portion of NH_4Cl and the NH_3 was evapd after adding 100 ml of dry Et_2O and heating the mixt gently over a hot water bath. The stirred Et_2O suspension was cooled, 100 ml of dry Et_2O satd with gaseous HCl was added, and the contents were stirred for 1 hr. The solids were filtered, washed with dry Et_2O, and treated with dry *i*-PrOH. The alcohol soln was concd to 25 ml under reduced pressure, dry Et_2O added, and crystn induced in an ice bath (0–5°). The crude product was filtd and 3 crystn from *i*-PrOH–Et_2O afforded 1.6 g (84%) of analytically pure *cis*-2·HCl as a white crystalline solid, mp 105–106°. *Anal.* ($C_4H_{10}NSCl$) C, H, S, N: calcd, 10.03; found, 10.72.

trans-2-Mercaptocyclobutylamine (2) Hydrochloride. *trans*-2 was prepd from *trans*-18·HCl by the method described for the cis isomer. This afforded 1.7 g (90%) of analytically pure *trans*-2·HCl as a white crystalline solid, mp 126–128°. *Anal.* ($C_4H_{10}NSCl$) C, H, N, S.

Biological studies were carried out using adipose tissue from non-fasted, white male Harlan Wistar rats according to methods previously published.[21] All drug concentrations were added in 0.1 ml of aqueous solution. β-Mercaptoethylamine hydrochloride was purchased from Aldrich Chemical Co., Milwaukee, Wis., and used in these studies without further purification.

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Antimalarials. 2. 2,6-Bis(aryl)-4-pyridinemethanols†,[1]

P. Blumbergs,* M. P. LaMontagne, A. Markovac, J. G. Moehring, A. B. Ash, and C. L. Stevens

Ash Stevens Inc., Detroit, Michigan 48202.

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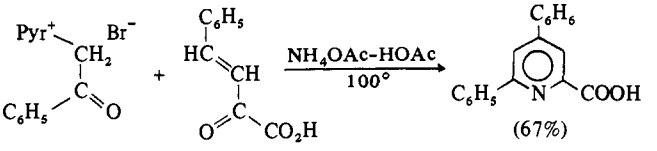
A series of 2,6-bis(aryl)-4-pyridinemethanols, where aryl is substituted phenyl, were prepared and screened for antimalarial activity. Substituents in the two phenyl rings included Cl, Br, F, and OCH_3 and 11 2,6-bis(phenyl)isonicotinic acids were prepared as starting materials. The amino alcohol side chain in the 4 position of the pyridine ring was varied to include a wide spectrum of α-alkyl(and di-alkyl)aminomethyl groups. Among the 33 compounds, 26 were curative, 3 were active, and 4 were inactive at 640 mg/kg against *Plasmodium berghei*. The 3 most active compounds were curative at 40 mg/kg and active at 20 mg/kg.

The work reported here evolved from a single lead in the World War II program wherein α-di-*n*-butylaminomethyl-2,6-diphenyl-4-pyridinemethanol (SN 10760) showed quinine indices of 1.0 and 3 against two malaria strains in the duck, although only 0.3 against *Plasmodium gallinaceum* in the chick.[2] It is interesting that the same compound (as WR 135642) in the Rane mouse screen‡ is noncurative, but active, at 640 mg/kg, admittedly against a different strain, *Plasmodium berghei*. Nevertheless, as will be shown, the data served to flag a lead which, by the introduction of electronegative substituents in the two phenyl rings and by varying the alkyl groups in the amino alcohol side chain, has resulted in candidate antimalarials of a high degree of activity against *Plasmodium berghei* as measured by the Rane test.‡

This paper will report the results for 29 2,6-bis(phenyl)-4-pyridinemethanols and 4 derivatives containing various substituents other than CF_3 in the two phenyl rings. The results for compounds bearing CF_3 groups on one or both phenyl rings are reported in a following paper.



Chemistry. Zecher and Krohnke[4] reported a ring-closure reaction for the preparation of variously substituted pico-

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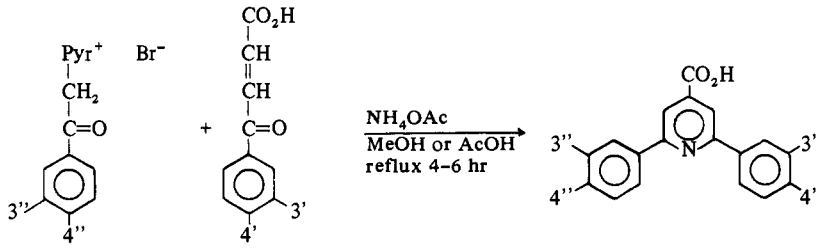
‡The antimalarial tests were performed by Dr. Leo Rane of the University of Miami.[3] See footnote *a*, Table IV. Testing results were supplied through the courtesy of Drs. Thomas R. Sweeney and Richard E. Strube of the Walter Reed Army Institute of Research.

Table I. 2,6-Bis(phenyl)isonicotinic Acids



No.	Substituents 3''	4''	3'	4'	Mp, °C	Yield, %	Formula	Analyses
Ia		Cl		Cl	286-288 (*i*-PrOH)	60	$C_{18}H_{11}Cl_2NO_2$	C, H, Cl, N
Ib		Br		Cl	285-287 (*i*-PrOH)	77	$C_{18}H_{11}BrClNO_2$	C, H, Hal
Ic		F		F	278-280 (EtOH)	55	$C_{18}H_{11}F_2NO_2$	C, H, F, N
Id		Br		Br	293-295 (*i*-PrOH)	53	$C_{18}H_{11}Br_2NO_2$	C, H, Br
Ie	Cl	Cl	Cl	Cl	330-332 (DMF-H_2O)	78	$C_{18}H_9Cl_4NO_2$	C, H, Cl
If		Cl	Cl	Cl	300 (EtOH)	81	$C_{18}H_{10}Cl_3NO_2$	C, H, N
Ig				Cl	254-258 (*i*-PrOH)	61	$C_{18}H_{12}ClNO_2$	C, H, N
Ih		Cl		OCH_3	240-242 (AcOH)	49	$C_{19}H_{14}ClNO_3$	C, H, Cl, N
Ii		OCH_3	Cl	Cl	245-247 (EtOH)	83	$C_{19}H_{13}Cl_2NO_3$	C, H, N
Ij					280-282 (EtOH)	63	$C_{18}H_{13}NO_2$	C, H, N
Ik		OCH_3		OCH_3	214-217 (AcOH)	36	$C_{20}H_{17}NO_4$	C, H, N

lines, as well as certain 4,6-diaryl-2-picolinic acids.

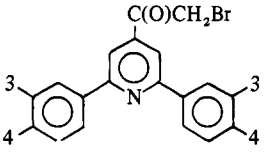
The method was extended in this laboratory to the synthesis of 2,6-bis(phenyl)isonicotinic acids by replacing the conjugated keto acid reactant of Zecher and Krohnke[4] with substituted benzoylacrylic acids.[5] The equation is shown in Table I, together with the 11 examples prepared in this work. Where the isonicotinic acid is symmetrical, the proper phenyl ring substituent is required on both reacting moieties. For unsymmetrical isonicotinic acids, the required substituent(s) may be present in either reactant.

The conversion of the isonicotinic acids to candidate antimalarials was accomplished by the procedure of Lutz and coworkers.[6] The 11 intermediate bromomethyl ketones are listed in Table II. These were reduced with $NaBH_4$ to yield crude epoxides which were treated with various amines to afford the candidate antimalarials of Table III (HCl salts). The compounds are listed in Table III according to the 2,6-bis(phenyl)-4-pyridyl group reflecting the isonicotinic acid from which they were prepared.

Biological Activity. The antimalarial activity against *Plasmodium berghei* in mice‡ is presented in Table IV. The compounds are listed in the descending order of antimalarial activity according to both the 11 2,6-bis(phenyl)-4-pyridyl basic structure categories, as well as the amino alcohol side chain within each category. Among the 29 compounds listed (excluding the derivatives **3a**, **4a**, **5b**, and **23b**), 23 are curative at a dosage of 640 mg/kg. The 3 most active compounds, **1**, **2**, and **3**, are curative at 40 mg/kg and are active at 20 mg/kg. It is interesting that these 3 compounds possess a secondary amine configuration (R_1 = H) in the side chain and that they are approximately one dosage level more active than the optimum dialkylaminomethyl analog (**4**).

In terms of compounds with the common di-*n*-butylaminomethyl side chain, the Rane data show that a single Cl substituent on each ring (**4**) resulted in optimum activity (except for the highly effective CF_3 group which will be reported in a following paper). Increasing the number of Cl substituents to three (**21**) or four (**23**) resulted in a marked decrease in activity. Replacement of one Cl with Br (**15**), or both with Br (**18**), resulted in a somewhat decreased activity. F is equally as effective as Br (compare **16** with **15** and **18**), but the activity dropped off dramatically as Cl was replaced with one H atom (**25**) or two H atoms (**28**).

Table II. Bromomethyl 2,6-Bis(phenyl)-4-pyridyl Ketones



No.[a]	Mp, °C	Yield, %[b]	Formula	Analyses
IIa	147-149 (EtOH)	72	$C_{19}H_{12}BrCl_2NO$	C, H, N
IIb	154-156 (EtOH)	37	$C_{19}H_{12}Br_2ClNO$	C, H, N
IIc	155-158 (*i*-PrOH)	54	$C_{19}H_{12}BrF_2NO$	C, H, N
IId	171-172 (C_6H_6-petr ether)	62	$C_{19}H_{20}Br_3NO$	C, H, Br
IIe	189-191 (*i*-PrOH-$CHCl_3$)	61	$C_{19}H_{20}BrCl_4NO$	C, H
IIf	136-137 (EtOH-CH_2Cl_2)	58	$C_{19}H_{11}BrCl_3NO$	C, H, N
IIg	102-105 (EtOH)	50	$C_{19}H_{13}BrClNO$	C, H, N
IIh	138-140 (*i*-PrOH)	76	$C_{20}H_{15}BrClNO_2$	C, H, N
IIi	117-118 (EtOH)	82	$C_{20}H_{14}BrCl_2NO_2$	C, H, N
IIj	116-118 (EtOH)	83	$C_{19}H_{14}BrNO$	C, H, N
IIk		*c*	$C_{21}H_{18}BrNO_3$	*c*

[a] For phenyl substituents, see Table I; IIa is prepared from Ia, etc. [b] From corresponding isonicotinic acid. [c] Not isolated.

The CH_3O group (**26**, **27**, and **29**) was the least effective of the substituents studied.

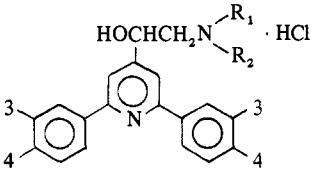
A comparison of dialkylaminomethyl analogs, where R_1 = R_2 in the 4-chlorophenyl series, shows that optimum activity was achieved with R_1 = R_2 = 1-butyl (**4**); the descending order of activity is 1-butyl (**4**) > 1-hexyl (**5**) > 1-propyl (**8**) > methyl (**10**) > ethyl (**11**) > 1-pentyl (**12**) > 1-heptyl (**14**).

Two derivatives of **4** were prepared, the *N*-oxide **4a** and the *O*-succinoyl derivative **4b**. Both possessed comparable activity to **4**. The *N*-succinoyl derivative **3a** was completely inactive. The *N*-oxide **23a** was comparable in activity to the parent compound **23**.

It should be noted that the 2,6-bis(aryl)-4-pyridinemethanols were significantly less phototoxic than the 2-phenyl-4-quinolinemethanols[7] and would not be excluded from clinical trials for this reason.§

§ Personal communication from W. E. Rothe, Walter Reed Army Institute of Research.

Table III. 2,6-Bis(phenyl)-4-pyridinemethanols



No.	R_1	R_2	Mp, °C	Yield, %[a]	Formula	Analyses[b]
			2,6-Bis(4-chlorophenyl)-			
1	H	2-Bu	224–225 (CH_3CN–EtOH)	55	$C_{23}H_{24}Cl_3N_2O$	
2	H	4-Hept	196–198 (CH_3CN–EtOH)	57	$C_{26}H_{31}Cl_3N_2O$	
3	H	1-Bu	169–171 (*i*-PrOH)[c]	38	$C_{26}H_{24}Cl_2N_2O$	Cl
4	1-Bu	1-Bu	231–233 (EtOH–Et_2O)	46	$C_{27}H_{33}Cl_3N_2O$	Cl
4a[d]	1-Bu	1-Bu	172–174 (EtOH)	47	$C_{27}H_{33}Cl_3N_2O_2$	O
5	1-Hex	1-Hex	210–211 (EtOH)	24	$C_{31}H_{41}Cl_3N_2O$	
4b[e]	1-Bu	1-Bu	157–159 (CH_3CN)	63	$C_{31}H_{37}Cl_3N_2O_4$	Cl
6	CH_3	2-Bu	185–188 (EtOH–Et_2O)	66	$C_{24}H_{27}Cl_3N_2O$	
7	CH_3	1-Bu	223–224 (CH_3CN–EtOH)	57	$C_{24}H_{27}Cl_3N_2O$	
8	1-Pro	1-Pro	250–252 (EtOH)	57	$C_{25}H_{29}Cl_3N_2O$	Cl
9	CH_3	CH_3	222–223 (EtOH–Et_2O)	25	$C_{21}H_{21}Cl_3N_2O$	
10	CH_3	*i*-Bu	220–222 (*i*-PrOH)	27	$C_{24}H_{27}Cl_3N_2O$	Cl
11	Et	Et	236–238 (EtOH–Et_2O)	42	$C_{23}H_{25}Cl_3N_2O$	Cl
12	1-Pent	1-Pent	228–230 (EtOH)	34	$C_{29}H_{37}Cl_3N_2O$	
13	H	Ada[f]	182–183 (EtOH)[c]	33	$C_{29}H_{30}Cl_2N_2O$	Cl
14	1-Hept	1-Hept	204–206 (EtOH–Et_2O)	33	$C_{33}H_{45}Cl_3N_2O$	Cl
3a[g]		1-Bu	104–107 (C_6H_6)	66	$C_{27}H_{28}Cl_2N_2O_4$	Cl
			2-(4-Bromophenyl)-6-(4-chlorophenyl)-			
15	1-Bu	1-Bu	236–238 (EtOH)	71	$C_{27}H_{33}BrCl_2N_2O$	Br, Cl
			2,6-Bis(4-fluorophenyl)-			
16	1-Bu	1-Bu	228–230 (MeOH–H_2O)	34	$C_{27}H_{33}ClF_2N_2O$	F
17	1-Hex	1-Hex	193–195 (EtOH)	28	$C_{33}H_{45}ClF_2N_2O$	F
			2,6-Bis(4-bromophenyl)-			
18	1-Bu	1-Bu	233–234 (MeOH–EtOH)	66	$C_{27}H_{33}Br_2ClN_2O$	
19	Et	Et	232–233 (EtOH–Et_2O)	47	$C_{23}H_{25}Br_2ClN_2O$	
20	1-Hept	1-Hept	208–209 (EtOH)	20	$C_{33}H_{45}Br_2ClN_2O$	
			2-(3,4-Dichlorophenyl)-6-(4-chlorophenyl)-			
21	1-Bu	1-Bu	216–217 (*i*-PrOH)	51	$C_{27}H_{32}Cl_4N_2O$	Cl
			2,6-Bis(3,4-dichlorophenyl)-			
22	Et	Et	245–247 (EtOH)	60	$C_{23}H_{23}Cl_5N_2O$	Cl
23	1-Bu	1-Bu	220–222 (EtOH)	71	$C_{27}H_{31}Cl_5N_2O$	Cl
23a[d]	1-Bu	1-Bu	174–175 (EtOH)	33	$C_{27}H_{31}Cl_5N_2O_2$	O
24	1-Hept	1-Hept	210–212 (EtOH)	39	$C_{33}H_{43}Cl_5N_2O$	Cl
			2-(4-Chlorophenyl)-6-phenyl-			
25	1-Bu	1-Bu	230–232 (EtOH)	59	$C_{27}H_{34}Cl_2N_2O$	Cl, O
			2-(4-Chlorophenyl)-6-(4-methoxyphenyl)-			
26	1-Bu	1-Bu	224–225 (*i*-PrOH)	40	$C_{28}H_{36}Cl_2N_2O_2$	Cl
			2-(3,4-Dichlorophenyl)-6-(4-methoxyphenyl)-			
27	1-Bu	1-Bu	209–210 (*i*-PrOH)	57	$C_{28}H_{35}Cl_3N_2O_2$	Cl
			2,6-Bis(phenyl)-			
28	1-Bu	1-Bu	204–206 (EtOH)	36	$C_{27}H_{35}ClN_2O$	
			2,6-Bis(4-methoxyphenyl)-			
29	1-Bu	1-Bu	215–216 (*i*-PrOH)	32	$C_{29}H_{39}ClN_2O_3$	Cl

[a] Yield based on bromomethyl ketones from Table II, except derivatives which are based on the parent amino alcohol. [b] In addition to C, H, N. [c] Free base. [d] *N*-oxide, HCl salt. [e] *O*-Succinoyl derivative, HCl salt. [f] Adamantyl. [g] *N*-Succinoyl derivative.

All structure–activity relationships are applicable, of course, only to the test under consideration and the relationship in higher animals may be quite different.

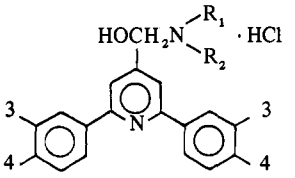
Experimental Section#

2,6-Bis(4-chlorophenyl)isonicotinic Acid (Ia). A stirred mixt of 4-chlorobenzoylacrylic acid (2.11 g, 10 mmoles), 4-chlorophenacylpyridinium bromide (3.13 g, 10 mmoles), AcOH (10 ml), Ac_2O (1 ml), and NH_4OAc (6 g) was refluxed for 4 hr. The hot mixt was dild with H_2O (35 ml), allowed to cool, and filtered. The solid was washed with H_2O and dissolved in warm aqueous 2% K_2CO_3 (150 ml). The soln was extd with $CHCl_3$ (x 5) and Et_2O (x 2), treated with charcoal while hot, and filtered. The filtrate was acidified with concd HCl to pH 2 and filtered. The solid product was washed with H_2O and recrystd from EtOH to yield Ia (1.85 g, 54%), mp 286–288°.

2-(4-Chlorophenyl)-6-(4-methoxyphenyl)isonicotonic Acid (Ih). A soln of 4-methoxybenzoylacrylic acid[5] (20.6 g, 0.1 mole), 4-chlorophenacylpyridinium bromide (31.2 g, 0.1 mole), and NH_4OAc (85 g) in MeOH (175 ml) was refluxed for 6 hr. The mixt was refrigerated overnight (5°). The ammonium salt was collected and dissolved in hot AcOH (250 ml), and the soln was allowed to cool. Filtration gave Ih (16.6 g, 49%), mp 240–242°.

#Melting points were taken in open capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. Analyses indicated by element symbols agree with calculated values within ±0.4%.

Table IV. Antimalarial Activity of 2,6-Bis(phenyl)-4-pyridinemethanols



No.	R_1	R_2	Increase in mean survival time, days, or no. of cures (C), five mice[a] Dosage, mg/kg 20	40	80	160	320	640
			2,6-Bis(4-chlorophenyl)-					
1	H	2-Bu	10.4(A)	3C	5C	5C	3C(2TD)[b]	2C(3TD)[b]
2	H	4-Hept	6.6(A)	3C	3C	4C	5C	5C
3	H	1-Bu	10.8(A)	1C	2C	3C	5C	5C
4	1-Bu	1-Bu	2.3	15.7(A)	3C	3C	4C	5C
4a[c]	1-Bu	1-Bu	1.1	8.5(A)	1C	3C	5C	5C
5	1-Hex	1-Hex	0.8	3.1	1C	2C	2C	5C
4b[d]	1-Bu	1-Bu	6.0	8.6(A)	17.0	5C	5C	5C
6	CH_3	2-Bu	3.9	6.9(A)	14.3	5C	5C	5C
7	CH_3	1-Bu	0.4	3.8	12.6(A)	5C	5C	5C
8	1-Pr	1-Pr	0.6	2.2	10.2(A)	2C	3C	4C
9	CH_3	CH_3	0.2	0.4	0.8	1C	3C	5C
10	CH_3	*i*-Bu	0.2	0.2	2.5	1C	4C	5C
11	Et	Et	0.4	0.8	4.6	19.2(A)	3C	5C
12	1-Pent	1-Pent	2.1	5.9	7.1(A)	12.5	2C	4C
13	H	Ada[f]	0.4	1.0	1.5	4.9	3C	3C
14	1-Hept	1-Hept	0.5	0.7	0.9	6.0	9.3(A)	11.7
3a[e]		1-Bu		Inactive				0.3
			2-(4-Bromophenyl)-6-(4-chlorophenyl)-					
15	1-Bu	1-Bu	2.8	5.8	8.4(A)	1C	4C	4C
			2,6-Bis(4-fluorophenyl)-					
16	1-Bu	1-Bu	0.3	3.3	4.7	1C	3C	3C
17	1-Hex	1-Hex	0.2	2.0	5.4	6.0	9.6(A)	14.8
			2,6-Bis(4-bromophenyl)-					
18	1-Bu	1-Bu	0.6	3.8	4.8	10.8(A)	3C	3C
19	Et	Et		0.2	3.8	15.6(A)	2C	4C
20	1-Hept	1-Hept			Inactive			0.4
			2-(3,4-Dichlorophenyl)-6-(4-chlorophenyl)-					
21	1-Bu	1-Bu	1.9	4.9	10.3(A)	12.9	1C	3C
			2,6-Bis(3,4-Dichlorophenyl)-					
22	Et	Et			0.2	9.2(A)	2C	3C
23	1-Bu	1-Bu	0.2	2.4	4.8	9.2(A)	1C	1C
23a[c]	1-Bu	1-Bu		0.6	4.0	9.3	12.9(A)	1C
24	1-Hept	1-Hept			Inactive			0.4
			2-(4-Chlorophenyl)-6-phenyl-					
25	1-Bu	1-Bu		0.6	4.6	8.6(A)	9.2	3C
			2-(4-Chlorophenyl)-6-(4-methoxyphenyl)-					
26	1-Bu	1-Bu	0.4	1.0	1.4	6.0(A)	12.6	2C
			2-(3,4-Dichlorophenyl)-6-(4-methoxyphenyl)-					
27	1-Bu	1-Bu	0.4	1.4	6.9(A)	9.4	10.2	1C
			2,6-Bis(phenyl)-					
28	1-Bu	1-Bu		0.2	1.8	3.2	6.0(A)	11.2
			2,6-Bis(4-methoxyphenyl)-					
29	1-Bu	1-Bu			Inactive			5.8

[a]The test method, described in ref 3, is a highly standardized procedure in which the *P. berghei* causes death of control mice at essentially 6.2 days. An increase in the mean survival time of 5 mice by more than 2.5 days beyond this time is statistically significant. Mice surviving more than 60 days are regarded as cured (C). A candidate drug is considered active (A) at a given dosage if one or more mice are alive on day 14. [b]TD = toxic death. [c]*N*-Oxide. [d]*O*-Succinate. [e]*N*-Succinate. [f]Adamantyl.

The above two procedures are representative of the prepn of the isonicotinic acids of Table I.

Bromomethyl 2-(4-Chlorophenyl)-6-(4-methoxyphenyl)-4-pyridyl Ketone (IIh). 2-(4-Chlorophenyl)-6-(4-methoxyphenyl)-isonicotinic acid (Ih) (15 g) in $SOCl_2$ (175 ml) was refluxed 4 hr. Excess $SOCl_2$ was removed, and the solid was recrystd from C_6H_6 to yield the acid chloride (14.1 g, 89%), mp 104–106°. *Anal.* ($C_{19}H_{13}NO_2Cl_2$) C, H, N, Cl. The acid chloride (8 g) in CH_2Cl_2 (50 ml) was added slowly to a soln of CH_2N_2 (*ca.* 5 g) in Et_2O (350 ml). The mixt was held at 0° overnight. Excess CH_2N_2 and solvents were removed (aspirator) to give a low-melting diazo ketone (8 g) with acceptable ir spectrum. The diazo ketone (4 g) in $CHCl_3$ (15 ml) was added to a mixt of 48% aqueous HBr (7.5 ml) and $CHCl_3$ (50 ml) at 5°. The soln was stirred 3 hr at 25° and was washed successively with aqueous 5% K_2CO_3 and H_2O (x 2). The organic layer was dried (Na_2SO_4) and the solvent was removed. The solid (4.3 g) was recrystd from *i*-PrOH to yield IIh (3.9 g, 76% from Ih), mp 138–140°. The above procedure is typical of the prepn of the bromomethyl ketones of Table II.

α-Di-*n*-butylaminomethyl-2,6-bis(3,4-dichlorophenyl)-4-pyridine-

methanol Hydrochloride (23). Bromomethyl 2,6-bis(3,4-dichlorophenyl)-4-pyridyl ketone (IIe) (2 g) was suspended in EtOH (40 ml). $NaBH_4$ (250 mg) was added, and the mixt was stirred for 1 hr at room temp. HCl (3 *N*) was added to decompose excess $NaBH_4$, and the mixt was neutralized with Na_2CO_3. Water (50 ml) was added, and the mixt was filtered. The solid was washed with H_2O (x 2, 20 ml) and dried *in vacuo*. There was obtained 1.6 g (95%) of crude epoxide, mp 138–145°, containing *ca.* 5% of an unknown by tlc. The epoxide (1.5 g) and $(n\text{-}C_4H_9)_2NH$ (5 ml) in EtOH (25 ml) were heated at reflux for 3 hr (complete by tlc). Solvent and excess amine were removed *in vacuo*. The residual oil in Et_2O–*i*-PrOH was treated with a satd soln of HCl in *i*-PrOH. The ppt was washed with Et_2O (x 3, 20 ml). Recrystn from EtOH afforded 1.5 g (71%) of 23, mp 220–222°. The above procedure is typical of the prepn of the 4-pyridinemethanols described in Table III.

Derivatives. The *N*-oxides 4a and 23a were prepd by treating the parent compds 4 and 23, respectively (as the free bases), in Et_2O with 40% AcO_2H in AcOH. The mixt was stirred 2 hr at 25°. For **4a**, the soln was washed with 20% NaOH (x 2) and water (x 2), and dried (Na_2SO_4). The solvent was removed, and the residue was dissolved in Et_2O. Et_2O–HCl was added, and the ppt was recrystd (EtOH) to give **4a** (HCl salt), mp 172–174°. In the case of 23a, the crude product pptd from the Et_2O reaction mixt as the AcOH salt. This ppt was slurried in MeOH and treated with a little concd HCl. Water was added to the soln to ppt 23a (HCl salt), mp 174–175° (EtOH).

The *O*-succinoyl derivative **4b** was prepd by heating parent compd 4 (free base) and succinic anhydride in Me_2CO for 1 hr. The solvent was removed. The residue was dissolved in Et_2O and treated with dry HCl. The mixt was stirred at 25° with an equal vol of H_2O for 1 hr. Filtration gave crude **4b**, mp 149–153° (HCl salt), recrystd from CH_3CN.

The *N*-succinoyl derivative 3a was prepd from parent compd 3 (free base) by treating an Me_2CO soln with succinic anhydride at 25° for 1 hr. The solvent was removed and recrystn from C_6H_6 gave **3a**, mp 104–107°.

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Folate Antagonists. 2. 2,4-Diamino-6-{[aralkyl and (heterocyclic)methyl]amino}quinazolines, a Novel Class of Antimetabolites of Interest in Drug-Resistant Malaria and Chagas' Disease†,‡

John Davoll, A. M. Johnson, H. J. Davies,

Chemistry Department, Research and Development Division, Parke, Davis and Company, Hounslow, Middlesex, England

O. D. Bird, J. Clarke, and Edward F. Elslager*

Chemistry Department, Research and Development Division, Parke, Davis and Company, Ann Arbor, Michigan 48106.
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Forty-six 2,4-diamino-6-{[benzyl and (heterocyclic)methyl]amino}quinazolines (VI) were synthesized from the appropriate 2,4-diamino-6-nitroquinazoline (III) by reduction to the corresponding 2,4,6-triaminoquinazoline (IV), condensation of IV with the appropriate benzaldehyde or heterocyclic aldehyde to give the requisite Schiff base V, and reduction of V with H_2 over Raney Ni or with $NaBH_4$. 2,4-Diamino-6-{[(2-chloro-1-naphthyl)methyl]amino}quinazoline (**70**) and 2,4-diamino-6-{[(2-naphthyl)methyl]amino}quinazoline (**71**) were prepared similarly from 2,4,6-triaminoquinazoline and 2-chloro-1-naphthaldehyde and 2-naphthaldehyde, respectively. The condensation of 2 equiv of 2,4,6-triaminoquinazoline with 1 equiv of terephthalaldehyde or 4,4′-(ethylenedioxy)dibenzaldehyde followed by reduction of the Schiff bases afforded 6,6′-[*p*-phenylenebis(methyleneimino)]bis(2,4-diaminoquinazoline) (**76**) and 6,6′-[ethylenebis(oxy-*p*-phenylenemethyleneimino)]bis(2,4-diaminoquinazoline) (**77**). Treatment of 2,4,6-triaminoquinazoline with an acetophenone diethyl ketal in the presence of I_2 gave the corresponding 2,4-diamino-6-[(α-methylbenzylidene)amino]quinazolines, which upon reduction with $NaBH_4$ or H_2/PtO_2 afforded the requisite 2,4-diamino-6-[(α-methylbenzyl)amino]quinazolines (**66, 68, 69**). Forty-four compds were active against *Plasmodium berghei* in mice and 27 ranged from 7 to 190 times as potent as quinine hydrochloride. 2,4-Diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (**15**) also exhibited strong effects against cycloguanil-, pyrimethamine-, DDS-, and chloroquine-resistant lines of *P. berghei*. Against *P. cynomolgi* in rhesus monkeys, 19 compds eliminated asexual parasites within 1–8 days, and 7 were curative. Twenty-eight quinazolines were active against *Trypanosoma cruzi* in chick embryo cell culture at 0.39–6.25 μg/ml, and six showed antitrypanosomal effects in mice. Data on the inhibitory effects of the triaminoquinazolines against *Streptococcus faecalis* R (*Strep. faecium* var. *durans*), *Strep. faecalis* A (aminopterin-, methotrexate-resistant), *Lactobacillus plantarum*, and *Pediococcus cerevisiae* are presented, and overall structure–activity relationships are discussed.

Recent reports from these laboratories have described the synthesis and biological properties of various quinazoline analogs of folic acid.[2-7] Among them, several 2,4-diamino- and 2-amino-4-hydroxyquinazoline Glu and Asp analogs[2] (I, where $x = 1$ or 2; R = H or CH_3; and X = OH or NH_2) exhibit potent inhibitory effects against *Streptococcus faecalis* R (ATCC 8043)[4] [*Strep. faecium* var. *durans* (SF/0)],[8,9]

†This is paper 24 of a series on antimalarial drugs. For paper 23, see ref 1.
‡For the previous paper on folate antagonists, see ref 2.