described above for **7a** (n = 2, 4) except that the vols of H_2O and DMF were increased 2.5–3 times.

IV. *S,S'*-3,8-Diazaundecamethylenebis(dihydrogen phosphorothioate) (8a) was prepared by the procedure used for the prepn of **7a** (n = 2,4).

V. *N,N'*-(*trans*-1,4-Cyclohexylene)bis(*S*-2-aminoethyl sodium hydrogen phosphorothioate) (12a, n = 0).—Powd **11a** (n = 0) (4.90 g, 10.0 mmoles) was added in portions to a stirred partial soln of Na_3SPO_3 (3.60 g, 20.0 mmoles) in H_2O (20 ml). More H_2O (20 ml) was added, but soln had not occurred after 1 hr of stirring. Addnl H_2O (40 ml) caused complete soln. After 10 min the soln was treated with EtOH to cause pptn of cryst product, which was collected and repptd from H_2O soln with EtOH. The collected product, washed with EtOH and Et_2O, was air-dried.

***N,N'*-(*trans*-1,4-Cyclohexylenedimethylene)bis(*S*-2-aminoethyl lithium hydrogen phosphorothioate) (12a, n = 1).**—Gradual addn of powd **11a** (n = 1) (7.51 g, 14.5 mmoles) to a stirred soln of $Li_3SPO_3 \cdot 6H_2O$ (6.72 g, 28.0 mmoles) in H_2O (75 ml) and DMAC (50 ml) was followed by a 3-hr stirring period. The resulting nearly clear soln was filtered and added dropwise to stirred EtOH (600 ml) to ppt hydrated **12a** (n = 1) as white solid, which was collected, washed with EtOH, air-dried, and then equilibrated at const 58% relative humidity.

VI. *N,N'*-(*cis*-1,4-Cyclohexylenedimethylene)bis(*S*-2-aminoethyl lithium hydrogen phosphorothioate) (13a) was prepd in the manner described for **12a** (n = 1).

2,2'-[*trans*-1,4-Cyclohexylenebis(methyleneimino)]diethanethiol Dihydrochloride (14a).—A soln of **12a**(n = 1)$\cdot 5.5H_2O$ (4.00 g, 7.50 mmoles) in 3 N HCl (20 ml) was heated at 90–95° for 10 min. Diln with EtOH afforded cryst **14a**, which was collected under N_2, washed with EtOH followed by Et_2O, and dried *in vacuo* (25–30°, P_2O_5); yield 86% (2.16 g), mp indefinite (gradual decompn at elevated temp without melting). *Anal.* ($C_{12}H_{26}N_2S_2 \cdot 2HCl$) C, H, N, S, SH.

2,2'-[*cis*-1,4-Cyclohexylenebis(methyleneimino)]diethanethiol Dihydrochloride (14b).—Hydrolysis of **13a**$\cdot 4.5H_2O$ (5.00 g, 9.70 mmoles) in 3 N HCl (25 ml) at 90–95° for 15 min was followed by diln with EtOH (250 ml) followed by Et_2O (250 ml); cryst **14b** sepd gradually. After refrign (4 hr), the product was collected under N_2, washed successively with EtOH–Et_2O soln (1:1), cold EtOH, then Et_2O, and dried *in vacuo* (25–30°, P_2O_5); yield 63% (2.06 g), mp 232–233° dec. *Anal.* ($C_{12}H_{26}N_2S_2 \cdot 2HCl$) C, H, N, S.

***N,N'*-Polymethylenebis(*S*-2-aminoethyl thioacetate) dihydrobromides (6d; n = 8, 9)** were prepd by treatment of AcSNa (prepd *in situ* from freshly distd AcSH and $NaHCO_3$ or NaOMe) with **5a** (n = 8,9) in DMF in a manner similar to that described earlier for the prepn of *S*-2-(2-piperidyl)ethyl thioacetate$\cdot 2HBr$.[14] The products were recrystd several times from EtOH. The yield of pure **6d** (n = 8), mp 209–210°, was 20%; that of pure **6d** (n = 9), mp 210–213°, was 29%. *Anal.* [$C_{16}H_{32}N_2O_2S_2 \cdot 2HBr$, **6d** ($n$ = 8)] C, H, Br, N, S. [$C_{17}H_{34}N_2O_2S_2 \cdot 2HBr$, **6d** ($n$ = 9)] C, H, Br, N, S.

Acknowledgments.—The authors are indebted to Dr. D. P. Jacobus, Dr. T. R. Sweeney, and Miss Marie M. Grenan for antiradiation data and to Dr. W. C. Coburn, Jr., and members of the Molecular Spectroscopy Section of Southern Research Institute for spectral data.

(14) J. R. Piper and T. P. Johnston, *J. Org. Chem.*, **28**, 981 (1963).

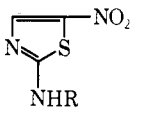
2-Amino-5-nitroimidazoles

LAIRD F. MILLER* AND RONALD E. BAMBURY

Hess and Clark, Division of Richardson-Merrell Inc., Ashland, Ohio 44805

Received May 8, 1971

2-Amino-5-nitrothiazole[1] (**1**) and its *N*-acetyl derivative (**2**) are known to possess activity against turkey blackhead (histomoniasis). In connection with another problem on which we were working, it came to our attention that no imidazole analogs of **1** or **2** were known. Their synthesis was therefore undertaken.



1, R = H
2, R = Ac

Two routes appeared to offer possibilities of obtaining the desired analogs: (a) nitration of a 2-amino- or 2-acetamidoimidazole; and (b) reaction of a 2-bromo-5-nitroimidazole with an amine or amine derivative. Nitrations were attempted using H_2SO_4–HNO_3, HNO_3–BF_3, N_2O_5–BF_3, acetyl nitrate, trifluoroacetyl nitrate, and amyl nitrate. No evidence of the desired products could be found and reactions most often led to destruction of the imidazole ring.

The bromoimidazole used for the second route was 2-bromo-4(5)-methyl-5(4)-nitroimidazole[2] (**3**), which was more conveniently prepared than 2-bromo-4(5)-nitroimidazole, and could be expected to show similar reactivity. However, treatment of I with piperidine, hydrazine, and potassium phthalimide gave no evidence of reaction, even under forcing conditions.

Shortly after these reactions were attempted, Barlin[3] reported the preparation of 1-methyl-5-nitro-2-piperidinoimidazole by refluxing 2-bromo-1-methyl-5-nitroimidazole with piperidine in EtOH, a reaction which we had previously attempted with **3**. A sample of **3** was methylated with Me_2SO_4 to give 2-bromo-1,4-dimethyl-5-nitroimidazole[2] (**4**). Reaction of **4** with piperidine in refluxing EtOH proceeded smoothly to give a high yield of 1,4-dimethyl-5-nitro-2-piperidinoimidazole (**5**). Similarly, reaction of **4** with NH_3 in EtOH in a sealed tube at 75° gave 2-amino-1,4-dimethyl-5-nitroimidazole (**6**). Acetylation of **6** gave a low yield of 2-acetamido-1,4-dimethyl-5-nitroimidazole (**7**).

Biological Screening.—Compds **5, 6**, and **7** were screened for antiprotozoal activity against *Eimeria tenella* and *E. acervulina* in chickens[4] and *Histomonas meleagridis* in turkeys;[5] **6** was also tested for activity against *Trichomonas vaginalis*[6] at The National Drug Co. No antiprotozoal activity was found. Additional screening for anthelmintic and antibacterial activity[7] also gave negative results.

Experimental Section

Melting points were taken in open capillary tubes with a calibrated thermometer using a Thomas-Hoover melting point apparatus. Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Compounds were analyzed for C, H, and N, and all values were within ±0.2% of theoretical. Solvents were removed under vacuum on a rotary evaporator. The prepns of 2-bromo-1,4-dimethyl-5-nitroimidazole[2] and its precursors [2-bromo-4(5)-methyl-5(4)-nitroimidazole,[2] 4(5)-methyl-5(4)-nitroimidazole,[8] and 4,(5)-methylimid-

* Address correspondence to this author at the Wm. S. Merrell Co., Division of Richardson-Merrell, Inc., Lockland Station, Cincinnati, Ohio 45215.

(1) Enheptin®.

(2) F. L. Pyman and G. M. Timmis, *J. Chem. Soc.*, **123**, 494 (1923).
(3) G. B. Barlin, *ibid.*, *B*, 641 (1967).
(4) C. A. Johnson and J. O'Connor, *Poultry Sci.*, **44**, 578 (1965).
(5) E. W. Berndt, H. Van Essen, and B. G. Held, *J. Med. Chem.*, **12**, 371 (1969).
(6) S. R. M. Bushby and F. C. Copp, *J. Pharm. Pharmacol.*, **7**, 112 (1955).
(7) H. K. Kim, H. K. Yaktin, and R. E. Bambury, *J. Med. Chem.*, **13**, 238 (1970).
(8) W. E. Allsebrook, J. M. Gulland, and L. F. Story, *J. Chem. Soc.*, 232 (1942).

azole[9]] were carried out by previously published procedures, as indicated.

1,4-Dimethyl-5-nitro-2-piperidinoimidazole (5).—A soln of 11.5 g (0.054 mole) of 2-bromo-1,4-dimethyl-5-nitroimidazole (**4**) and 37.5 ml (*ca.* 0.35 mole) of piperidine in 1 l. of abs EtOH was refluxed for 1 hr and the solvent was removed. The residue was dissolved in 200 ml of petr ether (bp 30–60°) and chilled to give **5** (10.5 g), mp 74–76.5°.

2-Amino-1,4-dimethyl-5-nitroimidazole (6).—A soln of **4** (25 g; 0.117 mole) in 80 ml of satd ammoniacal abs EtOH was heated for 16 hr at 75° in a sealed glass tube. The product crystd during the course of the reaction. Filtration of the solid gave 14.9 g of material which was recrystd from $MeNO_2$ to give **6**, mp 220° dec.

2-Acetamido-1,4-dimethyl-5-nitroimidazole (7).—A mixt of **6** (9 g; 0.058 mole) and 60 ml of AcCl was heated in a sealed glass tube at 100° for 6 hr during which time the solid gradually dissolved. Excess AcCl was evapd, and the residue was treated with aq $NaHCO_3$ and extd with $CHCl_3$. Removal of the solvent gave crude **7** (3.5 g), which was crystd from *i*-PrOH to give pure material, mp 165–167.5°.

Acknowledgments.—The authors wish to thank Mr. C. A. Johnson, Dr. J. R. Challey (Hess and Clark), and Dr. Herbert Megel (National Drug Co.) for the biological test data.

(9) R. W. Liggett and H. L. Hoffman, Jr., U. S. Patent 3,030,376 (1962).

Potential Antimalarials. 6. Some 2-Phenyl-6- and -8-quinolinemethanols[1,2] and 8-Phenyl-4-quinolinemethanols

J. B. WOMMACK, JR., T. G. BARBEE, JR.,[3] K. N. SUBBASWAMI, AND D. E. PEARSON*

Department of Chemistry, Vanderbilt University, Nashville, Tennessee 37203

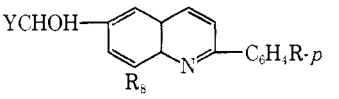
Received January 22, 1971

The aliphatic side chain of the 2-aryl-4-quinolinemethanols, 2-ArQCHOHCH$_2$NR$_2$ (Q = quinoline), potent but phototoxic antimalarials, has been placed in the 5,[4] 7,[1] 8,[5] and 3 positions.[6] Testing results for these compds indicate that activity and phototoxicity are for the most part inseparable with the possible exception of 6-chloro-8-(2-dibutylamino-1-hydroxyethyl)-2-(4-chlorophenyl)quinoline, the activity of which was low but the phototoxicity nil.[5] This paper completes the series in which the side chain is placed at the 6 position and, in 2 compds, at the 8 position. All these compds, the syntheses of which are described in the Experimental Section, have a low order of activity (see Tables I and II) and are no longer of interest as antimalarials.

Since the above approach to separation of antimalarial activity and phototoxicity had failed, it seemed feasible to place the aryl group at the 8 position (rather than the 2 position) and still retain blocking of the metabolic degradation of antimalarials without 2-aryl groups[7] on the assumption that degradation is a multi-center process involving the heterocyclic N. The results of testing compds of such a structure are shown in Table III. They indicate that the 8-phenyl-4-quinolinemethanol structure is promising as an antimalarial provided activity can be increased. Modification of the 8-Ph group may produce such an increase.

TABLE I

ACTIVITIES OF 6-QUINOLINEMETHANOLS

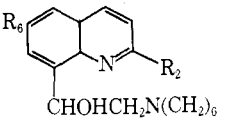


No.	Y	R_8	R	Dose, mg/kg	ΔMST,[b] days
4a[a]	$CH_2N(C_4H_9)_2$	Cl	H	320	7.4
4b	$CH_2N(CH_2)_5$	Cl	H	640	0.8
4c	$CH_2N(CH_2)_6$	Cl	H	640	1.6
9	$CH_2N(CH_2)_6$	CH_3	CH_3	320	1.0
11	$CH_2N(CH_2)_6$	CH_3	H	640	0.1
12	α-C_5H_4N (α-Pyridyl)	CH_3	H	640	0.4

[a] Phototoxic at 50 mg/kg. All activities were supplied by the Walter Reed Army Institute of Research. [b] Increased mean survival time in *P. berghei* test.

TABLE II

ACTIVITIES OF 8-QUINOLINEMETHANOLS[a]

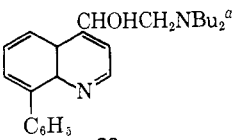


No.	R_2	R_6	Dose, mg/kg	ΔMST, days
16	C_6H_5	CH_3	640	1.2
17[b]	H	C_6H_5	640	0.1
	Quinine		640	7.1

[a] All activities were supplied by the Walter Reed Army Institute of Research. [b] Tested as the dihydrochloride.

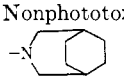
TABLE III

ACTIVITIES OF 8-PHENYL-4-QUINOLINEMETHANOLS



28a

Dose, mg/kg	ΔMST, days
40	0.3
80	2.7
160	4.3
320	6.9
640	2 cures

[a] Nonphototoxic at 50 mg/kg. If the NBu_2 group is replaced by  group, giving **28b**, the ΔMST drops to 0.

Experimental Section[8]

8-Chloro-2-phenyl-6-quinolinemethanols (4a, b, and c). 8-Chloro-6-methyl-2-phenylquinoline (1).—To a stirred, refluxing

(1) Paper 5: L. C. Washburn, T. G. Barbee, Jr., and D. E. Pearson, *J. Med. Chem.*, **13**, 1004 (1970).

(2) Contribution No. 893 to the Army Research Program on Malaria.

(3) Taken in part from the Ph.D. thesis of T. G. B.

(4) E. R. Atkinson and A. J. Puttick, *J. Med. Chem.*, **13**, 537 (1970); I. C. Popoff and C. B. Thanawalla, *ibid.*, **13**, 1002 (1970).

(5) J. S. Gillespie, Jr., S. P. Acharya, R. E. Davis, and B. K. Barman, *ibid.*, **13**, 860 (1970).

(6) R. E. Lutz, C. J. Ohnmacht, Jr., and F. Davis, *ibid.*, **14**, 17 (1971).

(7) A. Burger, "Medicinal Chemistry," Interscience, New York, N. Y., 1960, p 824.

(8) Analyses, by Galbraith Laboratories, Knoxville, Tenn., are within ±0.4% and are recorded with the Editor. Melting points are uncorrected and were taken with A. H. Thomas Uni-Melt apparatus. Nmr spectra of new compounds were compatible with the related structure and are on file with the authors.