Antimalarials. III. Benzothiazole Amino Alcohols[1a]

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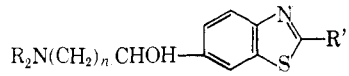
Amino alcohols carrying a $CHOH(CH_2)_{1-3}NR_2$ chain in position 6 of a benzothiazole nucleus, unsubstituted or substituted by phenyl or trifluoromethyl in the 2 position, have been synthesized by standard methods and tested for activity against *Plasmodium berghei* in mice. Several of the amino alcohols showed weak antimalarial activity but only at toxic doses.

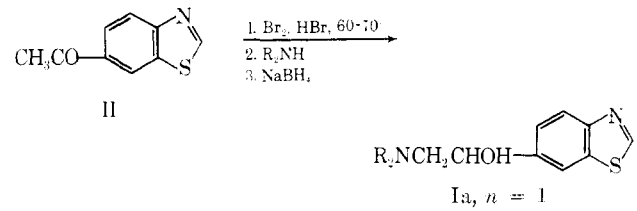
Bioisosteric substitution of benzothiazole for quinoline has been tried on three occasions,[2-4] each time for derivatives containing the dialkylaminoalkylamino chain characteristic of the prototypes, pamaquine and chloroquine. Only one group of authors[2] reported lack of antimalarial activity for their compounds, while the others[3,4] left biological behavior as unfinished business. In view of the renewed interest in amino alcohols incorporating some features of the quinine molecule[5] we investigated amino alcohols derived from benzothiazole as an extension of our studies of quinoline analogs.

All of the amino alcohols described in this paper carry the functional side chain in position 6 (I), that is, *para* to the ring nitrogen. This simulates a relationship to the 4-substituted quinoline amino alcohols as far as the benzothiazole system permits. Apart from the otherwise unsubstituted derivatives (Ia), 2-phenyl-substituted derivatives (Ib) were also prepared because 2-phenyl substitution in the quinoline series had proved advantageous to antimalarial potency,[6] perhaps due to inhibition of oxidative biotransformation. However, since the 2-phenyl-substituted quinolineamino alcohols cause photosensitization[7] and this may be associated with their increased conjugation,[8] 2-trifluoromethyl-substituted benzothiazoleamino alcohols (Ic) were prepared to avoid this effect; in the quinoline series, 2-CF_3 substitution furnished amino alcohols with moderate antimalarial activity and less photosensitizing properties.[9]



Ia, R′ = H
b, R′ = C_6H_5
c, R′ = CF_3
n = 1–3; R_2N = dialkylamino, piperidino

Chemistry.—For the synthesis of amino alcohols of type Ia (n = 1) *p*-aminoacetophenone was thiocyanated[10] and then converted to 5-acetyl-2-aminobenzenethiol[11] and this was cyclized with formic acid to 6-benzothiazolyl methyl ketone (II). Bromination of II was followed by treatment of the resulting bromo ketone with secondary amines and reduction of the amino ketones.



II

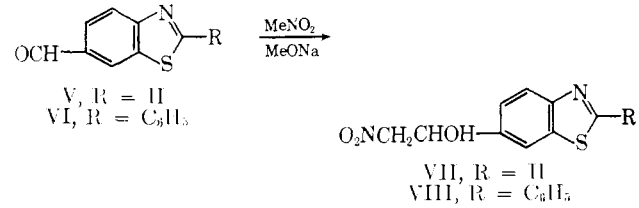
Ia, n = 1

The 2-phenyl (Ib, n = 1) and 2-trifluoromethyl (Ic, n = 1) analogs were obtained essentially by similar routes, benzoyl chloride[12] and trifluoroacetic anhydride, respectively, being used in dimethylaniline solution in the ring closure instead of formic acid. The bromination of the 2-substituted 6-benzothiazolyl methyl ketones in acetic acid always led to mixtures of mono- and dibromo ketones from which the monobromo ketone could be separated by repeated crystallization.

6-[3-Dimethylamino- (and piperidino-) 1-hydroxypropyl]benzothiazoles (Ia–c, n = 2) were prepared by reduction of the corresponding Mannich bases.

The synthesis of one example of a 6-(4-dialkylamino-1-hydroxybutyl)-2-phenylbenzothiazole [Ib, n = 3; R_2N = $N(CH_3)_2$] was accomplished by reducing ethyl 2-phenyl-6-benzothiazolecarboxylate (III, R = C_6H_5) to 2-phenyl-6-benzothiazolemethanol (IV), oxidizing IV to 2-phenyl-6-benzothiazolealdehyde (VI), and condensing this with γ-dimethylaminopropylmagnesium chloride (Scheme I).

The 2-unsubstituted aldehyde (V) was prepared by a similar sequence. Condensation of V and of VI with nitromethane yielded 1-(6-benzothiazolyl)-2-nitroethanol (VII) and its (2-phenyl-6-benzothiazolyl) derivative (VIII), respectively. Attempts to reduce these nitro alcohols to primary amino alcohols failed.



V, R = H
VI, R = C_6H_5

VII, R = H
VIII, R = C_6H_5

Biological Data. The twelve amino alcohols designated with Arabic numerals in Table I have been tested for activity against *Plasmodium berghei* in the

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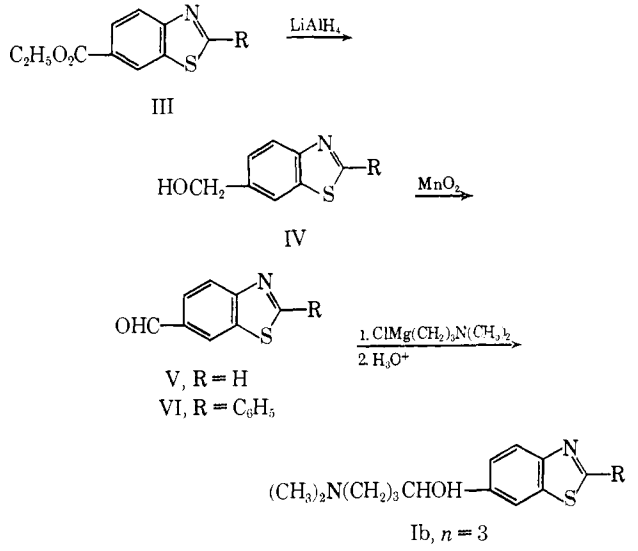
SCHEME I



mouse by the procedure of Rane, *et al.*[13] Deaths occurring on days 2–5 after infection were attributed to drug action; infected control animals did not die before day 6. These compounds were highly toxic at 160–640 mg/kg. They exhibited negligible antimalarial action at lower doses, were not curative at 40–640 mg/kg, and increased survival time from 0.3–2.9 days only. Substitution by phenyl or trifluoromethyl at position 2 did not affect antimalarial behavior.[14]

Experimental Section

Melting points (taken in a heating bath) and boiling points are uncorrected. Ir spectra (KBr) were taken on a Perkin-Elmer Spectrocord and agreed with expected absorption bands. Where analyses in Table I are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.3% of the theoretical values. Analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Yields, physical data, and solvents are listed in Table I.

6-Acetylbenzothiazole (II).—A stirred mixture of 4-amino-3-thiocyanoacetophenone[10,11] (48 g, 0.25 mole), $Na_2S \cdot 9H_2O$ (72 g), and H_2O (150 ml) was heated under reflux for 45 min, cooled, and filtered from some undissolved material. The filtrate was neutralized carefully with AcOH. The semisolid was extracted into ether, washed (H_2O), and dried ($MgSO_4$), and the residue from the ether solution was refluxed with 90% formic acid (64 g) and a spatula-full of Zn dust for 3 hr. The cooled dark mixture was stirred into H_2O (400 ml), and the yellow solid which separated was filtered off, washed (H_2O), dried, and crystallized (C_6H_6–petroleum ether (bp 30–60°), then EtOH), yield 30.5 g.

6-Acetyl-2-phenylbenzothiazole.—4-Amino-3-mercaptoacetophenone was converted to its hydrochloride with dry HCl in ether. The salt (30.5 g, 0.15 mole) was dissolved in dimethylaniline (210 ml) and the solution was treated slowly, with stirring and cooling, with 30 g (0.21 mole) of benzoyl chloride. After heating under reflux for 1 hr, the mixture was cooled, poured into 1300 ml of 3.9% HCl, and stirred for 2 hr. The solid ketone was filtered off, washed (H_2O), dried, and recrystallized from C_6H_6 yielding 28 g of pale yellow shiny flakes.

In a similar manner, 6-(2-trifluoromethylbenzothiazolyl) methyl ketone was prepared, using 0.29 mole of $(F_3CCO)_2O$/0.2 mole of starting aminothiol ketone. For additional data see Table I.

6-Bromoacetylbenzothiazole.—A solution of Br_2 (16 g, 0.1 mole) in 48% HBr (100 ml) was added dropwise to a hot stirred solution of ketone II (17.7 g, 0.1 mole) in 200 ml of 48% HBr over a period of 1 hr, the mixture being maintained at 60–65°. After additional stirring for 2 hr at 60–65° the mixture was cooled to 0° and the crystalline salt which separated was filtered off. This salt was stirred well with H_2O, filtered, washed (H_2O), dried, and crystallized from C_6H_6 as pale brown crystals, yield 19 g.

6-Bromoacetyl-2-phenylbenzothiazole.—A solution of 6-acetyl-2-phenylbenzothiazole (7.6 g, 0.03 mole) in AcOH (100 ml) was refluxed until clear. A solution of Br_2 (4.8 g, 0.03 mole) in AcOH (30 ml) was then added dropwise over 1 hr and refluxing was continued for another hour. A light yellow solid separated from the cooled solution. It was filtered off, washed (H_2O), dried, and recrystallized three times from C_6H_6 to separate the product from dibromoacetyl material; yield 4.5 g.

6-Dialkylamino- (or piperidino-) acetylbenzothiazoles.—The respective 6-bromoacetylbenzothiazoles were treated with a secondary amine in dry benzene or ether as specified in the footnotes to Table I. The precipitated amine hydrobromide was filtered off, and the filtrate was washed (H_2O), dried, and concentrated at reduced pressure. Solid amino ketones were purified by crystallization. Liquid products were reduced without purification.

6-[2-Dialkylamino- (or piperidino-) 1-hydroxyethyl]benzothiazoles (I, $n = 1$).—The appropriate aminomethyl ketone (0.02 mole) was dissolved or suspended in MeOH (50–75 ml) and a solution of $NaBH_4$ (0.01–0.015 mole) in H_2O (5 ml) and 2 *N* NaOH (1 ml) was added gradually with stirring at about 15°. After stirring the mixture for 3–5 hr at 25° about half of the solvent was removed, and the mixture was diluted with H_2O and allowed to stand overnight. Solid amino alcohols were collected, washed (H_2O), and recrystallized. Liquid products were extracted (Et_2O), dried, and converted to common salts. If these failed to crystallize, 1,1'-methylenebis(2-hydroxy-3-naphthoate) salts were prepared for testing purposes. Picrates for characterization were usually prepared in ether.

Mannich Bases.—A solution of a 6-benzothiazolyl methyl ketone (0.05 mole), a secondary amine hydrochloride (0.055 mole), paraformaldehyde (0.08–0.12 mole), and 1–2 ml of ethereal HCl in 3-methylbutanol (50 ml) was refluxed. If the reaction required 12 hr, the paraformaldehyde was added in two to three portions. The β-amino ketone hydrochlorides either crystallized on cooling or could be precipitated with ether. The bases were liberated with aqueous Na_2CO_3, purified, and reconverted to hydrochlorides in dry ether.

6-[3-Dimethylamino- (or piperidino-) 1-hydroxypropyl]benzothiazoles (I, $n = 2$).—The Mannich bases were obtained from their hydrochloride salts in MeOH–2 *N* NaOH and reduced with $NaBH_4$ as described for the preparation of I ($n = 1$) above.

6-Benzothiazolecarboxylic Acid (III, R = H) and Ethyl Ester.—A stirred mixture of ethyl 4-amino-3-thiocyanobenzoate[10] (22.2 g, 0.1 mole), $Na_2S \cdot 9H_2O$ (29 g, 0.12 mole), and H_2O (60 ml) was refluxed for 45 min, cooled, and filtered from any undissolved material. The filtrate was neutralized with AcOH, and the precipitating semisolid aminothiol was extracted (Et_2O), washed (H_2O), and dried ($MgSO_4$). Ether was removed under reduced pressure, and the residual aminothiol was cyclized by refluxing with 25 g of 90% formic acid and a little Zn dust for 3 hr. The cooled reaction mixture was poured into cold water, the slowly solidifying material was filtered off and boiled with 5% $NaHCO_3$, and the solid was again filtered off after cooling. It was dissolved in ether, dried ($MgSO_4$), and distilled. The ester had bp 122–125° (0.2 mm), yield 11.5 g.

The $NaHCO_3$ solution was acidified to furnish 3 g of the free acid.

Ethyl 2-Phenyl-6-benzothiazolecarboxylate (III, R = C_6H_5).—A crude mixture (11.7 g) of ethyl 4-amino-3-mercaptobenzoate and 4-amino-3-mercaptobenzoic acid hydrochlorides was dissolved in 75 ml of dimethylaniline and treated gradually, with cooling and stirring, with 10 g of benzoyl chloride. After refluxing for 90 min the mixture was cooled and poured into 400 ml of 9% HCl. A solid precipitated, was filtered off, and worked up as above.

6-Benzothiazolemethanol (IV, R = H) and 2-phenyl-6-benzothiazolemethanol (IV, R = C_6H_5) were prepared by reduction of ethyl 6-benzothiazolecarboxylate and ethyl 2-phenyl-6-benzothiazolecarboxylate, respectively, with $LiAlH_4$ by the method of Zubarovskii and Khodot.[15] Oxidation of these alcohols (0.05

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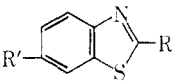
TABLE I

DERIVATIVES OF BENZOTHIAZOLE[a]



No.	R	R′	% yield	Solvent of crystn[b]	Mp, °C	Formula	Analyses
	H	$COCH_3$	69	PE–C_6H_6	94–95	C_9H_7NOS	C, H, N
	H	$COCH_2Br$	74	C_6H_6	133–135[c]	C_9H_6BrNOS	C, H, Br
1	H	$CHOHCH_2N(C_2H_5)_2 \cdot 2HBr$[d]	70	$MeNO_2$	110–112	$C_{13}H_{20}Br_2N_2OS$	C, H, N
		·Picrate		MeCN	178–180	$C_{19}H_{21}N_5O_8S$	C, H, N
	H	$CHOHCH_2N(C_4H_4)_2$[d]	69				
2		·1,1′-Methylenebis(2-hydroxy-3-naphthoate)[e]			128–130[f]	$C_{40}H_{42}N_2O_7S$	C, H, N
		·Picrate·HBr[g]		EtOH	153–154	$C_{28}H_{30}BrN_5O_8S$	C, H, N
3	H	$CHOHCH_2NC_5H_{10}$[d,h,i]	72	PE, EtOH	115–116	$C_{14}H_{18}N_2OS$	C, H, N
	H	$CO(CH_2)_2N(CH_3)_2 \cdot HCl$[j]	42	MeOH	210 dec	$C_{12}H_{15}ClN_2OS$	C, H, N
	H	$CO(CH_2)_2NC_5H_{10} \cdot HCl$[h,j]	54	EtOH–H_2O	232–233	$C_{15}H_{19}ClN_2OS$	C, H, N
4	H	$CHOH(CH_2)_2N(CH_3)_2 \cdot 2HCl$[k]	53	EtOH	175–176	$C_{12}H_{18}Cl_2N_2OS$	N
		·Picrate		MeCN	178–179	$C_{18}H_{19}N_5O_8S$	C, H, N
5	H	$CHOH(CH_2)_2NC_5H_{10} \cdot 2HCl$[h,k]	66	EtOH–Et_2O	168–169	$C_{15}H_{22}Cl_2N_2OS$	C, H, N
		·Picrate		MeCN	167–168	$C_{21}H_{23}N_5O_8S$	C, H, N
	C_6H_5	$COCH_3$	75	C_6H_6	191–192	$C_{15}H_{11}NOS$	C, H, N
	C_6H_5	$COCH_2Br$	45	C_6H_6	192–193	$C_{15}H_{10}BrNOS$	C, H, Br
	C_6H_5	$COCH_2NC_5H_{10}$[h,l]	96	EtOH	123–125	$C_{20}H_{20}N_2OS$	C, H, N
	C_6H_5	$COCH_2N(C_2H_5)_2$[l,m]	92				
		·Picrate		EtOAc	166 dec	$C_{25}H_{23}N_5O_8S$	C, H, N
6	C_6H_5	$CHOHCH_2NC_5H_{10}$[h]	82	EtOH	152–153	$C_{20}H_{22}N_2OS$	C, H, N
7	C_6H_5	$CHOHCH_2N(C_2H_5)_2$	71	Et_2O	84–86	$C_{19}H_{22}N_2OS$	C, H, N
	C_6H_5	$CO(CH_2)_2N(CH_3)_2 \cdot HCl$[n]	81	EtOH–H_2O	234	$C_{18}H_{19}ClN_2OS$	C, H, N
	C_6H_5	$CO(CH_2)_2NC_5H_{10} \cdot HCl$[h,n]	66	EtOH–H_2O	215	$C_{21}H_{23}ClN_2OS$	C, H, N
8	C_6H_5	$CHOH(CH_2)_2N(CH_3)_2$	81	PE	110–111	$C_{18}H_{20}N_2OS$	C, H, N
	C_6H_5	$CHOH(CH_2)_2NC_5H_{10}$[h]	88	EtOH	149–150	$C_{21}H_{24}N_2OS$	C, H, N
	C_6H_5	$CHOH(CH_2)_3N(CH_3)_2$	50	PE	118–119	$C_{19}H_{22}N_2OS$	C, H, N
	CF_3	$COCH_3$	65	EtOH	104–105	$C_{10}H_6F_3NOS$	C, H, N
	CF_3	$COCH_2Br$[o]	66	EtOH	113–114	$C_{10}H_5BrF_3NOS$	C, H, Br
	CF_3	$CHOHCH_2N(C_2H_5)_2$[p]					
		·Picrate		EtOAc	164–165	$C_{20}H_{20}F_3N_5O_8S$	C, H, N
9		·1,1′-Methylenebis(2-hydroxy-3-naphthoate)[q]	68			$C_{37}H_{33}F_3N_2O_7S \cdot 2H_2O$	C, H
10	CF_3	$CHOHCH_2NC_5H_{10} \cdot HCl$[h,p]	74	EtOH	260–262	$C_{15}H_{18}ClF_3N_2OS$	C, H, N
	CF_3	$CO(CH_2)_2N(CH_3)_2 \cdot HCl$[r]	64	MeCN	180–181	$C_{13}H_{14}ClF_3N_2OS$	C, H
	CF_3	$CO(CH_2)_2NC_5H_{10} \cdot HCl$[h,r]	57	MeCN	205–206	$C_{16}H_{18}ClF_3N_2OS$	C, H
11	CF_3	$CHOH(CH_2)_2N(CH_3)_2$	69	PE	104–105	$C_{13}H_{15}F_3N_2OS$	C, H
12	CF_3	$CHOH(CH_2)_2NC_5H_{10}$[h]	85	EtOH–H_2O	126–127	$C_{16}H_{19}F_3N_2OS$	C, H
	H	$CO_2C_2H_5$[s]	55	PE	61–62	$C_{10}H_9NO_2S$	C, H
	H	CO_2H[t]		EtOH	245–246		
	H	CH_2OH	74	C_6H_6	104–105	C_8H_7NOS	C, H
	H	CHO	78	Cyclohexane–C_6H_6	92–93	C_8H_5NOS	C, H, N
	H	$CHOHCH_2NO_2$	86	EtOH	130	$C_9H_8N_2O_3S$	C, H, N
	C_6H_5	CO_2H[u]		AcOH	265	$C_{14}H_9NO_2S$	C, H
	C_6H_5	$CO_2C_2H_5$	55	EtOH	123	$C_{16}H_{13}NO_2S$	C, H
	C_6H_5	CH_2OH	91	C_6H_6	129–131	$C_{14}H_{11}NOS$	C, H
	C_6H_5	CHO	69	C_6H_6	160–162	$C_{14}H_9NOS$	C, H
	C_6H_5	$CHOHCH_2NO_2$[v]	80	EtOH	180–181	$C_{15}H_{12}N_2O_3S$	C, H, N

[a] Compounds with Arabic numerals have been tested for antimalarial activity. [b] PE = petroleum ether (bp 30–60°). [c] Resolidified at 140°, decomposed at 230–240°. [d] The ketone, R = $COCH_2NR_2$, was prepared in C_6H_6 under N_2 at 27° for 3 hr. [e] Prepared by mixing equimolar amounts of the amine·HBr and the ammonium salt of the organic acid in H_2O, filtering, and drying (P_2O_5). [f] Double mp 128–130°, 240–250° dec. [g] Prepared from the hydrobromide. [h] NC_5H_{10} = piperidino. [i] Picrate from EtOAc, mp 163–164°, was not analyzed. [j] Mannich reaction time 1 hr, separated on cooling, light yellow solid, recrystallized after charcoal treatment. [k] Base was viscous liquid; dihydrochloride was prepared in dry Et_2O. [l] Prepared in C_6H_6 at 27° for 4 hr, then at 50° for 1 hr. [m] Decomposed on heating in solvents. [n] Reaction time 12 hr; separated on cooling. [o] Prepared from the ketone and Br_2 in AcOH at 60–70°. [p] From the bromo ketone in Et_2O at 27° for 24 hr. [q] Prepared from the crude base by the general procedure of J. H. Billman, D. G. Thomas, M. Hedrick, G. Schrotenboer, D. K. Barnes, J. Nemee, P. Trix, and E. Cleland, *J. Org. Chem.*, **11**, 773 (1964). [r] Reaction time 18 hr; separated on addition of Et_2O. [s] S. G. Fridman, *J. Gen. Chem. USSR*, **20**, 1191 (1950), gives mp 64°. [t] Lit.[s] mp 245°. [u] Lit.[s] mp 261°. [v] Prepared from aldehyde VI as described for the 2-unsubstituted derivative, but using THF instead of Et_2O.

mole) with active MnO_2 (80 g) in dry $CHCl_3$ (1 l.) at 27° for 24 hr, filtration from MnO and removal of the solvent gave **6-benzothiazolecarboxaldehyde (V)** and **2-phenyl-6-benzothiazolecarboxaldehyde (VI)**, respectively.

6-(4-Dimethylamino-1-hydroxybutyl)-2-phenylbenzothiazole (Ib, n = 3; R = C_6H_5).—A solution of 1.5 g (0.012 mole) of γ-dimethylaminopropyl chloride in THF (2 ml) was added dropwise to a stirred mixture of Mg (0.3 g, 2 mg-atoms), dry THF (2 ml), and I_2 (one crystal) which had been activated with 0.1 ml of MeI. When the vigorous reaction had subsided the mixture was heated at 60° for 4 hr, another 0.2 g of γ-dimethylaminopropyl chloride was added, and heating was continued for 1 hr.

A solution of aldehyde VI (1.2 g, 5 mmoles) in THF (15 ml) was then added dropwise at 20–30°, and the mixture was stirred and heated at 40–50° for 3 hr. It was decomposed with ice-cold saturated NH_4Cl and allowed to stand overnight. Ether and a little H_2O were added, the ether layer was separated, and the aqueous layer was extracted with ether. The combined ether extracts were dried ($MgSO_4$), the solvent was removed, and the residue was crystallized from petroleum ether, yielding 0.8 g of product.

6-(1-Hydroxy-2-nitroethyl)benzothiazole (VII).—A solution of 6-benzothiazolecarboxaldehyde (V) (3.25 g, 0.02 mole) and $MeNO_2$ (1.25 g, 0.02 mole) in dry Et_2O (75 ml) was added to a mixture of 4 ml of 5 *N* NaOMe in MeOH and ether (10 ml) over a period of 10 min. After being stirred at 28° for 1 hr, the mixture was treated with AcOH (3 ml) in ether (20 ml) and stirred for another 15 min, and NaOAc was filtered off and washed with ether. The residue from the ether solution was a pale yellow solid. It was washed (H_2O) and dried and weighed 3.85 g.

Antimalarials. IV.[1] A New Synthesis of α-(2-Pyridyl)- and α-(2-Piperidyl)-2-aryl-4-quinolinemethanols

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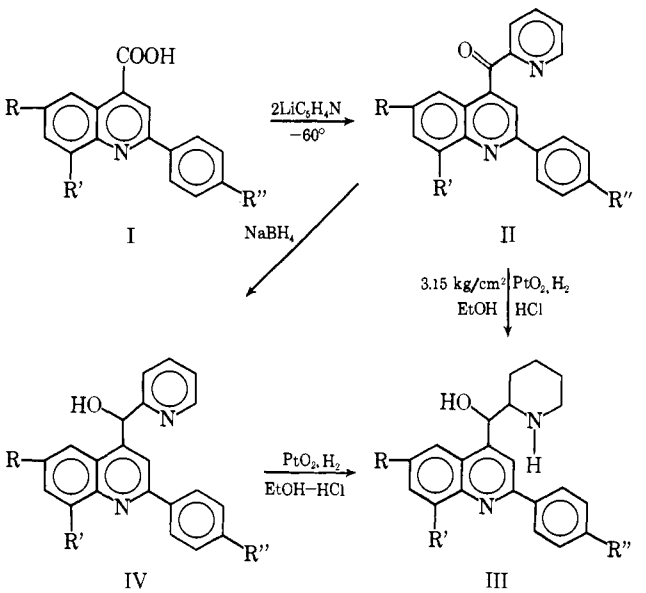
New convenient syntheses of α-(2-pyridyl)- and α-(2-piperidyl)-2-aryl-4-quinolinemethanols are reported. The key steps involve addition of pyridyllithium to quinoline-4-carboxylic acids and subsequent one-step selective catalytic 8 H hydrogenation of the ketopyridyl system to the α-piperidylmethanol. All of the α-piperidylmethanols were highly active against *Plasmodium berghei* in mice but were phototoxic, whereas the α-pyridyl analogs were considerably less phototoxic but were inactive.

This work is an extension of investigations carried out during the World War II antimalarial effort.[2] Earlier results had shown that 4-quinolylamino alcohols, particularly with a 2-aryl substituent as a deterrent to metabolic inactivation,[3] possessed considerable antiplasmodial activity against avian infections.[2,4,5]

α-Pyridyl- and α-Piperidylquinolinemethanols.—In a recent preliminary communication[1a] we have reported new syntheses for the title compounds. We now describe the details of the methods in full and report the antiplasmodial properties of these compounds.

The previous method for preparing α-piperidylquinolinemethanols was a tedious and cumbersome six-step synthesis starting from quinoline-4-carboxylic acids.[4] The new synthesis which we have developed is a convenient two-step process which also starts from quinoline-4-carboxylic acid (see Scheme I). The initial step involves conversion of the quinoline-4-carboxylic acid (I) by 2-pyridyllithium into the 2-pyridyl ketone II (Table I). The second step is the selective reduction of the 2-pyridyl and carbonyl groups of II by hydrogenation in acid solution over PtO_2 which produces the α-piperidylquinolinemethanols (III) (Table III). Recent reports of similar catalytic reductions include the selective reduction of the pyridine nucleus in 2-(2-pyridyl)-1,2-diarylalkanols[6]

SCHEME I



and reduction of the pyridine portion of a quinoline ring system.[7]

In the conversion II → III, the selectivity of reduction presumably arises from selective protonation of the α-pyridyl ring which enhances the susceptibility of that ring toward reduction. The presumption of preferential protonation of the α-pyridyl ring is based upon steric considerations. Indeed, the hydrobromides of many 2,8-disubstituted quinolines cannot be obtained, presumably because of this effect,[2] which demonstrates the sensitivity of protonation to steric effects by substituents adjacent to the ring nitrogen. The reduction of II probably proceeds stepwise, first by reduction of the carbonyl group which is in conjugation with the imino groups of the pyridyl and quinolyl rings, followed by preferential reduction of the pyridyl ring. In sup-

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