Synthesis of Potential Antimalarial Agents. II.[1] 6,8-Disubstituted Pyrido[2,3-*b*]pyrazines

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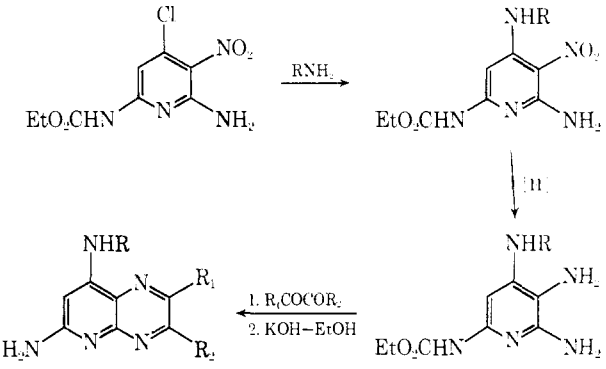
Resistance to chloroquine of strains of *Plasmodium berghei* and presumably of *Plasmodium falciparum* has been shown to involve the decreased accumulation of chloroquine in parasitized erythrocytes apparently caused by an impairment of the transport mechanism or a loss in the efficacy of intracellular binding to DNA.[2] As part of a program to develop compounds effective against chloroquine-resistant strains of *P. berghei*, the effect on antimalarial activity of the addition of (1) ring nitrogens, (2) exocyclic groups containing electron-rich centers, and (3) groups capable of hydrophobic bonding[3] to the quinoline ring was investigated by the preparation of some 6-amino-8-substituted aminopyrido[2,3-*b*]pyrazines.

Reaction of ethyl 6-amino-4-chloro-5-nitro-2-pyridinecarbamate[4] with N^1,N^1-diethyl-1,4-pentanediamine, *p*-chloroaniline, α-amino-*p*-toluenesulfonamide, *p*-(2-aminoethyl)benzenesulfonamide,[5] and *p*-(2-aminoethyl)-*N*,*N*-diethylbenzenesulfonamide, respectively, gave the corresponding 5-nitropyridines **1**–**5** (see Table I and Scheme I). Hydrogenolysis of these pyridines with Raney nickel gave the 5,6-diaminopyridines **6**–**9** and ethyl 5,6-diamino-4-{[4-(diethylamino)-1-methylbutyl]amino}-2-pyridinecarbamate. The latter was sensitive to air and was condensed *in situ* with 40% aqueous glyoxal, 30% aqueous pyruvaldehyde, benzil, *p*-chorophenylglyoxal, and 4,4′-dichlorobenzil, respectively, to give the ethyl pyrido[2,3-*b*]pyrazine-6-carbamates **10**, **12**, **14**, **16**, and **18**. The carbamates **10** and **12** were purified by column chromatography to give the products as amorphous glasses. The assignment of the orientation of the methyl group in **12**, and the *p*-chlorophenyl group in **16** is based on analogy with the direction of cyclization in the condensation of pyruvaldehyde with other 5,6-diaminopyridines.[6]

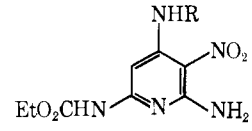
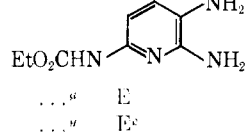
Similarly the condensation of the 5,6-diaminopyridines **6**–**9** with the α-dicarbonyl reagents described above gave the other pyrido[2,3-*b*]pyrazine-6-carba-

SCHEME I



mates listed in Table II. To eliminate the diaminopyridine as an impurity in the product, it is important to dissolve the diaminopyridine in DMF completely before the addition of the α-dicarbonyl compound.

TABLE I

Compd	R	Method	Reaction: Time, hr	Reaction: Temp, °C	Recrystn solvent[a]	Yield, %	Mp,[b] °C	Formula	Analyses
									
1	$CH_3CH(CH_2)_3NEt_2$	A	8	65	A, B, C	42	215[d]	$C_{17}H_{30}N_6O_4 \cdot HCl$	C, H, N
2	C_6H_4Cl-*p*	A	12	78	D	62	232–235[e]	$C_{14}H_{14}ClN_5O_4$	C, H, Cl, N
3	$CH_2C_6H_4SO_2NH_2$-*p*	A	8	65	C[f,c]	80	242–243	$C_{15}H_{18}N_6O_6S$	C, H, N
4	$CH_2CH_2C_6H_4SO_2NH_2$-*p*	A	2	65	C[f,c]	72	198–200	$C_{16}H_{20}N_6O_6S$	C, H, N
5	$CH_2CH_2C_6H_4SO_2NEt_2$-*p*	A	16	78	C[f]	93	168–169	$C_{20}H_{28}N_6O_6S$	C, H, N
									
6	C_6H_4Cl-*p*	B	...	...[g]	E	83	170–171[e]	$C_{14}H_{16}ClN_5O_2$	C, H, Cl, N
7	$CH_2C_6H_4SO_2NH_2$-*p*	B	...	...[g]	E[c]	85	223–226[e]	$C_{15}H_{20}N_6O_4S$	C, H, N
8	$CH_2CH_2C_6H_4SO_2NH_2$-*p*	B	...	...[g]	E	96	190–192[e]	$C_{16}N_{22}N_6O_4S$	C, H, N
9	$CH_2CH_2C_6H_4SO_2NEt_2$-*p*	B	...	...[g]	E	93	169–170[e]	$C_{20}H_{30}N_6O_4S$	C, H, N

[a] A, EtOH–Et_2O; B, EtOH–EtOAc; C, EtOH; D, DMF–EtOH; E, DMF–H_2O. [b] Melting points were determined with a Mel-Temp apparatus unless otherwise indicated. [c] Dried at 100° *in vacuo* over P_2O_5. [d] Kofler Heizbank apparatus. [e] Decomposition. [f] Trituration. [g] Room temperature.

(1) This work was carried out for the Division of Medicinal Chemistry, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Contract No. DA-49-193-MD-2999. This is Contribution No. 410 from the Army Research Program on Malaria.

(2) F. E. Hahn, R. L. O'Brien, J. Ciak, J. L. Allison, and J. G. Olenick, *Military Med.*, **131** (Suppl), 1071 (1966).

(3) B. R. Baker, "Design of Active-Site-Directed Irreversible Enzyme Inhibitors," John Wiley and Sons, Inc., New York, N. Y., 1967, p 39.

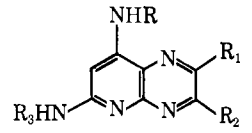
(4) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **31**, 1890 (1966).

(5) E. Miller, J. M. Sprague, L. W. Kissinger, and L. F. McBurney, *J. Amer. Chem. Soc.*, **62**, 2099 (1940).

(6) R. D. Elliott, C. Temple, Jr., and J. A. Montgomery, *J. Org. Chem.*, **33**, 2393 (1968).

TABLE II

PYRIDO[2,3-*b*]PYRAZINES



Compd	Method	Reaction: Time, hr	Reaction: Temp, °C	Time, hr	Temp, °C	Recrystn[a] solvent	Yield, %	Mp,[b,d] °C	Formula	Analyses
R = $CH_3CH(CH_2)_3NEt_2$										
10, $R_1 = R_2 = H$; $R_3 = CO_2Et$	C	48	...[c]				92	...[d]	$C_{16}H_{30}N_6O_2$	C, H, N
11, $R_1 = R_2 = R_3 = H$	D	7	78			A + B[e]	87	...[f]	$C_{16}H_{26}N_6 \cdot 2HCl$	C, H, Cl, N
12, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2Et$	C	48	...[c]			...[g]	81	...[d]	$C_{20}H_{32}N_6O_2$	C, H, N
13, $R_1 = R_3 = H$; $R_2 = CH_3$	D	7	78			D + B	85	...[f]	$C_{17}H_{28}N_6 \cdot 2HCl$	C, H, Cl, N
14, $R_1 = R_2 = C_6H_5$; $R_3 = CO_2Et$	E	24	...[c]	6	78	C + B[h]	78	211–213[i]	$C_{31}H_{38}N_6O_2 \cdot HCl$	C, H, Cl, N
15, $R_1 = R_2 = C_6H_5$; $R_3 = H$	D	7	78			...[j,h]	77	183–184	$C_{28}H_{34}N_6$	C, H, N
16, $R_1 = H$; $R_2 = C_6H_4Cl$-*p*; $R_3 = CO_2Et$	E	2	65	24	...[c]	A + B	84	136–139[i]	$C_{26}H_{33}ClN_6O_2 \cdot HCl$	C, H, Cl, N
17, $R_1 = R_3 = H$; $R_2 = C_6H_4Cl$-*p*	D	6	78			D + B[e]	50	116–118[k]	$C_{24}H_{29}ClN_6 \cdot 2HCl$	C, H, Cl, N
18, $R_1 = R_2 = C_6H_4Cl$-*p*; $R_3 = CO_2Et$	E	1	78	48	0	...[l]	85	80–82[m]	$C_{31}H_{36}Cl_2N_6O_2$	C, H, Cl, N
19, $R_1 = R_2 = C_6H_4Cl$-*p*; $R_3 = H$	D	7	78			...[n]	100	...[i]	$C_{29}H_{32}Cl_2N_6$	C, H, Cl, N
R = C_6H_4Cl-*p*										
20, $R_1 = R_2 = H$; $R_3 = CO_2Et$	F	2	55	24	...[c]	A + E	86	164–166[i]	$C_{16}H_{14}ClN_5O_2$	C, H, Cl, N
21, $R_1 = R_2 = R_3 = H$	G	6	78			F + B	71	...[f]	$C_{13}H_{10}ClN_5 \cdot HCl$	C, H, Cl, N
22, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2Et$	F	4	50	48	...[c]	A + E[g]	38	144–145[i]	$C_{17}H_{16}ClN_5O_2$	C, H, Cl, N
23, $R_1 = R_3 = H$; $R_2 = CH_3$	G	7	78			E[o]	97	264–265[i]	$C_{14}H_{12}ClN_5$	C, H, Cl, N
24, $R_1 = R_2 = C_6H_5$; $R_3 = CO_2Et$	F	6	...[c]	18	50	A[o,h]	94	243–246[i]	$C_{28}H_{22}ClN_5O_2$	C, H, Cl, N
25, $R_1 = R_2 = C_6H_5$; $R_3 = H$	G	7	78			F	96	225–228	$C_{23}H_{18}ClN_5 \cdot HCl$	C, H, Cl, N
26, $R_1 = H$; $R_2 = C_6H_4Cl$-*p*; $R_3 = CO_2Et$	F	0.5	60	2	...[c]	G + A	73	207–208[i]	$C_{22}H_{17}Cl_2N_5O_2$	C, H, Cl, N
27, $R_1 = R_3 = H$; $R_2 = C_6H_4Cl$-*p*	G	18	78			E[o]	88	315–316[i]	$C_{19}H_{13}Cl_2N_5$	C, H, Cl, N
28, $R_1 = R_2 = C_6H_4Cl$-*p*; $R_3 = CO_2Et$	F	1	78			A[p]	83	150[q]	$C_{28}H_{20}Cl_3N_5O_2$	C, H, N
29, $R_1 = R_2 = C_6H_4Cl$-*p*; $R_3 = H$	G	7	78			E[o]	88	...[i]	$C_{25}H_{16}Cl_3N_5$	C, H, Cl, N
R = $CH_2C_6H_4SO_2NH_2$-*p*										
30, $R_1 = R_2 = H$; $R_3 = CO_2Et$	F	1	60	24	...[c]	C[o,r]	97	254–256[i]	$C_{17}H_{18}N_6O_4S$	C, H, N
31, $R_1 = R_2 = R_3 = H$	G	4	150[s]			E[o,g]	49	278–279[i]	$C_{14}H_{14}N_6O_2S$	C, H, N
32, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2Et$	F	18	...[c]			C[o,r]	82	242–245[i]	$C_{18}H_{20}N_6O_4S$	C, H, N
33, $R_1 = R_3 = H$; $R_2 = CH_3$	G	7	78			F + B[r]	69	280–281[i]	$C_{15}H_{16}N_6O_2S \cdot HCl$	C, H, Cl, N
34, $R_1 = R_2 = C_6H_5$; $R_3 = CO_2Et$	F	48	...[c]	14	60	C[p,r]	81	251–253[i]	$C_{28}H_{26}N_6O_4S$	C, H, N
35, $R_1 = R_2 = C_6H_5$; $R_3 = H$	H	8	80	8	153	C[p,h]	59	281–283[i]	$C_{26}H_{22}N_6O_2S$	C, H, N
R = $CH_2CH_2C_6H_4SO_2NH_2$-*p*										
36, $R_1 = R_2 = H$; $R_3 = CO_2Et$	F	1	50	18	...[c]	A[o]	74	196–198[i]	$C_{18}H_{20}N_6O_4S$	C, H, N, S
37, $R_1 = R_2 = R_3 = H$	G	7	78			F + B	71	307–308[i]	$C_{15}H_{16}N_6O_2S \cdot HCl$	C, H, Cl, N
38, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2Et$	F	2	60	48	...[c]	C + E[g]	47	...[i]	$C_{19}H_{22}N_6O_4S$	C, H, N, S
39, $R_1 = R_3 = H$; $R_2 = CH_3$	G	7	78			...[t]	41	287–288[i]	$C_{16}H_{18}N_6O_2S \cdot 2H_2O$	C, H, N, S
40, $R_1 = R_2 = C_6H_5$; $R_3 = CO_2Et$	F	3	70	16	...[c]	A[o,r]	88	190–193[i,m]	$C_{30}H_{26}N_6O_4S$	C, H, N
41, $R_1 = R_2 = C_6H_5$; $R_3 = H$	G	7	78			G + C[g]	79	...[i]	$C_{27}H_{24}N_6O_2S$	C, H, N, S
R = $CH_2CH_2C_6H_4SO_2NEt_2$-*p*										
42, $R_1 = R_2 = H$; $R_3 = CO_2Et$	F	1	50	72	...[c]	...[u,e]	51	180–182[i]	$C_{22}H_{28}N_6O_4S$	C, H, N
43, $R_1 = R_2 = R_3 = H$	G	7	78			F + B[e]	85	116–118[i]	$C_{19}H_{24}N_6O_2S \cdot HCl$	C, H, Cl, N
44, $R_1 = H$; $R_2 = CH_3$; $R_3 = CO_2Et$	I	48	...[c]			A	54	142–145	$C_{23}H_{30}N_6O_4S$	C, H, N, S
45, $R_1 = R_2 = C_6H_5$; $R_3 = CO_2Et$	F	6	60			A[o]	83	151–153	$C_{34}H_{36}N_6O_4S$	C, H, N
46, $R_1 = R_2 = C_6H_5$; $R_3 = H$	G	7	78			C + B[h]	90	...[f]	$C_{31}H_{32}N_6O_2S \cdot HCl$	C, H, Cl, N
47, $R_1 = H$; $R_2 = C_6H_4Cl$-*p*; $R_3 = CO_2Et$	F	2	60	18	...[c]	A[p]	49	202–203[i,m]	$C_{28}H_{31}ClN_6O_4S$	C, H, Cl, N

[a] A, EtOH; B, Et_2O; C, MeOH; D, EtOH–HCl; E, H_2O; F, MeOH–HCl; G, DMF. [b] Melting points were determined with a Mel-Temp apparatus. [c] Room temperature. [d] Amber glass. [e] Dried *in vacuo* over P_2O_5 at 65°. [f] Indefinite. [g] Dried *in vacuo* over P_2O_5 at 78°. [h] Dried *in vacuo* over P_2O_5 at 110°. [i] Decomposition. [j] Extracted into C_6H_6 and treated with charcoal. [k] Resolidified and remelted 276–278° dec. [l] Extracted into Et_2O and washed (H_2O). [m] Presoftening. [n] Extracted into $CHCl_3$ and washed (H_2O). [o] Trituration. [p] Soxhlet extraction. [q] Resolidified and remelted at 222–224°. [r] Dried *in vacuo* over P_2O_5 at 100°. [s] Run in a glass-lined stainless steel bomb. [t] Precipitated from aqueous MeOH–NaOH with HCl. [u] Precipitated from aqueous EtOH–HCl with NaOH.

The resulting carbamates were converted to the corresponding 6-aminopyrido[2,3-*b*]pyrazine with refluxing ethanolic KOH with the exception of carbamate **30**, which did not react at this temperature. However, the conversion of **30** to **31** was successful with ethanolic KOH in a bomb at 150°. Also, the cleavage of the urethan group of **34** to give **35** was conveniently carried out in hot DMF.

The compounds listed in Tables I and II were evaluated against mice infected with a lethal dose of *P. berghei*.[7] No significant activity was observed in the nitropyridines (**1**–**5**), diaminopyridines (**6**–**9**), or pyrido[2,3-*b*]pyrazines containing a benzenesulfonamide moiety (**30**–**47**). Also no activity was observed in the *p*-chloroanilino derivatives **20**, **21**, **24**–**27**, and **29**. Preliminary results indicated that 6-amino-3-(*p*-chlorophenyl)-8-{[4-(diethylamino)-1-methylbutyl]amino}-pyrido[2,3-*b*]pyrazine (**17**) cured mice at doses of 320 and 640 mg/kg. This compound represents a new type of antimalarial structure. No significant activity was observed with the related compounds **10** and **14**–**16**. Screening results on some of the other pyrido[2,3-*b*]-pyrazines (**11**–**13**, **18**, **19**, **22**, **23**, and **28**) are incomplete.

(7) For a description of the test procedure, see T. S. Osdene, P. B. Russell, and L. Rane, *J. Med. Chem.*, **10**, 431 (1967).

Experimental Section[8]

Typical procedures are given for the preparation of the compounds listed in Tables I and II.

Method A. Ethyl 6-Amino-5-nitro-4-[(*p*-sulfamoylbenzyl)-amino]-2-pyridinecarbamate (3).—A mixture of α-amino-*p*-

(8) Silica gel H was obtained from Brinkmann Instruments, Inc., and Raney Active Catalyst No. 28 from W. R. Grace & Co. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

toluenesulfonamide hydrochloride (20.0 g, 90.0 mmoles), ethyl 6-amino-4-chloro-5-nitro-2-pyridinecarbamate (23.4 g, 89.0 mmoles), and Et_3N (25 ml) in 300 ml of MeOH was refluxed for 8 hr under N_2. The yellow solid which formed upon cooling was collected by filtration, triturated with boiling EtOH (200 ml), and dried (P_2O_5) at 100° for 8 hr; yield 29.5 g.

In the preparation of **1**·HCl the reaction was carried out in the absence of Et_3N.

Method B. Ethyl 5,6-Diamino-4-(*p*-chloroanilino)-2-pyridinecarbamate (6).—A suspension of **2** (5.0 g, 14.2 mmoles) in DMF (200 ml) was hydrogenated over RaNi catalyst (*ca.* 10 g) at an initial H_2 pressure of 3.68 kg/cm². After about 30 min the catalyst was removed by filtration under N_2. The colorless filtrate was poured into cold H_2O (1 l.) through which a vigorous stream of N_2 was bubbling. The precipitated white solid was collected by filtration under N_2 and dried *in vacuo* over P_2O_5; yield 3.8 g.

Method C. Ethyl 8-{[4-(Diethylamino)-1-methylbutyl]amino}-pyrido[2,3-*b*]pyrazine-6-carbamate (10).—A suspension of **1**·HCl (15.0 g, 35.8 mmoles) in EtOH (300 ml) was hydrogenated (Ra Ni) (*ca.* 10 g) at an initial H_2 pressure of 3.67 kg/cm². The catalyst was removed by filtration under N_2, and the nearly colorless filtrate was treated with a 40% aqueous solution of glyoxal (5.80 g, 39.4 mmoles). The resulting dark red solution was stirred under N_2 for 48 hr at room temperature. After evaporation of the solvent *in vacuo*, addition of H_2O (50 ml) and 10% NaOH (pH 8–9) caused separation of an orange oil, which was extracted with EtOAc (three 250-ml portions). Removal of the solvent left an oil, which did not solidify either as the free amine or as the corresponding HCl salt. A solution of the oil in $CHCl_3$ was poured onto a silica gel II column (150 g), which had been washed well with $CHCl_3$. The column was eluted successively with $CHCl_3$ and $CHCl_3$–MeOH (95:5). Evaporation of the 95:5 fraction and prolonged drying of the residue *in vacuo* yielded a brittle amber glass, which was shown to be homogeneous by tlc; yield 12.4 g.

Method D. 6-Amino-8-{[4-(diethylamino)-1-methylbutyl]amino}-3-methylpyrido[2,3-*b*]pyrazine Dihydrochloride (13).—A solution of **12** (5.50 g, 14.2 mmoles) and KOH pellets (4.0 g, 71 mmoles) in absolute EtOH (100 ml) was refluxed under N_2 for 7 hr, then cooled to room temperature. The reaction mixture was acidified with 5.5 *M* ethanolic HCl (40 ml), and the precipitated KCl was removed by filtration. The dark brown filtrate was treated with charcoal, concentrated to *ca.* one-third volume *in vacuo*, and diluted (Et_2O, 200 ml). The semisolid which precipitated was separated by decantation and redissolved in warm EtOH (200 ml) containing 5.5 *M* ethanolic HCl (20 ml). Et_2O (500 ml) was added in small portions over a 2-day period until precipitation of the product appeared complete. The off-white solid was collected by filtration under N_2 and dried *in vacuo* over P_2O_5; yield 4.70 g.

Method E. Ethyl 8-{[(4-Diethylamino)-1-methylbutyl]amino}-2,3-diphenylpyrido[2,3-*b*]pyrazine-6-carbamate Hydrochloride (14).—A solution of **1**·HCl (15.0 g, 35.8 mmoles) in MeOH (250 ml) was hydrogenated over RaNi at an initial pressure of 3.67 kg/cm². When the reduction was complete (3 hr), the catalyst was removed by filtration under N_2 and washed (MeOH). The combined filtrate and wash were treated with benzil (7.50 g, 35.8 mmoles); the resulting yellow solution was stirred under N_2 at room temperature for 24 hr, then at reflux temperature for 6 hr. The solvent was removed *in vacuo*, leaving a resinous mass which was purified by twice dissolving in MeOH and pouring into Et_2O. After the second precipitation the solid was collected by filtration, washed (Et_2O), and dried *in vacuo* over P_2O_5 at 110°; yield 15.7 g.

Method F. Ethyl 8-(*p*-Chloroanilino)-3-(*p*-chlorophenyl)-pyrido[2,3-*b*]pyrazine-6-carbamate (26).—To a solution of **6** (12.7 g, 39.5 mmoles) in DMF (20 ml) was added EtOH (200 ml) and *p*-chlorophenylglyoxal hydrate (7.8 g, 42.0 mmoles). The resulting bright orange solution was stirred on a 60° H_2O bath for 30 min under N_2. A yellow solid began to crystallize after about 10 min. After standing at room temperature for 2 hr, the solid was collected by filtration and dried *in vacuo* over P_2O_5; yield 17.2 g. This solid was recrystallized by dissolving in hot DMF, adding EtOH (800 ml), and cooling; yield 15.0 g.

Method G. 6-Amino-8-(*p*-chloroanilino)-2,3-bis(*p*-chlorophenyl)pyrido[2,3-*b*]pyrazine (29).—A suspension of **28** (16.8 g, 29.8 mmoles) and KOH pellets (8.40 g, 150 mmoles) in absolute EtOH (300 ml) was refluxed for 7 hr under N_2, then cooled to room temperature. The crystalline yellow solid was collected by filtration, washed with EtOH, and suspended in H_2O (400 ml) by vigorous stirring. Excess 6 *N* HCl (10 ml) was added, and stirring was continued until effervescence ceased. The mixture was readjusted to pH 8 with 10 *M* NaOH, and the yellow solid was collected by filtration, washed with H_2O, and dried *in vacuo* over P_2O_5 at 78°; yield 12.9 g.

Method H. α-{(6-Amino-2,3-diphenylpyrido[2,3-*b*]pyrazin-8-yl)amino}-*p*-toluenesulfonamide (35).—A solution of **3** (15.0 g, 36.6 mmoles) in DMF (250 ml) was hydrogenated over Ra Ni at an initial pressure of 3.67 kg/cm². When the reduction was complete, the catalyst was removed by filtration under N_2 and washed with DMF. Benzil (7.69 g, 36.6 mmoles) was added to the combined filtrate and wash, and the mixture was allowed to stand at room temperature overnight. Then the reaction mixture was heated under N_2 for 8 hr at 80° and 8 hr at reflux temperature on successive days. The reaction mixture was poured into 1 l. of H_2O, and the precipitated solid was collected by filtration and dried *in vacuo* over P_2O_5; yield 15.3 g. The product was extracted for 48 hr with MeOH in a Soxhlet apparatus. The yellow solid obtained from the cooled extract was dried *in vacuo* over P_2O_5 at 110°; yield 10.5 g.

Method I. Ethyl 8-{[*p*-(Diethylsulfamoyl)phenethyl]amino}-3-methylpyrido[2,3-*b*]pyrazine-6-carbamate (44).—A solution of **9** (20.9 g, 46.3 mmoles) in DMF (50 ml) was diluted with EtOH (350 ml) and a 30% solution of pyruvaldehyde (11.7 g, 48.6 mmoles). The red reaction mixture was stirred under N_2 for 48 hr; then the volatile matter was removed *in vacuo*, leaving a brown gummy residue. The gum was dissolved in a small volume of $CHCl_3$, and the solution was poured onto a silica gel II column (400 g) which had been washed with $CHCl_3$. The column was eluted first with $CHCl_3$, then with $CHCl_3$–MeOH (95:5). Evaporation of the solvent from the combined eluates gave 13.8 g (61%) of dark orange crystals. A contaminant, detected by thin layer chromatography, was present in the solid after four recrystallizations from EtOH and EtOH–H_2O. The solid was redissolved in $CHCl_3$ and added to another silica gel II column (200 g). Elution with $CHCl_3$ gave homogeneous yellow crystals upon evaporation of the $CHCl_3$. The combined fractions were recrystallized from hot EtOH; yield 12.2 g.

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Cyclization of Aniline–Acetylenedicarboxylate Adducts. A Modified Conrad–Limpach Method for the Synthesis of Potential Antimalarials[1]

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The interest in 4(1H)-quinolones has largely been directed toward their utility as intermediates in preparation of 4-aminoquinolines as antimalarial agents. In general such quinolones have been synthesized by thermal cyclization of the enamino esters obtained by condensation of anilines with ethoxymethylenemalonic ester (Gould–Jacobs reaction[2]) or β-keto esters

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(2) R. Gould and W. Jacobs, *J. Amer. Chem. Soc.*, **61**, 2890 (1939).