28}H_{28}ClF_3N_2O_2$	C,H,N,Cl,F
3ggg	$(CH_2)_3N(CH_2)_5$	3,4,5-$(OCH_3)_3$-C_6H_2	168–171	43	J	T-C_6H_6–ether	$C_{30}H_{36}ClN_3O_6$	C,H,N,Cl
3hhh	$(CH_2)_2N(C_2H_5)_2$	3,4,5-$(OCH_3)_3$-C_6H_2	174–176	42	J′	R-CH_2Cl_2–toluene	$C_{29}H_{34}ClN_3O_6$	C,H,N,Cl
3iii	$(CH_2)_3NHCH_2CH_2OH$	4-CF_3-C_6H_4	142–145	53	J′	R-CH_2Cl_2–toluene	$C_{25}H_{25}ClF_3N_3O_3$	C,H,N,Cl,F
3jjj	$CH_2CH(C_2H_5)NH(CH_2)_3CH_3$	4-CF_3-C_6H_4	162–164	81	J	R-CH_2Cl_2–i-Pr ether	$C_{28}H_{31}ClF_3N_3O_2$	C,H,N,Cl,F
3kkk	$(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	172–174	65	H	R-CH_2Cl_2–toluene	$C_{24}H_{24}Cl_3N_3O_2$	C,H,N,Cl
3lll	$(CH_2)_3N(CH_3)_2$	2-Cl-C_6H_4	165–167	80	H	R-CH_2Cl_2–C_6H_{14}	$C_{24}H_{25}Cl_2N_3O_2$	C,H,N,Cl
3mmm	$(CH_2)_3N(CH_3)_2$	4-C_6H_{11}-C_6H_4	198–199	83	H	R-CH_2Cl_2–CH_3CO_2Et	$C_{30}H_{36}ClN_3O_2$	C,H,N,Cl
3nnn	$(CH_2)_3N(CH_3)_2$	2-CF_3-C_6H_4	194–196	93	H	T-C_6H_{12}	$C_{28}H_{32}ClF_3N_3O_2$	C,H,N
3ooo	$(CH_2)_3N(CH_3)_2$	2-OCH_3-C_6H_4	186–188	78	H	T-C_6H_6, C_6H_{12}	$C_{25}H_{28}ClN_3O_3$	C,H,N
3ppp	$(CH_2)_3N(CH_3)_2$	4-OCH_3-C_6H_4	143–147	88	H	T-C_6H_6, C_6H_{12}	$C_{25}H_{28}ClN_3O_3{\cdot}0.1H_2O$	C,H,N,H_2O
3qqq	$(CH_2)_3N(CH_3)_2$	4-CH_3-C_6H_4	150–155	90	H	T-C_6H_6, C_6H_{12}	$C_{25}H_{28}ClN_3O_2{\cdot}H_2O$	C,H,N,H_2O
3rrr	$(CH_2)_3N(CH_3)_2$	4-C_5H_4N	174–175	89	H	R-CH_2Cl_2–ether	$C_{23}H_{25}ClN_4O_2$	C,H,N,Cl
3sss	$(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3-(2-CH_3)	192–195	45	H	R-CH_2CN	$C_{25}H_{26}Cl_4N_3O_2$	C,H,N,Cl
3ttt	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_3-(2-CH_3)	195–197	22	H	R-ether–pet. ether	$C_{28}H_{27}ClF_3N_3O_2$	C,H,N,Cl

[a] R = recrystallized, T = triturated. [b] Reactants stirred at ambient temperature overnight and then mixed with additional base under reflux for 1–2 h. [c] Oily free base converted to HCl salt. [d] 40% aqueous CH_3NH_2 used as starting amine. [e] Excess concentrated NH_4OH used as starting amine. [f] Reactants heated at reflux for 18.5 h and then mixed with additional base at reflux for 26 h; purified via the HCl salt. [g] Anal. calcd for Cl, 6.49; found, 6.90. [h] Dihydrochloride of the starting amine utilized; reactants were heated at reflux for 3.5 h, stirred at room temperature overnight, and then heated under reflux for 3 h. [i] Purification included chromatography over silica gel.

anhydrides was utilized to provide a variety of substituents in the C_5–C_8 positions. N-unsubstituted isatoic anhydrides could readily be alkylated, and these *N*-alkyl intermediates allowed the preparation of several N_{10}-alkyl acridinediones. These N_{10}-alkyl acridinediones had very limited antimalarial activity, and attempts to prepare the imines led only to aromatized products so this area was dropped.

The possibility existed that the product of the reaction between the 4-substituted-5-aryl-1,3-cyclohexanediones and *o*-nitrobenzaldehyde as well as with isatoic anhydride could be the 4-substituted isomer **10** and not the predicted (on steric considerations) 2-substituted isomer **8**. To address this possibility, a long-range ^{13}C–^1H NMR correlation experiment with fixed evolution time (XCORFE),[29] designed to exhibit coupling between ^{13}C and ^1H nuclei separated by two or three bonds, was performed. If the product was **8** (R_3 = CH_3), a three-bond coupling between the protons of the 2-CH_3 group and the 1-carbonyl carbon should be evident. Such was indeed the case. If, on the other hand, the product was the 4-methyl analog (i.e. **10**, R_3 = CH_3), no coupling would have been observed due to the five-bond distance between the nuclei. The same coupling was observed for the product with isatoic anhydride confirming the structures as 2-substituted.

10

Most N–OH and N–H acridinediones could be derivatized readily by treatment with simple alkylamines. More difficulty was encountered with isolation of imines from longer chain amines because of their reduced tendency to crystallize. The intermediate carbethoxycyclohexanedione (precursor of **4**) could also be isolated and converted to the corresponding 2-carbethoxyacridinedione but imino derivatives of these analogs could not be prepared, probably because of the enolic character of the ketone which was now part of a β-keto ester system.

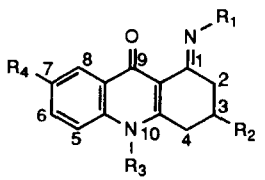
Several C2-substituted acridinediones and the corresponding imines were prepared. These compounds can exist as cis,trans isomers. In two cases we were able to separate the mixtures by column chromatography (**9kk**, **9ll**, and **9nn**, **9oo**). Preliminary stereochemical assignments were made on the basis of the NMR spectra of these compounds. However since biological activity was not affected in these cis,trans pairs, further studies to define their stereochemistry were abandoned.

It was important to examine some of the many features of this active structure in terms of the role they play in the biological activity. Exploration of a variety of these are described below.

To observe the effect of removal of the C_9-oxygen, a few representative compounds were synthesized (Scheme III). 2-Aminobenzaldehyde or 5-chloro-2-aminobenzaldehyde was allowed to react with a 5-substituted 1,3-cyclohexanedione in the presence of piperidine to afford the corresponding 3,4-dihydro-3-substituted-1(2*H*)-acridinone. Treatment of this with *N*,*N*-dimethyl-1,3-propanediamine and a catalytic amount of *p*-toluenesulfonic acid gave the imine derivative, whereas oxidation with *m*-chloroperoxybenzoic acid provided the N_{10}-oxide.

Alternatively, introduction of an amino side chain at C_9 was accomplished by two separate pathways. In the first (Scheme IV) 2-amino-5-chlorobenzonitrile was allowed to

Table IV. Imines of 3,4-Dihydro-1,9(2*H*,10*H*)-acridinediones



no.	R_1	R_2	R_3	R_4	mp, °C	yield, purified %	proc.	purification solvent(s)[a]	formula	analysis (±0.40)
9a	$(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	H	Cl	216–219	64	H	R-C_2H_5OH	$C_{24}H_{24}Cl_3N_3O$	C,H,N
9b	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	Cl	211–213	89	H	none	$C_{25}H_{25}ClF_3N_3O$	C,H,N,Cl,F
9c	$(CH_2)_3N(CH_3)_2$	C_6H_{11}	H	Cl	164–165	75	H	none	$C_{23}H_{30}ClN_3O$	C,H,N,Cl
9d	$(CH_2)_3N(CH_3)_2$	3-CF_3-C_6H_4	H	Cl	205–207	58	H	R-C_2H_5OH	$C_{25}H_{25}ClF_3N_3O$	C,H,N
9e	$(CH_2)_3CH_3$	3,4-Cl_2-C_6H_3	H	Cl	295–298 dec	82	H	R-DMF	$C_{22}H_{21}Cl_3N_2O$	C,H,N
9f	$(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	H	Cl	273–275 dec	80	H	R-DMF	$C_{25}H_{26}Cl_3N_3O$	C,H,N
9g	$(CH_2)_2N(CH_3)_2$	4-CF_3-C_6H_4	H	I	227–229	86	H	none	$C_{25}H_{25}F_3IN_3O$	C,H,N,F,I
9h	$(CH_2)CH(CH_3)N(CH_3)_2$	4-CF_3-C_6H_4	H	Cl	275–276	91	H	none	$C_{25}H_{25}ClF_3N_3O$	C,H,N
9i	$(CH_2)_2N(C_2H_5)_2$	4-CF_3-C_6H_4	H	Cl	233–235	69	H	none	$C_{26}H_{27}ClF_3N_3O$	C,H,N
9j	$(CH_2)_7N(C_2H_5)_2$	4-CF_3-C_6H_4	H	Cl	148–152	77	H	R-C_6H_{12}	$C_{31}H_{37}ClF_3N_3O$	C,H,N
9k	$(CH_2)_3CH_3$	4-CF_3-C_6H_4	H	Cl	262–266	78	H	R-DMF	$C_{24}H_{22}ClF_3N_2O$	C,H,N
9l	$CH(CH_3)(CH_2)_3N(C_2H_5)_2$	4-CF_3-C_6H_4	H	Cl	141–143	53	H	R-CH_3CN	$C_{26}H_{33}ClF_3N_3O$	C,H,N
9m	$(CH_2)_4N(C_2H_5)_2$	4-CF_3-C_6H_4	H	Cl	>300	29	H	none	$C_{26}H_{31}ClF_3N_3O$-0.5H_2O	C,H,N,H_2O
9n	$(CH_2)_3N(CH_3)_2$	2-Cl-C_6H_4	H	Cl	154–157	82	H	none	$C_{24}H_{25}Cl_2N_3O$	C,H,N,Cl
9o	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	NO_2	245–246	69	H	R-CH_2Cl_2–CH_3CO_2Et	$C_{25}H_{25}F_3N_4O_3$	C,H,N,F
9p	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	4-CF_3-C_6H_4	H	Cl	172–174	79	H	R-C_2H_5OH	$C_{26}H_{33}ClF_3N_3O$	C,H,N
9q	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	C_2H_5	206–208	69	H	none	$C_{27}H_{30}F_3N_3O$	C,H,N,F
9r	$(CH_2)_3N(CH_3)_2$	4-C_6H_{11}-C_6H_4	H	Cl	217–218	82	H	none	$C_{30}H_{36}ClN_3O$	C,H,N,Cl
9s	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	Br (5-Br)	186–187	89	H	none	$C_{25}H_{24}Br_2F_3N_3O$	C,H,N,Br,F
9t	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	Br	224–225	69	H	none	$C_{25}H_{25}BrF_3N_3O$	C,H,N,Br,F
9u	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	H	197–200	52	H	none	$C_{25}H_{26}F_3N_3O$	C,H,N,F
9v	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	OCH_3	228–232	71	H	none	$C_{26}H_{26}F_3N_3O_2$	C,H,N,F
9w	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	Cl (5-Cl)	163–165	81	H	none	$C_{25}H_{24}Cl_2F_3N_3O$	C,H,N,Cl,F
9x	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	F	221–223	81	H	none	$C_{25}H_{25}F_4N_3O$	C,H,N,F
9y	$(CH_2)_3N(CH_3)_2$	2-OCH_3-C_6H_4	H	Cl	184–185	62	H	R-C_2H_5OH	$C_{26}H_{28}ClN_3O_2$	C,[b]H,N,Cl
9z	$(CH_2)_3N(CH_3)_2$	4-CH_3-C_6H_4	H	Cl	213–215	68	H	R-$CH_3CO_2C_2H_5$	$C_{25}H_{28}ClN_3O$	C,H,N,Cl
9aa	$(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	H	Cl	168–170	39	H	R-CH_2Cl_2–CH_3CO_2Et	$C_{24}H_{24}Cl_3N_3O$	C,H,N,Cl
9bb	$(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	H	H (5-Cl)	206–207	96	H	none	$C_{24}H_{24}Cl_3N_3O$	C,H,N,Cl
9cc	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_3	H	H (8-Cl)	249–250	60	H[c]	R-CH_3OH–CH_3CO_2Et	$C_{25}H_{25}ClF_3N_3O$-2HCl-0.1H_2O	C,H,N,Cl,Cl$^-$, F,H_2O
9dd	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H	CF_3	201–204	94	H	R-CH_2Cl_2–C_6H_{14}	$C_{26}H_{25}F_6N_3O$	C,H,N,F
9ee	$(CH_2)_3N(CH_3)_2$	4-OCH_3-C_6H_4	H	Cl	204–205	53	H[d]	R-$CHCl_3$–CH_3OH	$C_{25}H_{28}ClN_3O_2$	C,H,N,Cl
9ff	$(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	H	H (5,8-Cl_2)	185–187	67	H	R-$CH_3CO_2C_2H_5$	$C_{24}H_{23}Cl_4N_3O$	C,H,N,Cl
9gg	$(CH_2)_3N(CH_3)_2$	4-C_5H_4N	H	Cl	208–210	84	H	R-CH_2Cl_2–CH_3CO_2Et	$C_{23}H_{25}ClN_4O$	C,H,N,Cl
9hh	$(CH_2)_3N(CH_3)_2$	4-SCH_3-C_6H_4	H	Cl	203–205	81	H	R-C_2H_5OH	$C_{25}H_{28}ClN_3OS$	C,H,N
9ii	$(CH_2)_3N(CH_3)_2$	4-NO_2-C_6H_4	H	Cl	202–205	60	H	R-C_2H_5OH	$C_{24}H_{25}ClN_4O_3$	C,H,N
9jj	$(CH_2)_3N(CH_3)_2$	2-C_5H_4N	H	Cl	168–170	73	H	none	$C_{23}H_{25}ClN_4O$	C,H,N,Cl
9kk	$(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	H (*cis*-2-CH_3)	Cl	147–150	21	H[d]	R-CH_3CN	$C_{25}H_{26}Cl_3N_3O$	C,H,N
9ll	$(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	H (*trans*-2-CH_3)	Cl	229–231	5	H[d]	R-C_2H_5OH	$C_{25}H_{26}Cl_3N_3O$	C,H,N
9mm	$(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	H (2-C_6H_5)[e]	Cl	198–200	84	H	R-CH_3CN	$C_{30}H_{28}Cl_3N_3O$	C,H,N
9nn	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H (*cis*-2-CH_3)	Cl	169–170	20	H[d]	R-$CHCl_3$–CH_3OH	$C_{26}H_{27}ClF_3N_3O$	C,H,N,Cl
9oo	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H (*trans*-2-CH_3)	Cl	171–172	22	H[d]	R-$CHCl_3$–CH_3OH	$C_{26}H_{27}ClF_3N_3O$	C,H,N,Cl
9pp	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H (2-C_2H_5)[e]	Cl	117–120	44	H	R-ether–pet. ether	$C_{27}H_{29}ClF_3N_3O$	C,H,N,Cl,F
9qq	$(CH_2)_3N(CH_3)_2$	4-Cl, 3-CF_3-C_6H_3	H	Cl	228–230	63	H	R-C_2H_5OH	$C_{25}H_{24}Cl_2F_3N_3O$	C,H,N,Cl
9rr	$(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	H (6-Cl)	H	200–201	69	H	none	$C_{24}H_{24}Cl_3N_3O$	C,H,N,Cl
9ss	$(CH_2)_2N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	H	Cl	223–225	90	H	none	$C_{25}H_{26}Cl_3N_3O$	C,H,N,Cl
9tt	$(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	H (2-CH_2-C_6H_5)[e]	Cl	>69	71	H[d]	R-$CHCl_3$–CH_3OH	$C_{31}H_{30}Cl_3N_3O$-0.5H_2O	C,H,N,H_2O
9uu	$(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	H (2-CH_3)[e]	Cl	165–178	36	H	R-ether–pet. ether	$C_{25}H_{26}Cl_3N_3O$	C,H,N,Cl
9vv	$(CH_2)_4N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	H	Cl	157–161	80	H	none	$C_{27}H_{30}Cl_3N_3O$	C,H,N,Cl
9ww	$(CH_2)_3N(CH_2)_4$	2,4-Cl_2-C_6H_3	H	Cl	176–177	74	H[f]	T-CH_3OH–ether	$C_{26}H_{26}Cl_3N_3O$	C,H,N,Cl

9xx	$(CH_2)_2N(CH_2CH_2OH)_2$	2,4-Cl_2-C_6H_3	H	Cl	160–162 (p.s.)	80	H[f]	R-CH_3OH-CH_2Cl_2	$C_{28}H_{36}Cl_3N_3O_3$·0.5H_2O	C,H,N,Cl,·H_2O
9yy	$CH_2CH(C_2H_5)NH$-n-C_4H_9	2,4-Cl_2-C_6H_3	H	Cl	173–175	83	H[f]	R-$CH_3CO_2C_2H_5$	$C_{27}H_{36}Cl_3N_3O$	C,H,N,Cl
9zz	$CH_2C(CH_3)_2CH_2N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	H	Cl	153–154	84	H[f]	R-$CH_3CO_2C_2H_5$	$C_{28}H_{38}Cl_3N_3O$	C,H,N,Cl
9aaa	$CH(CH_3)CH_2N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	H	Cl	157–160	64	H[f]	T-C_2H_5OH	$C_{28}H_{38}Cl_3N_3O$	C,H,N,Cl
9bbb	$(CH_2)_7N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	H	Cl	135–137	84	H[f]	R-CH_2Cl_2-i-Pr. ether	$C_{30}H_{36}Cl_3N_3O$	C,H,N,Cl
9ccc	H	4-CF_3-C_6H_4	H	Cl	260 dec	42	H[f,g]	R-DMF-CH_3CN	$C_{20}H_{11}ClF_3N_3O$	C,H,N
9ddd	$(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	H (6-Cl)	Cl	229–231	82	H	none	$C_{23}H_{25}ClF_3N_3O$	C,H,N
9eee	$(CH_2)_2NHCH_2CH_2OH$	2,4-Cl_2-C_6H_3	H	Cl	224–225	52	H[h]	R-C_2H_5OH	$C_{23}H_{25}Cl_3N_3O_2$	C,H,N,Cl
9fff	$(CH_2)_2NH_2$	2,4-Cl_2-C_6H_3	H	Cl	224–225	52	H[h]	R-C_2H_5OH	$C_{21}H_{19}Cl_3N_3O$	C,H,N,Cl

[a] R = recrystallized, T = triturated. [b] Anal. calcd for C, 63.55; found, 63.02. [c] Crude free base converted to HCl salt. [d] Purification included chromatography through silica gel. [e] Cis,trans mix. [f] DMF used in place of ethanol. [g] Excess concentrated NH_4OH used as starting amine. [h] Reaction stirred 1–2 min with DMF as solvent to prevent dimer formation.

react with a 5-substituted-1,3-cyclohexanedione in the presence of *p*-toluenesulfonic acid to afford 5-chloro-2-[(5-substituted-3-oxo-1-cyclohexenyl)amino]benzonitrile. Zinc chloride effected cyclization to 9-amino-7-chloro-3,4-dihydro-3-substituted-1(2*H*)-acridinone which when allowed to react with iodomethane and sodium hydride furnished 7-chloro-3,4-dihydro-9-(methylamino)-3-substituted-1(2*H*)-acridinone. The alternative pathway (Scheme V) involved treatment of 7,9-dichloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone with *N*,*N*-dimethyl-1,3-propanediamine to give 7-chloro-9-[[3-(dimethylamino)propyl]amino]-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone. The dichloro compound had been prepared by chlorination of 7-chloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1,9-(2*H*,10*H*)-acridinedione with phosphorus oxychloride. Unfortunately, all such major structural changes resulted in elimination of antimalarial activity.

Suppressive Antimalarial Screening in Mice

All of the compounds listed in Tables II–IV were tested initially against a normal drug-sensitive strain of *Plasmodium berghei* by the parenteral route.[20] The compounds were dissolved or suspended in sesame or peanut oil and were administered to mice in a single subcutaneous dose 72 h postinfection. The antimalarial activites are summaried in Tables V–VII.

As a class, the 3-aryl-10-hydroxy-3,4-dihydroacridine-1,9(2*H*,10*H*)-diones are very potent antimalarial agents, many of them showing curative activity below dosages of 20 mg/kg. The best compounds in this group (Table V) were the 3-(4-trifluoromethylphenyl) (floxacrine), the 3-(2,4-dichlorophenyl), the 3-(3,4-dichlorophenyl)-2-methyl, and the 3-(2,4-dichlorophenyl)-2-methyl analogs.

Contrary to a previous report,[21] we have found that removal of the N_{10}-oxygen does not completely eradicate antimalarial activity. The N_{10}-H acridinediones that we prepared generally displayed a high level of activity, albeit not quite that of their N_{10}-OH analogs. The two best compounds in this group were the 3-(2,4-dichlorophenyl) and the 3-(4-trifluoromethylphenyl) derivatives.

Except for the N_{10}-allyl derivative, which showed modest activity, the N_{10}-alkyl acridinediones reported here were all inactive.

Imines of the N_{10}-OH acridinediones showed activity roughly comparable to their precursors although some toxicity was evident at higher doses. Higher molecular weight sidechains tend to improve activity somewhat whereas those containing cyclic moieties show a small decrease.

Imines of the N_{10}-H acridinediones were surprisingly the most active compounds synthesized for this study, notably those of the 3-(2,4-dichlorophenyl) analog. Nearly all of the imines of 7-chloro-3-(2,4-dichlorophenyl)-3,4-di-

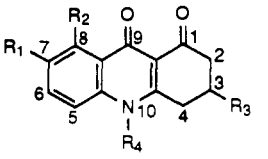
(18) Castle, R.; Adachi, K.; Guther, W. D. Cinnoline Chemistry XII. The Synthesis of 6-fluoro-4-methylcinnoline and other Cinnolines as Potential Antitumor Agents. *J. Heterocycl. Chem.* **1965**, *2*, 459–462.

(19) Hardtmann, G. E.; Koletar, G.; Pfister, O. R. The Chemistry of 2H-3,1-Benzoxazine-2,4(1H)dione (Isatoic Anhydrides) 1. The Synthesis of N-substituted 2H-3,1-benzoxazine-2,4(1H) diones. *J. Heterocycl. Chem.* **1975**, *12*, 565.

(20) Osdene, T. S.; Russell, P. B.; Rane, L. 2,4,7-Triamino-6-ortho-substituted Arylpteridines. A New Series of Antimalarial Agents. *J. Med. Chem.* **1967**, *10*, 431–434.

(21) Raether, W.; Durckheimer, W. Abstract of the 4th Intl. Congress of Parasitology. Congress Organizing Committee: Warsaw, 1978; Section D, p 105.

Table V. Effects of 7-Chloro-3-substituted-3,4-dihydro-10-substituted-1,9(2*H*,10*H*)-acridinediones against Trophozoite-Induced *P. berghei* in Mice



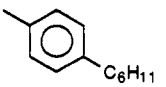
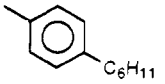
					ΔMST or C after single sc dose, mg/kg					
no.	R_1	R_2	R_3	R_4	640	320	160	80	40	20
8a	Cl	H	3,4-Cl_2-C_6H_3	OH	5C	5C	2C (11)	10.8	5.0	3.2
8b	Cl	H	$CH(CH_3)_2$	OH	5C	8.3	3.5	1.7	0.3	0.1
8c	Cl	H	3-CF_3-C_6H_4	OH	5C	5C	3C (13.4)	12.1	8.8	6.0
8d	Cl	H	3-CF_3-C_6H_4	ONa	5C	3C (16.0)	13.8	10	7.8	6.4
8e	Cl	H	3-CF_3-C_6H_4	H	5.3	3.3	2.3	0.3		
8f	H	H	3,4-Cl_2-C_6H_3	OH	2C (12.6)	1C (7.7)	5.1	3.1		
8g	Cl	Cl	3,4-Cl_2-C_6H_3	OH	0.3		0.1			
8h	Cl	H	C_6H_{11}	OH	1C (12.7)	6.5	2.9	2.5		
8i	Cl	H	3,4-Cl_2-C_6H_3	H	2C (11.2)	1C (10.2)	1C (7.7)	2.1		
8j	Cl	H	4-CF_3-C_6H_4	OH	3C (3.4)	5C	5C	5C	5C	4C (8.9)
8k	Cl	H	1-$C_{10}H_7$	OH	4C (13.7)	2C (5.7)	6.9	2.3		
8l	Cl	H	3,4,5-$(OCH_3)_3C_6H_2$	OH	7.0	2.7	1.8	1.3		
8m	Cl	H	4-$Et_2NCH_2CH_2OC_6H_4$	ONa	5.3		1.5			
8n	Cl	H	4-$Me_2NC_6H_4$	OH	5C	3C (6.8)	1C (6.6)	5.8	1.6	
8o	Cl	H	3-Br-C_6H_4	OH	4C (7.9)	1C (10.7)	1C (9.2)	5.9	2.5	0.1
8p	Cl	H	2,6-Cl_2-C_6H_3	OH	2C (11.2)	3C (23.9)	1C (5.8)	5.1	1.5	0.7
8q	H	H	$CH(CH_3)_2$	CH_3	0.5		0.2		−0.2	
8r	Cl	H	C_6H_5	OH	3C (11.5)	2C (9.3)	2C (5.7)	5.6	4.0	1.8
8s	Cl	H	$(CH_2)_5$	OH	0.0		0.2		0.0	
8t	Cl	H	$CH(CH_3)_2$	H	4C (14.6)	3C (15.6)	9.6	3.2	1.6	1.0
8u	Cl	H	3,4-Cl_2-C_6H_3	CH_3	0.2		0.6		0.0	
8v	Cl	H	4-CF_3-C_6H_4	H	5C	5C	5C	4C (9.4)	2C (9.9)	1C (8.9)
8w	Cl	H	2,4-Cl_2-C_6H_3	OH	5C	5C	5C	5C	5C	2C (1.9)
8x	Cl	H		H	0.2		0.0		0.6	
8y	Cl	H	3,4-Cl_2-C_6H_3 (2-Me)	OH	5C	5C	5C	5C	4C (9.6)	3C (7.6)
8z	Cl	H	4-CF_3-C_6H_4 (6-F)	OH	5T	5T	5T	5T	5T	9.0
8aa	Cl	Cl	4-CF_3-C_6H_4	OH	2C (9.8)	3C (7.0)	2C (7.0)	7.8	7.0	4.5
8bb	Cl	H	4-CF_3-C_6H_4	C_2H_5	1T (0.0)		2T (0.0)		2T (0.0)	
8cc	Cl	H	4-CF_3-C_6H_4	n-C_4H_9	0.4		−0.2		−0.2	
8dd	Cl	H	4-CF_3-C_6H_4	CH_2-C_6H_5	1T (0.3)		0.0		0.2	
8ee	Cl	H	2-Cl-C_6H_4	OH	4C (9.0)		1C (4.5)		4.6	1.7
8ff	I	H	4-CF_3-C_6H_4	H	0.4		0.4		0.2	
8gg	Cl	H	4-CF_3-C_6H_4	$CH_2CH{=}CH_2$	4C (15.0)		12.6		1C (8.5)	
8hh	Cl	H	4-CF_3-C_6H_4	n-C_6H_{13}	0.1		0.0		0.1	
8ii	Cl	H	2-Cl-C_6H_4	H	1C (9.6)		1C (0.4)	5.5	2.7	1.5
8jj	O_2N	H	4-CF_3-C_6H_4	H	1C (6.9)		2.8		4.1	0.7
8kk	Cl	H		OH	4.1		1.3		0.9	
8ll	Cl	H	2-CF_3-C_6H_4	OH	8.3		4.5		2.7	0.6
8mm	Cl	H	4-CH_3-C_6H_4	OH	6.9		3.1	2.8	0.6	0.8
8nn	Cl	H	2-OCH_3-C_6H_4	OH	3T	2.2		1.8	2.2	0.8
8oo	Cl	H	4-OCH_3-C_6H_4	OH	5.7	4.6	1.4	1.2	0.6	0.6
8pp	H_5C_2	H	4-CF_3-C_6H_4	H	0.2		0.4		0.0	
8qq	Cl	H		H	1.6		0.2		0.2	
8rr	Cl	H	4-F-C_6H_4	OH	5C	5C	4C (8.8)	4C (9.8)	2C (19.4)	5.0
8ss	Br	H	4-CF_3-C_6H_4 (5-Br)	H	0.0		0.2		0.6	
8tt	H	H	$(CH_3)_2$	H	5C		2C (5.6)		3.8	
8uu	Br	H	4-CF_3-C_6H_4	H	4C (12.8)	3C (10.6)	1C (4.4)	3.0	5.0	3.6
8vv	H	H	4-CF_3-C_6H_4	H	5C	5C	4C (10.8)	8.2	4.6	2.7
8ww	Cl	H	2-CF_3-C_6H_4	H	8.3		8.5		0.7	
8xx	Cl	H	4-CH_3-C_6H_4	H	2C (11.7)		2C (8.7)		3.9	
8yy	Cl	H	2-OCH_3-C_6H_4	H	5C		4C (0.7)		8.3	
8zz	H_3CO	H	4-CF_3-C_6H_4	H	4.4	2.3	2.9	0.1	−0.3	
8aaa	Cl	H	4-CF_3-C_6H_4 (5-Cl)	H	0.0		0.4		−0.2	
8bbb	H	Cl	4-CF_3-C_6H_4	H	5C		5C		8.7	
8ccc	F	H	4-CF_3-C_6H_4	H	5C		8.9		7.1	
8ddd	Cl	H	2,4-Cl_2-C_6H_3	H	5C	5C	4C (17.8)	4C (15.8)	3C (18.1)	2C (10.3)
8eee	Cl	H	3,4-Cl_2-C_6H_3	H (2-CH_3)	5C	5C	5C	5C	3C (10.8)	8.2
8fff	H	Cl	2,4-Cl_2-C_6H_3	H (5-Cl)	−0.1		0.3		0.1	
8ggg	H	H	2.4-Cl_2-C_6H_3	H (5-Cl)	4T (2.0)	2T (4.0)	2T (1.3)	1T (5.3)	1T (1.3)	1T (0.3)

Table V (Continued)

					ΔMST or C after single sc dose, mg/kg					
no.	R_1	R_2	R_3	R_4	640	320	160	80	40	20
8hhh	CF_3	H	4-CF_3-C_6H_4	H	−0.1		0.1		0.1	
8iii	Cl	H	4-CO_2H-C_6H_4	OH	4T (0.9)		1T (−0.1)		−0.1	
8jjj	Cl	H	4-OCH_3-C_6H_4	H	−0.1		0.1		−0.1	
8kkk	Cl	H	4-C_5H_4N	OH	2.0		0.2		0.0	
8lll	Cl	H	4-C_5H_4N	H	2.2		0.8		0.2	
8mmm	Cl	H	4-SCH_3-C_6H_4	H	12.4		8.6		4.4	
8nnn	Cl	H	4-NO_2-C_6H_4	H	2C (13.3)		4.6		0.8	
8ooo	Cl	H	4-CF_3-C_6H_4	H (2-C_2H_5)	1.6		1.2		0.6	
8ppp	Cl	H	4-$CF_3C_6H_4$	H (2-CH_3)	4C (8.8)	5C	2C (12.8)	7.5	5.7	3.9
8qqq	Cl	H	2-C_5H_4N	H	4.4	7.3	2.4	1.1		
8rrr	Cl	H	3,4-Cl_2-C_6H_3	H (2-C_6H_5)	1.4		0.4		0.0	
8sss	Cl	H	4-Cl,3-CF_3-C_6H_3	H	2C (5.7)	1C (5.0)	1C (1.5)	1.1	0.7	0.9
8ttt	Cl	H	2,4-Cl_2-C_6H_3	OH (2-CH_3)	5C	5C	5C	5C	5C	2C (10.7)
8uuu	H	H	2,4-Cl_2-C_6H_3	H (6-Cl)	1.3		0.1		−0.1	
8vvv	Cl	H	2,4-Cl_2-C_6H_3	H (2-CH_3)	5C	2C (17.1)	2C (15.1)	2C (10.8)	1C (9.3)	8.2
8www	Cl	H	4-CF_3-C_6H_4	OH (2-CH_3)	5C	5C	5C	2C (14.1)	7.8	5.2
8xxx	Cl	H	H	H (2-C_6H_5)	0.0		0.0	0	0.2	
8yyy	H	H	4-CF_3-C_6H_4	H (6-Cl)	0.4		0.2		−0.4	

hydro-1,9(2*H*,10*H*)-acridinedione were totally curative at 20 mg/kg. Two of these, the *N,N*-(dimethylpropyl)imino and the *N,N*-(diethylethyl)imino analogs, were curative at doses as low as 5 mg/kg.

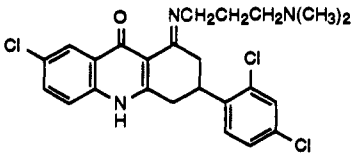
In general, for all of these compounds a C_3-aryl substituent is necessary for high activity. At C_3 alkyl substituents impart marginal activity or are completely inactive. Among C_3-aryl groups activity is enhanced by electron-withdrawing groups (e.g. halogen(s), CF_3) and diminished by electron-donating groups (e.g. OCH_3, $(OCH_3)_3$, CH_3).

Methyl groups in the C_2-position are well tolerated in terms of antimalarial activity. Ethyl and phenyl groups at C_2 have deleterious effects, the latter greater than the former.

For these compounds, the C_7-chlorine is necessary for the highest degree of activity. Unsubstitution or multisubstitution in positions C_5–C_8 give agents of lowered effectiveness.

Our limited experience with acridinediones containing reduced functionalities at C_1 or C_9 indicates the diketo or keto–imino groups are necessary for activity.

Walter Reed Army Institute of Research submitted imine **9aa** for advanced studies in monkeys. Floxacrine in these studies administered for 3 days against infections of the Uganda Palo Alto (chloroquine sensitive) strain at doses up to 16.0 mg/kg led to recrudescences consistently.



9aa

At 16.0 mg/kg only two of six animals were cleared of the parasitemia, i.e., cured. In contrast imine **9aa** cleared primary parasitemias of this strain at doses as low as 1.0 mg/kg. Cures were obtained at 4.0 mg/kg. Moreover **9aa** was similarly effective against a chloroquine-, quinine-, and pyrimethamine-resistant (Smith) strain with clearance of parasitemia at 1.0 mg/kg, three to four cures at 4.0 mg/kg and complete cures at 16.0 mg/kg. In addition the *N*-hydroxy analog **3kkk** effected parasite clearance against the resistant Smith strain at doses of 4.0, 8.0, and 16.0 mg/kg, and four primary infections were cured at doses of 8.0 and 16.0 mg/kg. Against the Uganda Palo Alto strain it cleared parasitemias through 2.0 mg/kg, cured one of two animals at 2.0 mg/kg, two of three animals at 4.0 mg/kg, and all animals at 8.0 and 16 mg/kg. Thus the acridinedione imines possess potent antimalarial properties, with the exciting potential for overcoming drug resistance. Further studies are in progress at Walter Reed toward a trial of one of these agents in man.

Experimental Section

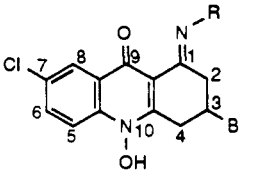
Melting points were taken on a Thomas-Hoover capillary melting point apparatus. Satisfactory IR and NMR spectra were obtained for all compounds. The IR spectra were recorded on a Nicolet 205X FT/IR. Mass spectra were obtained on a Finnigan 4000 mass spectrometer with an INCOS 2300 data system using direct introduction, electron impact at 70 eV, and 150 °C. Routine proton magnetic resonance spectra were recorded on a Varian EM-390 or XL-200 spectrometer operating at 90 or 200 MHz, respectively. Chemical shifts are reported in δ units in parts per million downfield from internal tetramethylsilane; coupling constants are in Hertz. The XCORFE spectra for 8y and **8eee** were recorded on a Varian XL-300 spectrometer equipped with a Varian 5-mm broad-band switchable probe tuned for ^{13}C (75 MHz) on the observe coil and ^1H (300 MHz) on the decoupler coil. The sample concentration in each case was 60 mg in 0.6 mL of TFA-*d*. The XCORFE spectra were obtained in absolute value mode by acquiring 256 blocks of 2048 complex data points over a ^{13}C sweep width of 15552.1 Hz for **8eee** and 15267.2 Hz for 8y and a ^1H sweep width of 3631.1 Hz for **8eee** and 2919.7 Hz for 8y. A fixed evolution time of 3.57 ms and a 35- or 44-ms refocusing delay after the final Bird pulse were utilized. Filters were applied to the t_2 fids (RE = 0.004, AF = 0.016 for **8eee**; SE = 3.18, AF = 0.04 for 8y) and the t_1 interferograms (RE = 0.004, AF = 0.018 for **8eee**; SE = 3.18, AF = 0.053 for 8y).

The COSY spectra for 11 and 12 were acquired on a Varian XL-300 spectrometer operating at 300 MHz in absolute value mode. The sample concentration was 15 mg in 0.6 mL of DMSO-d_6. The COSY experiments were performed using 256 blocks of 1024 complex data points over the entire ^1H spectrum using a 45° observe pulse to minimize diagonal elements. Filters were applied to t_2 fids (RE = 0.012, AF = 0.046 for 12; RE = 0.014, AF = 0.057 for 11) and the t_1 interferograms (RE = 0.006, AF = 0.023 for 11; RE = 0.007, AF = 0.028 for 12).

Procedure A. The aldehydes used in Scheme I were generally obtained from commercial sources. The two, whose preparation are shown below, were synthesized in our lab on the basis of literature procedures.

4-Cyclohexylbenzaldehyde.[22] A mixture of 25.3 g (0.15 mol) of cyclohexylbenzene, 21.0 g (0.15 mol) of hexamethylenetetramine, and 300 g of trifluoroacetic acid was heated under reflux for 17 h. Concentration of the reddish-brown solution in vacuo

Table VI. Effects of Imines of 7-Chloro-3-substituted-3,4-dihydro-10-hydroxy-1,9(2*H*,10*H*)-acridinediones against Trophozoite-Induced *P. berghei* in Mice



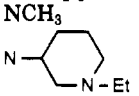
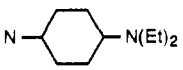
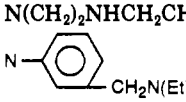
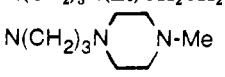
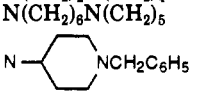
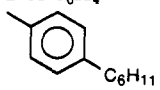
no.	NR	B	ΔMST or C after single sc dose, mg/kg					
			640	320	160	80	40	20
3a	$N(CH_2)_3N(Me)_2$	3,4-Cl_2-C_6H_3	5C	5C	5C	3C (17.2)	3C (12.7)	7.1
3b	$N(CH_2)_3CH_3$	3,4-Cl_2-C_6H_3	5C	5C	3C (9.9)	8.3	6.1	2.5
3c	$N(CH_2)_3N(Me)_2$	4-CF_3-C_6H_4	5T,1C	3T,2C	2T,3C	4C	5C	5C
3d	$N(CH_2)_2N(Et)_2$	3,4-Cl_2-C_6H_3	5C	5C	5C	3C (12.7)	3C (8.8)	1C (10.5)
3e	$NO(CH_2)_2N(Et_2)$	3,4-Cl_2-C_6H_3	8.7	3.7	2.1	0.9		
3f	$N(CH_2)_3N(Et)_2$	3,4-Cl_2-C_6H_3	5C	5C	4C (12.7)	2C (11.7)	8.5	5.3
3g	$N(CH_2)_3N(Me)_2$	1-naphthyl	5C	4C (4.7)	1C (9.3)	7.1	2.6	
3h	$N(CH_2)_3N(Me)_2$	3,4,5-$(OMe)_3C_6H_2$	4.3	4.0	1.0			
3i	$N(CH_2)_3N(Me)_2$	3-CF_3-C_6H_4	5C	5C	4C (12.4)	9.6	6.9	4.8
3j	$N(CH_2)_6CH_3$	3-CF_3-C_6H_4	5C	5C	3C (5.0)	2.8		
3k	$N(CH_2)_3OCH_3$	3-CF_3-C_6H_4	5C	3C (13.8)	1C (5.1)	1.0		
3l	$NCH_2C_6H_3$-3,4-Cl_2	3-CF_3-C_6H_4	5C	2C (11.5)	8.4	4.4		
3m	$N(CH_2)_7N(Me)_2$	3,4-Cl_2-C_6H_3	5C	5C	5C	11.3	6.5	
3n	$N(CH_2)_3N(CH_2)_5$	3,4-Cl_2-C_6H_3	5C	5C	4C (8.7)	9.2	5.9	
3o	$NCH(CH_3)(CH_2)_3N(Et)_2$	3,4-Cl_2-C_6H_3	5C	5C	5C	1C (9.6)	1C (6.1)	
3p	$N(CH_2)_3N(Me)_2$	4-Me_2N-C_6H_4	5C	3C (7.4)	6.8	0.9		
3q	$N(CH_2)_3SCH_3$	3,4-Cl_2-C_6H_3	1C (3.7)	4.1	1.7			
3r	$N(CH_2)_3N(CH_3)_2$	2,6-Cl_2-C_6H_3	5C	1C (7.2)	1C (9.4)	4.1	1.2	
3s	$N(CH_2)_3N(Me)_2$	3-Br-C_6H_4	5C	2C (10.2)	9.4	5.3	1.6	
3t	NCH_3	3,4-Cl_2-C_6H_3	3C (10.8)	10.7	6.4	3.3		
3u		3,4-Cl_2-C_6H_3	5C	4C (8.8)	2C (8.3)	7.2	3.2	
3v	$N(CH_2)_3N(Me)_2$	C_6H_5	5C	8.8	4.2	1.2	0.6	
3w	$N(CH_2)_2N(Et)CH_2C(OH)(CH_3)_2$	3,4-Cl_2-C_6H_3		5C	5C	4C (8.0)	8.2	6.3
3x	$N(CH_2)_2N[CH_2CH(CH_3)_2]_2$	3,4-Cl_2-C_6H_3	5C	1C (13.0)	2C (9.7)	1C (6.3)	1C (5.3)	3.6
3y	$N(CH_2)_3N(CH_2CH_2OH)_2$	3,4-Cl_2-C_6H_3	5C	5C	4C (10.6)	1C (7.9)	5.6	1.2
3z	$N(CH_2)_3NHCH_2CH_2OH$	3,4-Cl_2-C_6H_3	5C	4C (11.6)	3C (9.6)	1C (7.9)	6.6	2.0
3aa		3,4-Cl_2-C_6H_3	5C	3C (12.1)	5C	7.2	5.6	
3bb	NH	3-CF_3-C_6H_4	8.2	7.6	3.8	3.4	1.4	
3cc	$N(CH_2)_2NHCH_2CH{=}CH_2$	3-CF_3-C_6H_4	5C	5C	5C	1C (9.4)	2C (5.9)	3.0
3dd		3,4-Cl_2-C_6H_3	4C (42.6)	4C (22.6)	2C (10.3)	8.0	6.6	1.6
3ee	$N(CH_2)_3N(Me)_2$	$(CH_2)_5$	5T		5T		5T	
3ff	$NCH_2CH(Et)NHBu$	3-CF_3-C_6H_4	5C	5C	5C	1C (10.9)	6.8	5.6
3gg	$N(CH_2)_2N(Bu)_2$	3-CF_3-C_6H_4	5C	5C	3C (11.6)	7.0	1C (9.6)	5.4
3hh	$N(CH_2)_3N(Me)_2$	$(CH_3)_2$	2.8		0.4		0.2	
3ii	$N(CH_2)_3NHBu$	3,4-Cl_2-C_6H_3	5C	5C	4C (10.6)	1C (9.1)	9.4	4.4
3jj	$N(CH_2)_3N(Et)CH_2CH_2OH$	3,4-Cl_2-C_6H_3	5C	5C	3C (10.1)	1C (9.6)	8.6	
3kk		3,4-Cl_2-C_6H_3	5C	5C	5C	10.6	7.4	
3ll	$N(CH_2)_4N(CH_2)_4$	3-CF_3-C_6H_4	5T	4T (0.5)	5T	3.7	3T (4.6)	
3mm	$NCH_2C(CH_3)_2CH_2N(Et)_2$	3,4-Cl_2-C_6H_3	5C	4C (13.6)	4C (14.6)	2C (10.3)	1C (9.6)	4.0
3nn	$N(CH_2)_5N(CH_2)_4$	3-CF_3-C_6H_4	5T		5T		4T (0.6)	
3oo	$NCH_2CH(CH_3)N(Me)_2$	3-CF_3-C_6H_4	5C	5C	4C (8.6)	9.2	1C (11.9)	4.0
3pp	$N(CH_2)_3N(CH_2)_4$	3-CF_3-C_6H_4	4C (25.6)	5C	3C (9.6)	6.0	6.2	
3qq	$N(CH_2)_2N(CH_2)_4$	3-CF_3-C_6H_4	4C,1T	5C	4C (9.6)	8.0	6.6	
3rr	$N(CH_2)_6N(CH_2)_5$	3-CF_3-C_6H_4	5T	5T	2C,3T	6.4	4.0	
3ss		3-CF_3-C_6H_4	1C (11.1)	8.4	2C (8.6)	3.8	6.8	
3tt	$N(CH_2)_2N(Et)_2$	4-CF_3-C_6H_4	3C,2T	4C,1T	4C,1T	5C	2C (10.8)	1C (10.5)
3uu	$N(CH_2)_3N(CH_2)_4$	4-CF_3-C_6H_4	1C,4T	3C,1T	5C	5C	2C (10.8)	1C (11.0)
3vv	$N(CH_2)_3N(Et)_2$	4-CF_3-C_6H_4	5T	2C,3T	2C,3T	2C,3T	3C (16.8)	2C (10.1)
3ww	$N(CH_2)_4N(Et)_2$	4-CF_3-C_6H_4	4T	4C	5C	5C	4C (10.5)	2C (14.0)
3xx	$N(CH_2)_3N(CH_2CH_2OH)_2$	4-CF_3-C_6H_4	5C	5C	5C	1C (9.5)	4C (14.8)	2C (12.0)
3yy	$N(CH_2)_3N(CH_2)_5$	4-CF_3-C_6H_4	1C,4T	5C	5C	3C (12.0)	3C (10.0)	8.5
3zz	$NCH_2C(CH_3)_2CH_2N(Et)_2$	4-CF_3-C_6H_4	3C,2T	5C	5C	4C (12.5)	3C (11.2)	3C (13.0)
3aaa	$N(CH_2)_3N(Et)_2$	3,4,5-$(OMe)_3$-C_6H_2	6.1		0.7		0.4	
3bbb	$N(CH_2)_3CH_3$	4-CF_3-C_6H_4	5C	5C	5C	3C (10.2)	1C (8.5)	5.3
3ccc	$N(CH_2)_6CH_3$	4-CF_3-C_6H_4	4C,1T	3C (14.7)	5C	5C	4.3	

Table VI (Continued)

no.	NR	B	ΔMST or C after single sc dose, mg/kg					
			640	320	160	80	40	20
3ddd	$N(CH_2)_3N(CH_2)_4$	3,4,5-$(OMe)_3$-C_6H_2	6.4		0.6		0.2	
3eee	$NCH_2C(CH_3)_2CH_2N(Et)_2$	3,4,5-$(OMe)_3$-C_6H_2	4.7		0.7		0.5	
3fff	$N(CH_2)_2NHCH_2CH{=}CH_2$	4-CF_3-C_6H_4	5T	5T	5C	1C,3T	2C (8.4)	7.8
3ggg	$N(CH_2)_3N(CH_2)_5$	3,4,5-$(OCH_3)_3$-C_6H_2	1T (4.5)		1.4		0.3	
3hhh	$N(CH_2)_2N(C_2H_5)_2$	3,4,5-$(OCH_3)_3$-C_6H_2	6.0	5.0	1.2		0.8	
3iii	$N(CH_2)_3NHCH_2CH_2OH$	4-CF_3-C_6H_4	1C,4T	4C,1T	5C	5C	3C (10.7)	6.4
3jjj	$NCH_2C[NH(CH_2)_3CH_3]HCH_2CH_3$	4-CF_3-C_6H_4	4C,1T	5C	5C	4C	2C (7.7)	2C (6.0)
3kkk	$N(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	4C,1T	5C	5C	5C	5C	4C (10.6)
3lll	$N(CH_2)_3N(CH_3)_2$	2-Cl-C_6H_4	5T		1T (4.0)		2T (3.0)	
3mmm	$N(CH_2)_3N(CH_3)_2$		5C		3C (9.4)		5.0	
3nnn	$N(CH_2)_3N(CH_3)_2$	2-CF_3-C_6H_4	5C	5C	4C (8.0)	1C (7.5)	3.8	
3ooo	$N(CH_2)_3N(CH_3)_2$	2-OCH_3-C_6H_4	5T		5T		1T (0.3)	
3ppp	$N(CH_2)_3N(CH_3)_2$	4-OCH_3-C_6H_4	3C (8.4)	6.5	0.7	0.1		
3qqq	$N(CH_2)_3N(CH_3)_2$	4-CH_3-C_6H_4	4C (1.0)	2C (6.0)	3.0	1.8	0.2	
3rrr	$N(CH_2)_3N(CH_3)_2$	4-C_5H_4N	1.4		0.0		0.0	
3sss	$N(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3(2-CH_3)	1C (1.8)	4C (2.8)	5C	4C (16.8)	5C	1C (11.1)
3ttt	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4(2-CH_3)	5T	5T	5T	5C	2C (10.2)	8.1

yielded 25 mL of an oil which was taken up in 1200 mL of ice–water, and the resulting two-phase mixture was stirred for 45 min. Saturated aqueous potassium carbonate was added until the mixture was clearly alkaline and then it was extracted with ether. The extract was dried over magnesium sulfate and concentrated in vacuo to yield 29.0 g of an oil which consisted of 92% of a major component according to gas chromatography and showed strong aldehyde bands in the infrared spectrum at 2740 (C(O)—H) and at 1705 (C=O) cm^{-1}. Yield = 95%.

4-[Bis(methylthio)methyl]-1-chloro-2-(trifluoromethyl)-benzene.[23] To a stirred mixture of 4.70 g (0.19 mol) of magnesium granules in 200 mL of freshly distilled tetrahydrofuran was added dropwise 41.78 g (0.16 mol) of 5-bromo-2-chlorobenzotrifluoride. After complete dissolution of the magnesium a solution of 20.00 g (0.16 mol) of methyl [(methylthio)methyl]sulfoxide in 20 mL of tetrahydrofuran was added dropwise and stirring was continued for 5 h at room temperature. The reaction mixture was filtered, and the filtrate was poured into 500 mL of 1 N hydrochloric acid. The organic layer was separated, and the aqueous layer was extracted with chloroform (500 mL × 2). The organic solutions were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo to give a brown oil. The IR and NMR spectra were consistent with the desired product. It was used directly in the next step without further purification.

4-Chloro-3-(trifluoromethyl)benzaldehyde.[23] To a mixture of 45.00 g (0.16 mol) of crude 4-[bis(methylthio)methyl]-1-chloro-2-(trifluoromethyl)benzene, 40 g of silica gel, and 40 g of water was added, dropwise, a solution of 37.80 g (0.28 mol) of sulfuryl chloride in 100 mL of chloroform. The mixture was stirred at 0 °C for 2 h, after which 10 g of anhydrous potassium carbonate was added, and the stirring was continued for another 10 min. The resulting mixture was extracted with chloroform (500 mL × 3) and filtered. The filtrate was washed with water, dried over magnesium sulfate, and filtered, and the solvent was removed in vacuo to give a brown oil. Distillation under reduced pressure afforded 28.54 g (86%, 2 steps) of a colorless liquid, bp 54 °C (10 mm). The IR and NMR spectra were consistent with the desired product.

4-(4-Methylphenyl)-3-buten-2-one.[24] A mixture of 17.0 g (0.14 mol) of 4-methylbenzaldehyde, 80 mL of acetone, and 12.5 g of 50% aqueous sodium hydroxide in 450 mL of water was stirred at room temperature for 3 days. The mixture was extracted with chloroform, and the organic extracts were combined, dried over magnesium sulfate, filtered, and concentrated in vacuo to provide 22.9 g (97%) of the title compound as a yellow oil. This material was shown by VPC to contain 96% of a major component and was used as is in the next step.

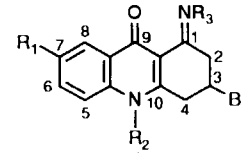
5-(4-Methylphenyl)cyclohexane-1,3-dione (4o).[25-27] To 3.2 g (0.14 mol) of sodium spheres dissolved in 90 mL of anhydrous ethanol was added 23.0 g (0.14 mol) of diethyl malonate followed by 23.0 g of 96% 4-(4-methylphenyl)-3-buten-2-one. The solution was heated under reflux for 6 h, allowed to cool to room temperature overnight, and filtered to provide a crude solid. The filtrate was concentrated in vacuo to a gum which was suspended in water and washed with chloroform to remove unchanged starting material and other organic-soluble impurities. The aqueous layer was concentrated in vacuo to a crude solid. This solid was combined with the crude solid obtained above, 100 mL of 2 N NaOH was added, and the resulting solution was heated under reflux for 2 h. To the cooled, basic reaction mixture was added 100 mL of 5 N sulfuric acid. The suspension which resulted was heated under reflux for 4.5 h, allowed to cool to room temperature, and filtered to provide, after trituration with toluene and drying, 21.4 g (77.3%) of the product, mp 180–182 °C.

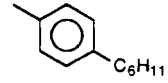
Compounds in Table I prepared similarly are designated by procedure A.

Procedure A2. 6-(4-Pyridinyl)-2-hydroxy-4-oxo-2-cyclohexene-1-carboxylic Acid, Ethyl Ester, Monosodium Salt. A solution of 21.4 g (0.20 mol) of 4-pyridinecarboxaldehyde and 66.9 g (0.21 mol) of 1-(triphenylphosphoranylidene)-2-propanone in 500 mL of toluene was heated under reflux for 1 h and was then concentrated in vacuo to dryness. The residual solid was dissolved in 200 mL of ethanol, and the resulting solution was added to a mixture of 32.0 g (0.20 mol) of diethyl malonate in a solution of 4.6 g (0.20 mol) of sodium in 400 mL of ethanol. The resulting purple-red solution was heated under reflux for 2 h, and then was concentrated in vacuo to approximately 200 mL. The suspension was cooled to 0 °C, and the solid was collected. It was triturated in 100 mL of ethanol to remove pink coloring, collected, and dried in vacuo at 80 °C for 6 h to afford 44.8 g (79%)

(22) Smith, W. E. Formylation of Aromatic Compounds with Hexamethylenetetramine and Trifluoroacetic Acid. *J. Org. Chem.* **1972**, *37*, 3972–3973.
(23) Hojo, M.; Masuda, R.; Saeki, T.; Fujimori, K.; Tsutsumi, S. An Alternative Synthetic Method for Aldehydes, Reaction of Methyl Methylthiomethyl Sulfoxide with Grignard Reagents. *Tetrahedron Lett.* **1977**, 3883–3886.
(24) Johnston, R. L.; Jones, L. A. Preparation of *m*- and *o*-Substituted Benzalacetones. *J. Chem. Eng. Data* **1971**, *16*, 112–116.
(25) Hinkel, L. E.; Ayling, E. E.; Dippy, J. F. V. Substituted Phenyldihydroresorcinols. *J. Chem. Soc.* **1935**, 539–540.
(26) Neilsen, A. T.; Houlihan, W. J. *Org. Reactions* **1968**, *16*, 81.
(27) Method of Borsche, W. Addition of Phenylacetic acid Ethyl Ester to Unsaturated Compounds. *Chem. Ber.* **1909**, *42*, 4496.
(28) Chemistry of Isatoic Anhydride, Commercial Bulletin, Maumee Chemicals.
(29) XCORFE is a standard pulse sequence supplied by Varian whose details are set forth in: Reynolds, W. F.; Hughes, D. W.; Perpick-Dumont, M.; Enriquez, R. G. *J. Magn. Reson.* **1985**, *63*, 413.

Table VII. Effects of Imines of 7-Substituted-3,4-dihydro-3-substituted-1,9(2*H*,10*H*)-acridinediones against Trophozoite-Induced *P. berghei* in Mice



					ΔMST or C after single sc dose, mg/kg					
no.	R_1	R_2	NR_3	B	640	320	160	80	40	20
9a	Cl	H	$N(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	5C	5C	5C	4C (11.8)	3C (9.8)	9.2
9b	Cl	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	2C,3T	2C,2T	3C,1T	5C	5C	3C (10.4)
9c	Cl	H	$N(CH_2)_3N(CH_3)_2$		1T (0.4)		0.0		0.6	
9d	Cl	H	$N(CH_2)_3N(CH_3)_2$	3-CF_3-C_6H_4	5C	5C	5C	1C (14.4)	6.6	
9e	Cl	H	$N(CH_2)_3CH_3$	3,4-Cl_2-C_6H_3	1T (2.5)	1.2	5T	3T (1.5)	4T	5T
9f	Cl	H	$N(CH_2)_2N(C_2H_5)_2$	3,4-Cl_2-C_6H_3	5C	3C (20.0)	5C	4C (8.0)	4C (8.0)	2C (9.3)
9g	I	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	1C,1T (14.0)		2C (7.3)		3.0	
9h	Cl	H	$NCH_2C(CH_3)HN(CH_3)_2$	4-CF_3-C_6H_4	5C		5C		5C	
9i	Cl	H	$N(CH_2)_2N(C_2H_5)_2$	4-CF_3-C_6H_4	5C		5C		3C (17.6)	
9j	Cl	H	$N(CH_2)_7N(C_2H_5)_2$	4-CF_3-C_6H_4	3C (0.1)		3C (23.1)		4C (9.6)	
9k	Cl	H	$N(CH_2)_3CH_3$	4-CF_3-C_6H_4	5C		1C (10.1)		6.0	
9l	Cl	H	$NC(CH_3)H(CH_2)_3N(C_2H_5)_2$	4-CF_3-C_6H_4	2C (3.3)	3C (2T)	5C	4C (1T)	5C	3C (10.8)
9m	Cl	H	$N(CH_2)_4N(C_2H_5)_2$	4-CF_3-C_6H_4	5C	5C	5C	5C	4C (13.6)	2C (18.6)
9n	Cl	H	$N(CH_2)_3N(CH_3)_2$	2-Cl-C_6H_4	5C	5C	2C (11.3)	6.3	5.6	
9o	O_2N	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	1C (4T)	3C (2T)	4C (11.6)	1C (8.9)	5.4	2.2
9p	Cl	H	$NCH_2C(CH_3)_2CH_2N(C_2H_5)_2$	4-CF_3-C_6H_4	4C (1.3)	4C (49.6)	5C	4C (13.6)	2C (10.3)	2C (8.6)
9q	H_5C_2	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	4T (1.4)		1T (1.9)		0.6	
9r	Cl	H	$N(CH_2)_3N(CH_3)_2$		3C (9.6)	5C	2C (10.3)	7.2	7.0	2.8
9s	Br (5-Br)	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	0.4		0.2		0.2	
9t	Br	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	2C (25.7)	5C	5C	5C	1C (9.3)	6.0
9u	H	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	5T		5T		5T	1T (5.3)
9v	H_3CO	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	5C	5C	2C (8.7)	6.1	5.5	0.7
9w	Cl (5-Cl)	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4						
9x	F	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	5T		4T (1C)		4C (14.9)	
9y	Cl	H	$N(CH_2)_3N(CH_3)_2$	2-OCH_3-C_6H_4	2C (6.4)		6.7		1.7	
9z	Cl	H	$N(CH_2)_3N(CH_3)_2$	4-CH_3-C_6H_4	2C (9.8)	2C (6.5)	6.6	1.4	0.8	
9aa	Cl	H	$N(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	5C	5C 3C (13.6) at 10	5C 1C (7.4) at 5	5C	5C	5C
9bb	H	H (5-Cl)	$N(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	5T	5T	5T	4T	1T (0.5)	0.0
9cc	H	H (8-Cl)	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	5C		4C (24.9)		7.7	
9dd	CF_3	H	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	5C		7.1		3.1	
9ee	Cl	H	$N(CH_2)_3N(CH_3)_2$	4-OCH_3-C_6H_4	1C (11.2)		4.5		0.5	
9ff	H	H (5,8-Cl_2)	$N(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3		0.0		0.0		1.2
9gg	Cl	H	$N(CH_2)_3N(CH_3)_2$	4-C_5H_4N	4.3	2.5	1.3	1.3	0.1	0.7
9hh	Cl	H	$N(CH_2)_3N(CH_3)_2$	4-SCH_3-C_6H_4	4C (1T)	3C (12.8)	1C (9.8)	1C (4.6)	3.4	2.8
9ii	Cl	H	$N(CH_2)_3N(CH_3)_2$	4-NO_2-C_6H_4	1C (11.8)	11.6	8.6	3.0	1.0	0.4
9jj	Cl	H	$N(CH_2)_3N(CH_3)_2$	2-C_5H_4N						
9kk	Cl	H (2-CH_3) cis	$N(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	4C (1T)	5C	5C	4C (10.7)	4C (21.0)	7.8
9ll	Cl	H (2-CH_3) trans	$N(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3		5C	5C	4C (15.0)	1C (7.2)	5.3
9mm	Cl	H (2-C_6H_5)	$N(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	5C	5C	2C (12.2)	1C (14.2)	7.7	3.1
9nn	Cl	H (2-CH_3) cis	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	1T (2.3)	3.1	4C (3.0)	5C	5C	4C (10.7)
9oo	Cl	H (2-CH_3) trans	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	1C (2.7)	4C (3.7)	5C	5C	5C	1C (11.0)

9pp	Cl	H (2-C_2H_5)	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	4C (6.7)	2C (10.0)	3C (10.2)	5.3	3.3	0.3	
9qq	Cl	H	$N(CH_2)_3N(CH_3)_2$	4-Cl_3-3-CF_3-C_6H_3	5C	5C	5C	5C	4C (8.7)	7.5	
9rr	H	H (6-Cl)	$N(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	3C,2T	5C	4C (13.8)	12.0	1C (6.3)	2.8	
9ss	Cl	H	$N(CH_2)_2N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	5C	5C	(5C at 10)
9tt	Cl	H (2-$CH_2C_6H_4$)	$N(CH_2)_3N(CH_3)_2$	3,4-Cl_2-C_6H_3	5T	7.7	6.1	0.7	0.5	-0.1	
9uu	Cl	H (2-CH_3)	$N(CH_2)_3N(CH_3)_2$	2,4-Cl_2-C_6H_3	3C (2.9)	4C (3.9)	5C	5C	4C (19.9)	3C (0.1)	
9vv	Cl	H	$N(CH_2)_4N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	5C	5C	(2C at 10)
9ww	Cl	H	$N(CH_2)_3N(CH_2)_4$	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	5C	4C (22.9)	(1C at 10)
9xx	Cl	H	$N(CH_2)_3N(CH_2CH_2OH)_2$	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	4C (10.9)	4C (10.9)	(1C at 10)
9yy	Cl	H	$NCH_2C(CH_2CH_3)HNH$-n-C_4H_9	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	5C	5C	(4C at 10)
9zz	Cl	H	$NCH_2C(CH_3)_2CH_2N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	4C (13.7)	3C (12.7)	
9aaa	Cl	H	$NC(CH_3)_2H(CH_2)_3N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	4C (13.7)	3C (10.2)	
9bbb	Cl	H	$N(CH_2)_7N(C_2H_5)_2$	2,4-Cl_2-C_6H_3	5C	4C (3.7)	4C (0.7)	5C	4C (9.7)	4C (6.7)	
9ccc	Cl	H	NH	4-CF_3-C_6H_4	5C	5C	5C	5C	5C	1C (11.2)	
9ddd	H	H (6-Cl)	$N(CH_2)_3N(CH_3)_2$	4-CF_3-C_6H_4	5T	5T	5T	3T (6.4)	3T (5.4)	2.1	
9eee	Cl	H	$N(CH_2)_2NHCH_2CH_2OH$	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	5C	5C	
9fff	Cl	H	$N(CH_2)_2NH_2$	2,4-Cl_2-C_6H_3	5C	5C	5C	5C	5C		

of the title compound, mp 262–263 °C. This product was used without further purification in the next step.

5-(4-Pyridinyl)-1,3-cyclohexanedione (4s). A turbid solution of 28.3 g (0.1 mol) of 6-(4-pyridinyl)-2-hydroxy-4-oxo-2-cyclohexene-1-carboxylic acid, ethyl ester, monosodium salt in 75 mL of 10% sodium hydroxide, and 175 mL of water was heated under reflux for 2 h and then was filtered through Celite. The clear filtrate was acidified slowly with 16 mL of concentrated sulfuric acid, causing some frothing. The resulting solution was heated on a steam bath for 4 h and then was cooled to 5 °C and neutralized to pH 7 by the dropwise addition of 10% sodium hydroxide. The solution was seeded and cooled to induce crystallization. The suspension was kept at 0 °C for 16 h, and then the solid was collected and washed with water to remove inorganic salts. Drying in vacuo at 60 °C over phosphorus pentoxide for 16 h provided 13.5 g (71%) of the title compound, mp 195–201 °C. An analytical sample, mp 197–198 °C, was obtained by recrystallization from *N,N*-dimethylformamide and drying in vacuo at 60 °C for 16 h. Anal. ($C_{11}H_{11}NO_2$) C, H, N.

Compounds in Table I prepared similarly are designated by procedure A2.

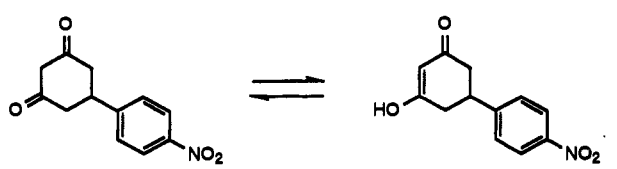
Procedure A3. 4-(2,4-Dichlorophenyl)-3-methyl-3-buten-2-one.[30] Hydrogen chloride gas was bubbled into a mixture of 35.00 g (0.20 mol) of 2,4-dichlorobenzaldehyde and 28.80 g (0.40 mol) of 2-butanone for 2 h at 0 °C. The resulting mixture was kept cool overnight, poured into 300 mL of 2 N sodium hydroxide solution and extracted with diethyl ether (500 mL × 3). The ether solution was dried over magnesium sulfate and filtered, and the filtrate was concentrated in vacuo to give a dark brown solid. Recrystallization from *n*-hexane gave 30.50 g (67%) of a white solid, mp 72–73 °C. The IR and NMR spectra were consistent with the structure of the desired product.

5-(2,4-Dichlorophenyl)-4-methyl-1,3-cyclohexanedione (4t). To a solution of 1.93 g (0.084 mol) of sodium spheres in 100 mL of ethanol was added 12.33 g (0.077 mol) of diethyl malonate. To the solution was added a solution of 16.04 g (0.070 mol) of 4-(2,4-dichlorophenyl)-3-methyl-3-buten-2-one in 100 mL of ethanol. The solution was heated under reflux for 2 h, during which time a white solid precipitated. The reaction mixture was concentrated to dryness in vacuo, treated with 150 mL of 2 N aqueous sodium hydroxide, and filtered. The filtrate was heated under reflux for 2 h, cooled, and acidified with 50% sulfuric acid to pH 2. The resulting mixture was heated under reflux for 2 h, and the gummy material solidified when the reaction mixture was cooled. The solid was collected and recrystallized from acetonitrile to give 7.50 g (40%, three steps) of a pale yellow solid, mp 182–184 °C. The IR and NMR spectra were consistent with the desired structure.

Compounds in Table I prepared similarly are designated by procedure A3.

Procedure A4. 5-(4-Nitrophenyl)-1,3-cyclohexanedione (4w). To a mixture of 1.00 g (0.00531 mol) of 5-phenyl-1,3-cyclohexanedione in 5 mL of concentrated sulfuric acid, cooled in an ice bath, was added dropwise 0.37 mL (0.00584 mol) of concentrated nitric acid. The reaction mixture was stirred at 0 °C for 1 h. The resulting solution was poured into ice–water. The solid which precipitated was collected by filtration, washed with water, and recrystallized from acetonitrile to give 0.50 g (40%) of the product as an off-white solid, mp 225 °C dec. Anal. ($C_{12}H_{11}NO_4$) C, H, N.

The position of the nitro group was shown to be on the 4-position of the phenyl group by the para splitting observed in the NMR spectrum. Note that the product exists not in the cyclohexanedione but in the eneone tautomer illustrated:



NMR (90 MHz, Me_2SO-d_6): δ = 2.2–2.9 (m, 4), 3.3–3.7 (m, 1), 5.3 (s, 1), 7.6 (d, *J* = 9 Hz, 1), 8.1 (d, *J* = 9 Hz).

(30) Unterhalt, B. Unsaturated Oximes, 18. (Dichlorophenyl)alkenones and Their Oximes. *Arch. Pharm.* 1978, *311*, 262–267.

Procedure A5. 3-(1-Pyrrolidinyl)-5-[4-(trifluoromethyl)phenyl]-2-cyclohexen-1-one.[14,16] A solution of 76.87 g (0.3 mol) of 5-[4-(trifluoromethyl)phenyl]-1,3-cyclohexanedione, 42.67 g (0.60 mol) of pyrrolidine, and a trace of *p*-toluenesulfonic acid in 500 mL of benzene was heated under reflux, using a Dean–Stark trap, until 0.3 mol of water had been collected. The solution was concentrated in vacuo to dryness. The yellow solid was recrystallized from tetrahydrofuran–ethyl ether to give 83.50 g (90%) of the product as a yellow solid, mp 168–169 °C.

4-Ethyl-3-(1-pyrrolidinyl)-5-[4-(trifluoromethyl)phenyl]-2-cyclohexen-1-one and 6-Ethyl-3-(1-pyrrolidinyl)-5-[4-(trifluoromethyl)phenyl]-2-cyclohexen-1-one. To a chilled solution (–65 °C) of 7.7 mL (0.055 mol) of diisopropylamine in 20 mL of dry tetrahydrofuran under nitrogen was added dropwise 23.1 mL (0.055 mol) of 15.25% solution of *n*-butyllithium in hexane. The mixture was stirred at room temperature for 30 min. To the resulting solution of lithium diisopropylamide was added dropwise a solution of 15.45 g (0.050 mol) of 3-(1-pyrrolidinyl)-5-[4-(trifluoromethyl)phenyl]-2-cyclohexen-1-one in 150 mL of dry tetrahydrofuran at –65 °C. The solution was stirred at room temperature for 1 h, following which 4.8 mL (0.060 mol) of ethyl iodide was added at –65 °C. The resulting solution was stirred at that temperature for 1 h, allowed to stir at room temperature for 16 h and then poured into a saturated aqueous solution of sodium chloride. The organic layer was separated, and the aqueous layer was extracted with chloroform (200 mL × 3). The combined organic layer was dried over sodium sulfate, filtered, and concentrated in vacuo to give a brown oily residue. It was chromatographed over 500 g of silica gel with $CHCl_3$–acetone = 4:1 as the eluent to provide 10.5 g (74%) of the major product (R_f = 0.5) as an off-white solid, mp 134–135 °C, and 1.0 g (7%) of a minor product as a white hygroscopic solid (R_f = 0.4). The major product was a mixture of the cis and trans isomers of 4-ethyl-3-(pyrrolidinyl)-5-[4-(trifluoromethyl)-phenyl]-2-cyclohexen-1-one and the minor product a mixture of the cis and trans isomers of 6-ethyl-3-(pyrrolidinyl)-5-[4-(trifluoromethyl)phenyl]-2-cyclohexen-1-one according to their NMR spectra, gas chromatography analysis, and the precedent of the published literature.[15,16] Anal. Major product ($C_{19}H_{22}F_3NO$) C, H, N, F.

***cis*- and *trans*-4-Ethyl-5-[4-(trifluoromethyl)phenyl]-1,3-cyclohexanedione (4x).**[17] A solution of 6.8 g (0.020 mol) of the mixture of *cis*- and *trans*-4-ethyl-3-(1-pyrrolidinyl)-5-[4-(trifluoromethyl)phenyl]-2-cyclohexen-1-one in 25 mL of ethanol containing 10 mL of 10% aqueous hydrochloric acid was heated under reflux overnight. The resulting solution was concentrated to dryness in vacuo and partitioned between chloroform and 2 N aqueous sodium hydroxide solution. The chloroform layer was evaporated to dryness to give mainly unhydrolyzed starting material. The aqueous sodium hydroxide solution was neutralized with 6 N hydrochloric acid and extracted with chloroform. The chloroform solution was dried over sodium sulfate and concentrated in vacuo to give 2.9 g of the product. The unchanged starting material which was recovered above from the chloroform extract was treated similarly to give an additional 1.1 g of the product. The total yield was 4.0 g (70%), mp 160–163 °C. The NMR spectrum and gas chromatography analysis indicated that the product was a mixture of cis and trans isomers of 4-ethyl-5-[4-(trifluoromethyl)phenyl]-1,3-cyclohexanedione. Anal. ($C_{15}H_{15}F_3O_2$), C, H.

Compounds in Table I prepared similarly are designated procedure A5.

Procedure A6. 5-(3,4-Dichlorophenyl)-4-phenyl-1,3-cyclohexanedione (4aa). To a solution of 4.8 g (0.21 mol) of sodium spheres in 90 mL of ethanol was added 34.0 g (0.207 mol) of ethyl phenylacetate, followed by 37.0 g (0.160 mol) of 4-(3,4-dichlorophenyl)-3-buten-2-one. The dark brown solution was heated under reflux for 3 h, then diluted with 500 mL of water. A gum was precipitated from which the supernatant was decanted. The ethanol–water supernatant was heated on a steam bath to remove the ethanol. The resulting aqueous solution was acidified with acetic acid and the light yellow solid which formed was collected. Attempted recrystallization from ethanol–water gave an oil. The mixture was concentrated in vacuo to remove the ethanol and resulted in a milky white solid suspended in the water and a gum which solidified on the bottom of the flask. The aqueous suspension was decanted, diluted with water and 30 mL of acetic acid, and filtered to give 19.28 g of the product, mp 85–90 °C.

Procedure B. 7-Chloro-3,4-dihydro-10-hydroxy-3-(4-methoxyphenyl)-1,9(2*H*,10*H*)acridinedione (8oo). A mixture of 4.5 g (0.030 mol) of 2-nitrobenzaldehyde and 5.0 g (0.023 mol) of 5-(4-methoxyphenyl)cyclohexane-1,3-dione in 35 mL of concentrated hydrochloric acid and 35 mL of glacial acetic acid was heated at 85 °C for 4 h. The acidic solution was poured into 1.5 L of ice-cold water to precipitate a beige solid. Trituration overnight with ethanol at room temperature gave 7.0 g (82.7%) of the title compound, mp 255 °C dec. Anal. ($C_{20}H_{16}ClNO_4$) C, H, N.

8y: XCORFE NMR (300 MHz, TFA-*d*) δ 1.30 (d, *J* = 6.6 Hz, 3), 3.2–3.4 (m, 2), 3.6–3.8 (m, 1), 4.0–4.3 (m, 1), 7.29 (d, *J* = 8.4 Hz, 1), 7.53 (s, 1), 7.60 (d, *J* = 8.4 Hz, 1), 8.26 (d, *J* = 9.2 Hz, 1), 8.49 (d, *J* = 9.2 Hz, 1), 8.71 (s, 1).

Compounds in Table II prepared similarly are designated procedure B.

Procedure C. 7-Chloro-3,4-dihydro-10-hydroxy-3-[3-(trifluoromethyl)phenyl]-1,9(2*H*,10*H*)-acridinedione, Sodium Salt, Monohydrate (8d). To 1.0 g (0.00245 mol) of 7-chloro-3,4-dihydro-10-hydroxy-3-[3-(trifluoromethyl)phenyl]-1,9-(2*H*,10*H*)-acridinedione suspended in 25 mL of methanol was added 0.14 g (0.00245 mol) of sodium methoxide. Most of the suspended material dissolved initially, and a new precipitate formed immediately after the addition. The yellow suspension was stirred at room temperature for 3 h, and the yellow precipitate was collected. Recrystallization from ethanol gave 0.8 g (73%) of the title compound, mp 315–320 °C dec, with darkening from 290 °C. Anal. ($C_{20}H_{12}ClF_3NO_3Na\cdot H_2O$) C, H, N, Cl, Na; H_2O: calcd 4.02, found 3.31.

The NMR spectrum confirmed the presence of at least 1 mol of water.

Procedure D. 7-Chloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1,9(2*H*,10*H*)-acridinedione (8v). To a suspension of 7-chloro-3,4-dihydro-10-hydroxy-3-[4-(trifluoromethyl)phenyl-1,9(2*H*,10*H*)-acridinedione (10 g, 0.0245 mol) in 200 mL of chloroform at 5 °C was added dropwise 20.2 g (0.147 mol) of phosphorus trichloride. During the addition, an orange-red solution was formed. It was heated to reflux for 1 h and then concentrated in vacuo to a dark tan solid residue, which was suspended in 100 mL of ethanol. The solid was collected and dried in vacuo at 90 °C for 112 h to afford 6.3 g (66%) of the title compound, mp 342–346 °C. Anal. ($C_{20}H_{13}ClF_3NO_2$), C, H, N, Cl, F.

Compounds in Table II prepared similarly are designated procedure D.

Procedure E.[3] To provide an example of a 10-hydroxyacridinedione without a chlorine at C_7 the literature procedure below was used. Only material containing a small amount of the C_7-Cl analog could be obtained. Alternatively a 10-H example (8vv) was prepared cleanly by procedure F.

3-(3,4-Dichlorophenyl)-3,4-dihydro-10-hydroxy-1,9-(2*H*,10*H*)-acridinedione (8f). A suspension of 2.35 g (0.0156 mol) of *o*-nitrobenzaldehyde, 4.0 g (0.0156 mol) of 5-(3,4-dichlorophenyl)-1,3-cyclohexanedione, and 3.4 g (0.031 mol) of hydroquinone in 30 mL of glacial acetic acid was heated at 80–90 °C. The resulting solution was treated with hydrogen chloride gas for 3 h while the temperature was maintained at 80–90 °C. The mixture was cooled and the resulting semisolid mass was triturated with water. The solid was collected, air dried, and triturated with ethanol to yield 4.0 g (67.9%) of the title compound as a very pale green solid, mp 257–260 °C dec, containing about 10% of 7-chloro-3-(3,4-dichlorophenyl)-3,4-dihydro-10-hydroxy-1,9(2*H*,10*H*)-acridinedione. Anal. Calcd for $C_{19}H_{13}Cl_2NO_3$: C, 60.98; H, 3.50; N, 3.74; Cl, 18.95. Anal. Calcd for $C_{19}H_{13}Cl_2NO_3$ + 0.1Cl): C, 60.41; H, 3.47; N, 3.71; Cl, 19.71. Found: C, 60.22; H, 3.77; N, 3.66; Cl, 19.45; Cl^-, 0.00.

Procedure F. The NH isatoic anhydrides utilized for Procedure F, when not commercially available, were prepared by one of two routes—chromium trioxide oxidation of the corresponding isatin[18] or condensation of the corresponding anthranilic acid with phosgene.[28] The N-substituted isatoic anhydrides were synthesized by reaction of the NH isatoic anhydrides with the requisite alkylbromides and sodium hydride.[18]

6-Chloro-3-(2,4-dichlorophenyl)-3,4-dihydro-1,9-(2*H*,10*H*)-acridinedione (8uuu). To a suspension of 1.9 g (0.04 mol) of 50% sodium hydride in 15 mL of *N*,*N*-dimethylformamide at −10 °C was added dropwise a solution of 10.3 g (0.04 mol) of 5-(2,4-dichlorophenyl)-1,3-cyclohexanedione in 70 mL of *N*,*N*-dimethylformamide. Frothing and a temperature rise to about 5 °C occurred. The resulting mixture was stirred at room temperature for 1 h and then cooled to 5 °C. A solution of 7.9 g (0.04 mol) of 4-chloroisatoic anhydride in 60 mL of *N*,*N*-dimethylformamide was added in a stream. The resulting orange solution was heated to 90 °C for 4 h. It was poured into 2000 mL of ice–water containing 15 mL of concentrated hydrochloric acid. The off-white solid which separated was collected and washed with water. It was triturated in a mixture of 300 mL of ethanol and 200 mL of *N*,*N*-dimethylformamide on a steam bath for 40 min. The suspension was cooled to 5 °C, the solid was collected and rinsed consecutively with ethanol and then ether. Drying in vacuo at 90 °C for 6 h afforded 11.2 g (71%) of the title compound, mp >330 °C. An analytical sample was obtained by recrystallizing 2.4 g of the product from *N*,*N*-dimethylformamide–ethanol. Drying in vacuo at 90 °C for 6 h provided 2.1 g (88% recovery), mp 342–344 °C. Anal. ($C_{19}H_{12}Cl_3NO_2$) C, H, N, Cl.

8eee: XCORFE NMR (300 MHz, TFA-*d*) δ 1.32 (d, *J* = 5.6 Hz, 3), 3.2–3.4 (m, 1), 3.4–3.5 (m, 1), 3.6–4.0 (m, 2), 7.29 (d, *J* = 6.2 Hz, 1), 7.52 (s, 1), 7.59 (d, *J* = 7.9 Hz, 1), 8.07 (d, *J* = 8.4 Hz, 1), 8.20 (d, *J* = 6.7 Hz, 1), 8.67 (s, 1).

Compounds in Table II prepared similarly are designated Procedure F.

Procedure G. 7-Chloro-3,4-dihydro-3,3-dimethyl-1,9-(2*H*,10*H*)-acridinedione (8t). To a mixture of 25.0 g (0.086 mol) of 7-chloro-3,4-dihydro-10-hydroxy-3,4-dimethyl-1,9(2*H*,10*H*)-acridinedione in 700 mL of methanol was added dropwise a solution of 4.9 g (0.086 mol) of sodium methoxide in 25 mL of methanol. To this mixture was added a solution of 8.0 mL (0.086 mol) of iodomethane in 25 mL of methanol, and the mixture was heated under reflux for 1 h. There was no evidence of a reaction, according to TLC, so an additional 40 mL of iodomethane was added, and the mixture was heated under reflux overnight. The initial suspension became a solution, and then a solid was deposited. This was removed by filtration and washed with methanol to give 13.8 g (58%) of the product, mp >280 °C (lit.[4] mp 300 °C). Anal. ($C_{15}H_{17}ClNO_2$), C, H, N.

Addition of 4.9 g (0.086 mol) of sodium methoxide and 40 mL (0.65 mol) of iodomethane to the above filtrate and heating the solution under reflux overnight gave an additional 7.3 g of product; total yield 89%.

This compound was originally synthesized[3] by deoxygenation with phosphorus trichloride.

Procedure I.[31] **3,4-Dihydro-3,3-dimethyl-1,9(2*H*,10*H*)-acridinedione (8tt).** A solution of 5.6 g (0.04 mol) of 5,5-dimethylcyclohexane-1,3-dione, 6.0 g (0.04 mol) of methylanthranilate, and 0.8 g (0.004 mol) of *p*-toluenesulfonic acid, monohydrate in 150 mL of toluene was heated under reflux with a Dean–Stark water separator for 5 h. At this time 5.9 g (0.044 mol) of zinc chloride was added and refluxing was continued for 24 h. The solvent was decanted, and the residual gum was triturated with several portions of water. Subsequent trituration with methanol–ether gradually induced crystallization. The solid was collected and suspended in 100 mL of *N*,*N*-dimethylformamide. The suspension was heated on a steam bath for 0.5 h, cooled to 0 °C and the solid collected. Drying in vacuo at 90 °C for 16 h afforded 1.7 g (18% over 2 steps) of the title compound, mp 347–348 °C. An analytical sample with no change in melting point was obtained by recrystallization from *N*,*N*-dimethylformamide–methanol. Recovery = 71%. Anal. ($C_{15}H_{15}NO_2$) C, H, N.

Procedure H. 7-Chloro-1,3,4,10-tetrahydro-10-hydroxy-1-[[3-(1-piperidinyl)propyl]imino]-3-[4-(trifluoromethyl)-phenyl]-9(2*H*)-acridinone (3yy). To 3.3 g (0.008 mol) of 7-chloro-3,4-dihydro-10-hydroxy-3-[4-(trifluoromethyl)phenyl]-1,9(2*H*,10*H*)-acridinedione in 140 mL of ethanol was added a solution of 1.1 g (0.008 mol) of 1-piperidinepropanamine in 10 mL of ethanol. The resulting red solution was heated under reflux for 1.5 h and then allowed to cool to room temperature. The reaction mixture was concentrated to dryness in vacuo. The red solid residue was recrystallized from dichloromethane–ether. Drying in vacuo at 80 °C for 4 h afforded 4.1 g (95%) of the title compound, mp 194–195 °C. Anal. ($C_{28}H_{29}ClF_3N_3O_2$) C, H, N, Cl, F.

Compounds in Tables III and IV prepared similarly are designated procedure H.

Procedure J. 7-Chloro-1,3,4,10-tetrahydro-10-hydroxy-1-[[2-(2-propenylamino)ethyl]imino]-3-[4-(trifluoromethyl)phenyl]-9(2*H*)-acridinone (3fff). To 3.3 g (0.008 mol) of 7-chloro-3,4-dihydro-10-hydroxy-3-[4-(trifluoromethyl)-phenyl]-1,9(2*H*,10*H*)-acridinedione in 90 mL of benzene was used a solution of 0.8 g (0.008 mol) of *N*-2-propenyl-1,2-ethanediamine in 10 mL of benzene. The resulting red solution was heated under reflux for 2 h while water was removed with a Dean–Stark trap and then allowed to cool to room temperature. The reaction mixture was concentrated to dryness in vacuo. The residual solid was recrystallized from ethyl acetate–ether. Drying in vacuo at 50 °C for 16 h afforded 3.1 g (78%) of the title compound, mp 116–119 °C. Anal. ($C_{25}H_{23}ClF_3N_3O_2$) C, H, N, Cl, F.

Compounds in Tables III prepared similarly are designated procedure J.

4-(Acetyloxy)-7-chloro-3,4-dihydro-3,3-dimethyl-1,9-(2*H*,10*H*)-acridinedione. A mixture of 4.0 g (0.014 mol) of 7-chloro-3,4-dihydro-10-hydroxy-3,3-dimethyl-1,9(2*H*,10*H*)-acridinedione in 40 mL of acetic anhydride was heated on a steam bath for 1.45 h. The resulting solution was evaporated in vacuo, and the residue was recrystallized twice from cyclohexane and once from ethanol to give 1.7 g (36%) of product, mp 170 °C with resolidification, and melting again at 217–222 °C. Anal. ($C_{17}H_{16}ClNO_4$) C, H, N.

The product was determined to be 4-(acetyloxy)-7-chloro-3,4-dihydro-3,3-dimethyl-1,9(2*H*,10*H*)-acridinedione and not the expected 10-(acetyloxy)-7-chloro-3,4-dihydro-3,3-dimethyl-1,9-(2*H*,10*H*)-acridinedione on the basis of its NMR spectrum. In $CDCl_3$ with two drops of DMSO added, there were two, three-proton singlets at 1.1–1.2 δ, assigned to the *gem*-dimethyl groups. There was also a three-proton singlet at 2.2 δ assigned to the acetyloxy group. A sharp two-proton doublet of doublets centered at 2.8 δ was assigned to the nonequivalent methylene protons. A one-proton singlet at 6.05 δ was assigned the methine proton. The three aromatic protons occurred as a multiplet at 7.6–8.3 δ and the nitrogen proton as a broad, exchangeable peak at 14 δ. Of critical importance here was the one-proton singlet at 6.05 δ, which excluded the 10-(acetyloxy)-acridinedione structure.

4-(Acetyloxy)-7-chloro-3-(3,4-dichlorophenyl)-3,4-dihydro-1,9(2*H*,10*H*)-acridinedione (6). To a stirred mixture of 2.2 g (0.0054 mol) of 7-chloro-3-(3,4-dichlorophenyl)-3,4-dihydro-10-hydroxy-1,9(2*H*,10*H*)-acridinedione in 100 mL of dry benzene was added 0.42 mL (0.0059 mol) of acetyl chloride. The mixture was stirred at room temperature for 4 h, an additional 0.42 mL of acetyl chloride was added, and the mixture was stirred overnight. The mixture was evaporated in vacuo. The residue was triturated with 400 mL of hot ethanol and filtered to give 0.8 g of product. The cooled triturate gave a second crop of 0.6 g of product. The two crops were combined to give 1.4 g (58%) of product, mp 239–241 °C dec. Anal. ($C_{21}H_{14}Cl_3NO_4$) C, H, N.

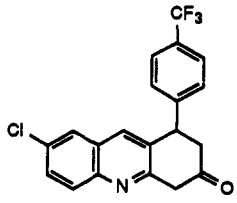
The NMR (DMSO) spectrum showed two sets of doublets for the methine proton and two broad singlets for the nitrogen proton. This suggests the presence of geometric isomers.

1-(Acetyloxy)-7-chloro-3-(3,4-dichlorophenyl)-9(10*H*)-acridinone (7). To a stirred, cooled mixture of 8.91 g (0.0218 mol) of 7-chloro-3-(3,4-dichlorophenyl)-3,4-dihydro-10-hydroxy-1,9(2*H*,10*H*)-acridinedione in 100 mL of pyridine was added dropwise, during 10 min, 12.4 mL (0.13 mol) of acetic anhydride. The resulting mixture was stirred at room temperature overnight and filtered to give 4.10 g of material. The solid was triturated in 200 mL of boiling ethanol to give 2.29 g (24.3%) of slightly impure product. Upon cooling, the filtrate deposited a solid which was collected by filtration to give 0.79 g (8.4%) of product as a light yellow powder: mp 268–278 °C; NMR (90 MHz, TFA-*d*) δ = 2.3 (s, 3, CH_3), 7.4–8.7 (m, 8, ArH); MS *m*/*e* = 431 (M^+); IR (KBr) ν 3320, 1740, 1635 cm^{-1}; IR ($CHCl_3$) ν 3340, 1740, 1635, 1610 cm^{-1}. Anal. ($C_{21}H_{12}Cl_3NO_3$) C, H, N.

(31) Sivaswami, T. S.; Iyer, B. M. Studies with Methone: Part I. *Curr. Sci. (India)* **1950**, *19*, 180.

7-Chloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1-(2*H*)-acridinone (11). A mixture of 24.46 g (0.157 mol) of crude 2-amino-5-chlorobenzaldehyde and 16.68 g (0.0651 mol) of 5-[4-(trifluoromethyl)phenyl]-1,3-cyclohexanedione in 200 mL of ethanol and 2.0 mL of piperidine was heated under reflux overnight. The resulting mixture was cooled and filtered to give 16.20 g of solid. Recrystallization from acetonitrile gave 12.24 g [50% based on 5-[4-(trifluoromethyl)phenyl]-1,3-cyclohexanedione] of the product as shiny, off-white crystals, mp 200–202 °C. Anal. ($C_{20}H_{13}ClF_3NO$) C, H, N.

Since the possibility existed that the product was the following 1-phenyl structures,



a COSY[32] spectrum was obtained to identify protons directly coupled with each other. One of the five aliphatic resonances was coupled to all four remaining aliphatic resonances. Only structure 11 is consistent with this observation.

NMR (300 MHz, Me_2SO-d_6): δ 2.9–3.0 (m, 1), 3.1–3.3 (m, 1), 3.3–3.5 (m, 1), 3.5–3.7 (m, 1), 3.7–3.9 (m, 1), 7.66 (d, J = 8.1 Hz, 2), 7.74 (d, J = 8.4 Hz, 2), 7.89 (dd, J = 9.3, 2.3 Hz, 1), 8.03 (d, J = 9.0 Hz, 1), 8.36 (d, J = 2.2 Hz, 1), 8.94 (s, 1).

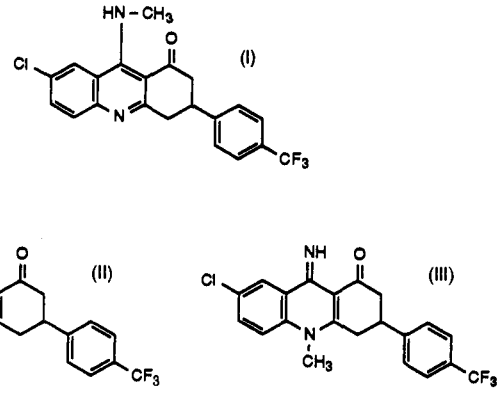
***N'*-[7-Chloro-1,2,3,4-tetrahydro-3-[4-(trifluoromethyl)-phenyl]-1-acridinylidene]-*N*,*N*-dimethyl-1,3-propanediamine.** A solution of 2.00 g (0.00532 mol) of 7-chloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone, 6.0 g (0.059 mol) of *N*,*N*-dimethyl-1,3-propanediamine, and a catalytic amount of 4-toluenesulfonic acid, monohydrate in 100 mL of toluene was heated under reflux overnight. The solution was cooled and evaporated in vacuo to give a yellow solid. Two recrystallizations from acetonitrile gave 1.93 g (78.8%) of the product as a brilliant yellow solid, mp 146–148 °C. Anal. ($C_{25}H_{25}ClF_3N_3$) C, H, N.

7-Chloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1-(2*H*)-acridinone, 10-Oxide. To a solution of 5.00 g (0.0133 mol) of 7-chloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone in 125 mL of chloroform cooled in an ice bath was added dropwise during 1 h a solution of 2.97 g (0.0146 mol) of 85% *m*-chloroperoxybenzoic acid in 75 mL of chloroform. The solution was allowed to stir at room temperature overnight, an additional 1.50 g of *m*-chloroperoxybenzoic acid in 70 mL of chloroform was added to the reaction solution, and stirring was continued overnight. The reaction solution was extracted with a saturated sodium carbonate solution, washed with a saturated sodium chloride solution, dried (Na_2SO_4), and evaporated in vacuo to give 5.22 g of a yellow solid. The solid was triturated in 300 mL of boiling ethanol to give 3.53 g of impure product. Another 0.58 g of product was collected from the cooled triturate (crude yield 79%). Recrystallization of 1.90 g of material gave 1.48 g (78% recovery) of the product as a dull yellow solid, mp 238 °C dec. Anal. ($C_{20}H_{13}ClF_3NO_2$) C, H, N.

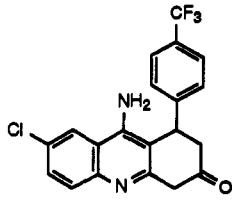
5-Chloro-2-[[5-[4-(trifluoromethyl)phenyl]-3-oxo-1-cyclohexenyl]amino]benzonitrile. A mixture of 15.26 g (0.01 mol) of 2-amino-5-chlorobenzonitrile, 25.62 g (0.10 mol) of 5-[4-(trifluoromethyl)phenyl]-1,3-cyclohexanedione, and 1.00 g of 4-toluenesulfonic acid monohydrate in 750 mL of toluene was heated under reflux with a Dean–Stark trap for 8 h. The resulting solution was cooled and filtered to give 36.04 g (90.58%) of product as a cream solid, mp 246 °C dec. Anal. ($C_{20}H_{14}ClF_3N_2O$) C, H, N.

9-Amino-7-chloro-3,4-dihydro-3-[4-(trifluoromethyl)-phenyl]-1(2*H*)-acridinone (12). A mixture of 36.0 g (0.0921 mol) of 5-chloro-2-[[5-[4-(trifluoromethyl)phenyl]-3-oxo-1-cyclohexenyl]amino]benzonitrile and 1.00 g (0.00734 mol) of zinc chloride in 1.5 L of xylene was heated under reflux with a Dean–Stark trap for 3 h. The mixture was filtered hot and the small amount of solid collected was discarded. The filtrate was cooled and filtered to give 27.89 g (77.5%) of product as a dark cream solid, mp 265 °C dec. Anal. ($C_{20}H_{14}ClF_3N_2O$) C, H, N.

Scheme VI



Since the possibility existed that the product was the 1-phenyl analog shown,



a COSY spectrum was obtained. One of the five aliphatic resonances was coupled to all remaining four aliphatic resonances and only structure 12 with its 3-hydrogen adjacent to the other four aliphatic protons is consistent with this observation. The COSY spectrum also addressed the tautomeric form of the product. The two hydrogens on nitrogens were observed to be coupled to one another providing evidence that the material exists in the amino tautomeric form depicted: NMR (300 MHz, Me_2SO-d_6) δ 2.7–2.9 (m, 1), 3.0–3.1 (m, 1), 3.1–3.2 (m, 1), 3.3–3.4 (m, 1), 3.5–3.7 (m, 1), 7.63 (d, J = 8.4 Hz, 2), 7.7–7.8 (m, 4), 8.54 (s, 1), 8.58 (br s, exchangeable), 10.02 (br s, exchangeable).

7-Chloro-3,4-dihydro-9-(methylamino)-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone. To a mixture of 2.0 g (0.00572 mol) of 9-amino-7-chloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone in 30 mL of *N*,*N*-dimethylformamide was added a mixture of 0.14 g (0.0056 mol) of sodium hydride (from 0.28 g of 50% suspension in oil washed with hexane) in 5 mL of *N*,*N*-dimethylformamide. The resulting dark brown solution was stirred at room temperature for 15 min and treated with a solution of 0.79 g (0.0056 mol) of iodomethane in 10 mL of *N*,*N*-dimethylformamide. After 1 h another 0.40 g of iodomethane was added. After 1 h a mixture of 0.05 g of sodium hydride (from 0.10 g of 50% suspension in oil washed with hexane) in 3 mL of *N*,*N*-dimethylformamide, followed by a solution of 0.40 g of iodomethane in 5 mL of *N*,*N*-dimethylformamide was added to the reaction solution. The solution was stirred at room temperature overnight, diluted with ice–water, and filtered. The collected solid was recrystallized twice from acetonitrile to give 0.50 g (24%) of product as a shiny, gold solid, mp 224–226 °C. Anal. ($C_{21}H_{16}ClF_3N_2O$) C, H, N.

The NMR of the product confirmed that methylation had occurred on the 9-amino group and not the ring nitrogen (see Scheme VI). The methyl group absorbed as a doublet, being split by the hydrogen on the nitrogen, which coalesced to a singlet upon the addition of D_2O: NMR (90 MHz, $CDCl_3$) δ 2.8–3.4 (m, 5), 3.5 (d, J = 6 Hz, 3, coalesces to singlet upon D_2O addition), 7.3–7.8 (m, 6), 8.3 (d, J = 2 Hz, 1), 9.5 (br, 1, exchangeable).

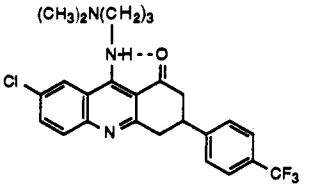
7,9-Dichloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone. A mixture of 10.0 g (0.0255 mol) of 7-chloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1,9(2*H*,10*H*)-acridinedione and 250 mL of phosphorus oxychloride was heated under reflux for 1 h. The resulting black solution was cooled and evaporated in vacuo to give a black solid. The solid was dissolved

(32) Bax, A. D.; Freeman, R.; Morris, G. A. *J. Magn. Reson.* 1981, *42*, 169.

in chloroform and dropped into a vigorously stirred, ice cold, dilute sodium hydrogen carbonate solution. The layers were separated, and the chloroform solution was washed with dilute sodium hydrogen carbonate and then with a saturated aqueous solution of sodium chloride. The solution was filtered through Celite, dried ($MgSO_4$), and evaporated in vacuo to give 8.62 g of a black solid. Chromatography over 500 g of silica gel with chloroform as the eluent gave 1.29 g (12.3%) of the product as a gray solid, mp 161–163 °C. Anal. ($C_{20}H_{12}Cl_2F_3NO$) H, N; C: calcd, 58.55; found, 58.03.

7-Chloro-9-[[3-(dimethylamino)propyl]amino]-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone. A mixture of 1.3 g (0.0032 mol) of 7,9-dichloro-3,4-dihydro-3-[4-(trifluoromethyl)phenyl]-1(2*H*)-acridinone and 0.36 g (0.0035 mol) of *N,N*-dimethyl-1,3-propanediamine in 100 mL of ethanol was heated under reflux for 3 h. To the solution was added another 3.2 g of *N,N*-dimethyl-1,3-propanediamine, and the solution was heated under reflux for 30 min. The solution was cooled and filtered to give a solid. Recrystallization from acetonitrile gave 0.75 g (50%) of the product as a pale yellow solid, mp 147–149 °C. Anal. ($C_{25}H_{25}ClF_3N_3O$) H, N; C: calcd, 63.09; found, 62.53.

An infrared spectrum of the compound in a chloroform solution showed no free NH stretch, which suggests the compound exists in the intramolecularly hydrogen bonded form:



Acknowledgment. We thank Dr. F. M. MacKellar and associates for the microanalytical and spectral data and Drs. M. Musallam and R. Engle of the Walter Reed Army Institute of Research for biological data.

Supplementary Material Available: Contour plots of the XCORFE spectra of 8y and 8eee and the COSY spectra of 11 and 12 (5 pages). Ordering information is given on any current masthead page.