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Antimalarials. Some 9-Substituted Amino-6-chloro-2-methoxyacridines

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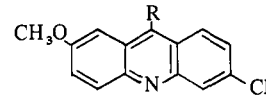
Some time ago[1] we prepared chloroquine analogs incorporating acetylenic and *cis*- and *trans*-ethylenic functions in the side chain which showed interesting antimalarial properties. In two other publications[2,3] we reported many 4-substituted amino-7-chloroquinolines out of which some showed greater antimalarial activity and lower toxicity than chloroquine. In this communication, we report some 9-substituted amino-6-chloro-2-methoxyacridines incorporating these side-chain functions and their comparative antimalarial activity.

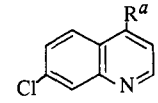
Biological Activity. The compounds were tested for their antimalarial activity against *Plasmodium berghei* in mice according to a procedure already published.[4] The test results are given in Table I. The new compounds show greater activity and less toxicity than the parent drugs. The chloroquine derivatives are found to have greater curative power than the quinacrine derivatives.

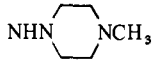
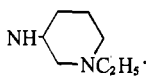
Experimental Section

General Procedure. A mixture of 6,9-dichloro-2-methoxyacridine (0.05 mol) and 75 ml of phenol was heated at 120° for 0.5 hr. It was cooled to 40°, K_2CO_3 (0.1 mol) added, and the mixture stirred for 0.5 hr. The required side-chain amine[1-3] (0.06 mol) was added and the reaction mixture heated at the appropriate temperature (see Table II) for 4 hr. It was cooled and poured into 2 *N* NaOH

Table I. Comparative Antimalarial Activity



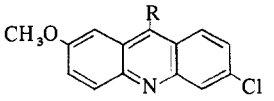


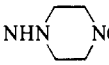
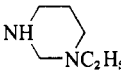
Serial no.		Dose, mg/kg	C[b]	TD	T–C	Remarks[c]	C	TD	T–C	Remarks
1	$NHCH(CH_3)C(H)=C(H)CH_2N(C_2H_5)_2 \cdot 2HCl$	20	0	0	?.7		0	0	9.7	Active
		80	0	0	7.5	Active	5	0		Curative
		320	4	0		Curative	4	1		Curative; toxic
		640		5		Toxic	3	2		Curative; toxic
2	$NHCH(CH_3)C(H)=C(H)CH_2N(C_2H_5)_2 \cdot 2HCl$	20	0	0	6.1		2	0		Curative
		80	1	0		Curative	2	0		Curative
		320	3	0		Curative	0	5		Toxic
		640	2	3		Curative; toxic	0	5		Toxic
3	$NHCH(CH_3)C{\equiv}CCH_2N(C_2H_5)_2$	20	0	0	0.7		0	0	8.5	Active
		80	0	0	4.3		0	0	13.5	Active
		320	0	0	11.7	Active	5	0		Curative
		640	0	0	15.1	Active	5	0		Curative
4	$NHNHCH_2CH_2N(CH_3)_2$	20	0	0	3.2		0	0	5.3	
		80	0	0	10.9	Active	0	0	9.0	Active
		320	5	0		Curative	1	0		Curative
		640					4	0		Curative
5	$NHN(CH_2)_3N(CH_3)_2 \cdot 2HCl$	20	0	0	4.5		0	0	2.5	
		80	0	0	8.7	Active	0	0	4.3	
		320	1	0		Curative	4	0		Curative
		640	3	0		Curative	5	0		Curative
6	$NHNHCH_2CH_2N(CH_3)_2 \cdot 2HCl$	20	0	0	0.7		0	0	3.5	
		80	0	0	6.5		0	0	7.3	Active
		320	0	0	10.7	Active	4	0		Curative
		640	3	0		Curative	5	0		Curative
7		20	0	0	0.3		3	0		Curative
		80	0	0	3.5		3	0		Curative
		320	0	0	8.5	Active	5	0		Curative
		640	2	0		Curative	5	0		Curative
8		20	0	0	3.3		0	0	9.7	Active
		80	4	0		Curative	3	0		Curative
		320	5	0		Curative	5	0		Curative
		640					5	0		Curative
9	$NHCH(CH_3)(CH_2)_3N(C_2H_5)_2$			Quinacrine				Chloroquine		
		20	0	0	0.7		0	0	6.5	
		80	0	0	1.5		0	1	8.9	Active; toxic
		320	0	0	7.3	Active	0	5		Toxic
		640	0	0	16.3	Active				

[a] Preparation and test results of these compounds have also been reported earlier.[1-3] [b] C, cures; TD, toxic deaths when mice die in 2–5 days post infection, attributed to drug toxicity; T–C, increase in mean survival time of the treated mice over the control group. [c] A compound is active if the T–C exceeds 6.1 days and curative if one or more mice live for 60 days or more post infection. Five mice were used in each test.

†Formerly Tara Singh.

Table II. Chemical Data



Serial no.	R	Reaction temp, °C	Yield, %	Crystn solvent	Mp, °C[a]	Formula	Analyses
1	$NHCH(CH_3)-C(H)=C(H)CH_2N(C_2H_5)_2\cdot 2HCl$	120	16.0	EtOH	240–241 dec	$C_{23}H_{28}ClN_3O\cdot 2HCl$	C, H, N
2	$NHCH(CH_3)-C(H)=C(H)CH_2N(C_2H_5)_2\cdot 2HCl$	120	70.0	MeOH–EtOH	249–250 dec	$C_{23}H_{28}ClN_3O\cdot 2HCl$	C, H, N
3	$NHCH(CH_3)C\equiv CCH_2N(C_2H_5)_2\cdot 2HCl$	140–150	50.0	EtOH–*i*-PrOH	225–226 dec	$C_{23}H_{26}ClN_3O\cdot 2HCl$	C, H,[b] N
4	$NHNHCH(CH_3)CH_2N(CH_3)_2$	90–100	30.0	Cyclohexane	104–105.5	$C_{19}H_{23}ClN_4O$	C, H, N
5	$NHNHCH(CH_3)CH_2CH_2N(CH_3)_2\cdot 2HCl$	90–100	17.0	*i*-PrOH	233.5–235 dec	$C_{20}H_{25}ClN_4O\cdot 2HCl$	C, H, N[c]
6	$NHNHCH(C_2H_5)CH_2N(CH_3)_2\cdot 2HCl$	90–100	18.0	*i*-PrOH	238–240 dec	$C_{20}H_{25}ClN_4O\cdot 2HCl$	C,[d] H, N
7		110–115	64.0	EtOH–petroleum ether	123 (previous shrinkage)	$C_{19}H_{21}ClN_4O$	C, H, N
8		120–130	22.0	EtOH	285–288 dec	$C_{21}H_{24}ClN_3O\cdot 2HCl\ 0.5H_2O$	C, H, N

[a] All melting points are uncorrected. [b] H: calcd, 6.01; found, 6.43. [c] N: calcd, 12.56; found, 12.15. [d] C: calcd, 53.64; found, 54.17.

solution; the product was extracted with ether or CH_2Cl_2 several times, the combined extracts were dried (K_2CO_3) and filtered, and solvent was removed under reduced pressure. The product was purified by column chromatography on basic alumina, activity 1, using ether as en eluting solvent and then crystallized either as a free base or as hydrochloride salt.

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Communications to the Editor

Synthesis of an Androgenic–Anabolic Nonsteroid

Sir:

We describe the synthesis of tricyclic compounds corresponding to steroids lacking ring A which have significant androgenic activity. This finding is of importance in connection with the question of whether the intact steroid nucleus is a *sine qua non* for the production of various kinds of hormonal effects. Numerous synthetic estrogens lacking the steroid nucleus have been synthesized[1] and have found utility as drugs for contraceptive, antineoplastic, and obstetrical purposes, but attempts to find similar agents in the androgens have produced only inactive compounds[2] or compounds having only 1–2% of the activity of testosterone.[3] Our recent studies on the structural requirements in the A ring of steroids for androgenic action[4] indicated that only the steric, and not the electronic, characteristics of ring A are important in eliciting this biological response. Therefore, it appeared feasible to prepare a nonsteroidal androgen lacking an A ring but in which hydrogen atoms of methyl groups at C-10 and C-5 would replace the carbon atoms at C-2 and C-3. In such a compound, the conformation of the carbon atoms of the C-5 and C-10 methyl groups is fixed because of the relatively inflexible nature of the condensed tricyclic ring system and although the hydrogen atoms may assume a variety of conformations, the most stable is a staggered chair-like structure placing hydrogen atoms in the approximate vicinity of C-2 and C-3 in ring A (Figure 1). Thus, this molecule could assume the conformation of an androstane derivative flattened at C-2 and/or C-3 which we have shown to be important for hormonal activity.[4]

Reduction of 1,4-dibromo-1,4-*seco*-2,3-bisnor-5α-androstan-17β-ol acetate[5] with lithium aluminum hydride gave **1**, mp 115–117°, which on acetylation (Ac_2O) furnished **2**, mp 82–83°. Similarly, reduction of 1,4-dibromo-7α-methyl-1,4-*seco*-2,3-bisnor-5α-androstan-17β-ol[6] yielded **4**, mp 117–118°. Oxidation of **1** with 8 *N* chromium trioxide in acetone solution followed by treatment with methylmagnesium bromide in ether solution gave **3**, mp 132–134°. Dehydrohalogenation of 1,4-dibromo-1,4-*seco*-2,3-bisnor-5α-estran-