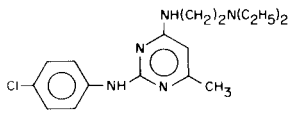
[[(Dialkylamino)alkyl]amino]pyrimido[1,2-*a*]benzimidazoles, 2,3-Dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazoles, and *s*-Triazolo[1,5-*a*]pyrimidines as Potential Antimalarial Agents (1,2)

Leslie M. Werbel, Ann Curry, Edward F. Elslager, Carolyn A. Hess, Marland P. Hutt, and Carl Youngstrom

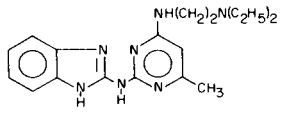
Department of Chemistry, Medical and Scientific Affairs Division
Parke, Davis and Company

The structure of the product of the reaction of 2-aminobenzimidazole with ethyl acetoacetate has been established by NMR spectroscopy as 2-methylpyrimido[1,2-*a*]benzimidazol-4-ol (III). 7(and 8)-Chloro-2-methylpyrimido[1,2-*a*]benzimidazol-4-ol (VI and VIII, R = OH), 2-(trifluoromethyl)pyrimido[1,2-*a*]benzimidazol-4-ol (X), 2,7,8-trimethylpyrimido[1,2-*a*]benzimidazol-4-ol (XII), 2-benzyl-1,2,3,4-tetrahydropyrido[4',3':4,5]pyrimido[1,2-*a*]benzimidazol-12-ol (XIII), 1,2,3,4-tetrahydrobenzimidazo[2,1-*b*]quinazolin-12-ol (XIV), and 2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazol-11-ol (XV) were prepared in a similar manner. Chlorination of III, VI and VIII, XV, and 5-methyl-*s*-triazolo[1,5-*a*]pyrimidin-7-ol (XXV, R = OH) with phosphorus oxychloride afforded the corresponding chloroheterocycles, which were condensed with the appropriate *N*,*N*-dialkylalkylenediamine or N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine to give various 4-[[(dialkylamino)alkyl]amino]-2-methylpyrimido[1,2-*a*]benzimidazoles (Va-e, VII, IX), 11-[[(dialkylamino)alkyl]amino]-2,3-dihydro-1*H*-cyclopenta[4,5]-pyrimido[1,2-*a*]benzimidazoles (XVIa and b), and 7-[[(dialkylamino)alkyl]amino]-5-methyl-*s*-triazolo[1,5-*a*]pyrimidines (XXVb-e). None of these compounds displayed significant antimalarial activity against *Plasmodium berghei* in the mouse.

At the onset of the British war-time antimalarial program, sponsored by the Medical Research Council, it was decided to break away from the traditional quinoline and acridine types and to devise novel hybrids of quinacrine and sulfadiazine (3). Fortuitously, this approach rapidly led to the discovery that various 2-(arylamino)-4-[[(dialkylamino)alkyl]amino]-6-methylpyrimidines, exemplified by I, possessed strong therapeutic effects against *Plasmodium gallinaceum* in the chick (3). Later it was



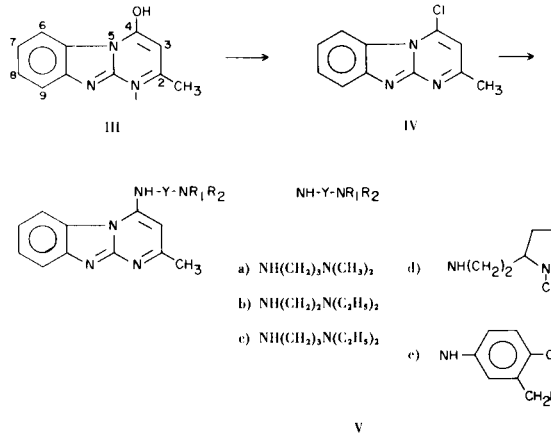
I



II

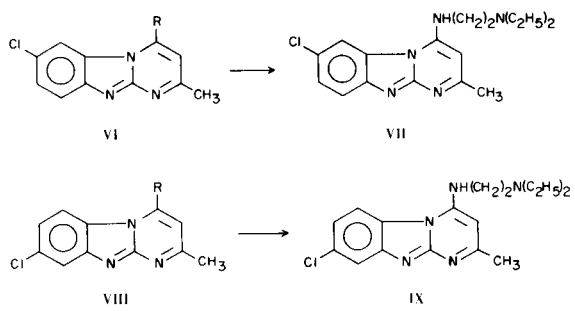
shown that similarly constituted benzimidazole derivatives, such as II, also were active (3). Recent awareness of the gravity of the situation created by the possibility of widespread resistance of *Plasmodium falciparum* to the 4-aminoquinolines (4) has triggered an intensive search for new types of fast-acting suppressive antimalarial drugs. In light of this need, the earlier experience in the British program, and the knowledge that the introduction of a basic side-chain into certain heterocyclic systems afforded derivatives with pronounced antimalarial properties, series of 4-[[(dialkylamino)alkyl]amino]-2-methylpyrimido-[1,2-*a*]benzimidazoles (Va-e, VII, IX), 11-[[(dialkylamino)alkyl]amino]-2,3-dihydro-1*H*-cyclopenta[4,5]-pyrimido[1,2-*a*]benzimidazoles (XVIa and b), and 7-[[(dialkylamino)alkyl]amino]-5-methyl-*s*-triazolo[1,5-*a*]-pyrimidines (XXVb-e) have been synthesized for antimalarial evaluation.

The condensation of 2-aminobenzimidazole with β-keto esters reportedly gives 2-substituted pyrimido[1,2-*a*]benzimidazol-4-ols (5-7). Such materials exist in the tautomeric keto form as evidenced by a lactam carbonyl at 1690 cm^{-1} in their infrared spectra. This is consistent with the behavior of 4-pyridinols, 4-quinolinols, and allied heterocyclic systems (8). In the present work these intermediates are depicted in the phenolic form to facilitate visualization of the subsequent reaction sequence. Chlorination of 2-methylpyrimido[1,2-*a*]benzimidazol-4-ol (III) (7) with phosphorus oxychloride gave 4-chloro-2-methylpyrimido[1,2-*a*]benzimidazole (IV) (73%) (7). Conden-



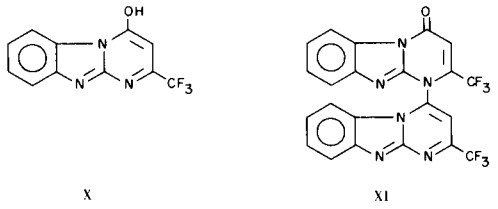
sation of IV with the appropriate diamine in chloroform afforded the corresponding 4-[[(dialkylamino)alkyl]-amino]-2-methylpyrimido[1,2-*a*]benzimidazoles (Va-e, Table I) in 10-65% yield.

The cyclization of 2-amino-5-chlorobenzimidazole and ethyl acetoacetate gave a crude product which apparently contained both 7(and 8)-chloro-2-methylpyrimido[1,2-*a*]-benzimidazol-4-ol (VI and VIII, R = OH). Chlorination of this mixture with phosphorus oxychloride provided a



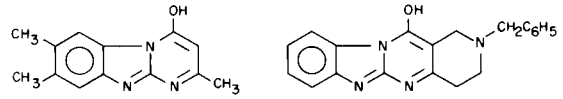
mixture of 4,7(and 8)-dichloro-2-methylpyrimido[1,2-*a*]-benzimidazole (VI and VIII, R = Cl) which could not be separated or sufficiently purified for analysis. Treatment of this mixture with *N,N*-diethylethylenediamine afforded 7(and 8)-chloro-4-[[2-(diethylamino)ethyl]amino]-2-methylpyrimido[1,2-*a*]benzimidazole (VII and IX) (Table I) which were separated by fractional crystallization. Spectroscopic evidence for their structure assignments is discussed later in the paper.

Cyclization of 2-aminobenzimidazole and ethyl trifluoroacetoacetate gave 2-(trifluoromethyl)pyrimido-[1,2-*a*]benzimidazol-4-ol (X) (14%). Treatment of X with phosphorus oxychloride produced, instead of the expected chloro compound, a substance which appears to be 2,2′-(trifluoromethyl)[1,4′-bipyrimido[1,2-*a*]benzimidazole]-4(1*H*)-one (XI) (36%). This is presumed to result from the condensation of the expected chloro compound with unreacted starting material X. All other attempts to

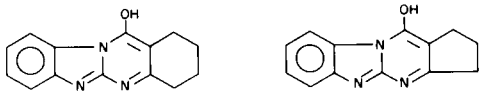


chlorinate X were unsuccessful.

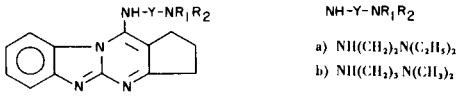
In an analogous manner the condensation of 2-amino-5,6-dimethylbenzimidazole with ethyl acetoacetate and 2-aminobenzimidazole with ethyl 1-benzyl-4-oxonipecotate, ethyl 2-oxocyclohexanecarboxylate, and ethyl 2-oxocyclopentanecarboxylate afforded 2,7,8-trimethylpyrimido[1,2-*a*]benzimidazol-4-ol (XII) (36%), 2-benzyl-1,2,3,4-tetrahydropyrido[4′,3′:4,5]pyrimido[1,2-*a*]benzimidazol-12-ol (XIII) (6%), 1,2,3,4-tetrahydrobenzimidazo-



[2,1-*b*]quinazolin-12-ol (XIV) (35%) (7), and 2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazol-11-ol (XV) (34%) (7), respectively. The latter compound was



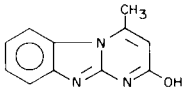
chlorinated with phosphorus oxychloride to give 11-chloro-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]-benzimidazole, which upon treatment with *N,N*-diethylethylenediamine or *N,N*-dimethyl-1,3-propanediamine in chloroform afforded 11-[[2-(diethylamino)ethyl]amino]-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazole (XVIa) (30%) and 11-[[3-(dimethylamino)propyl]-amino]-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]-benzimidazole (XVIb) (23%), respectively. Preliminary



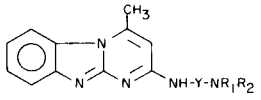
antimalarial studies indicated that the 4-[[(dialkylamino)-alkyl]amino]-2-methylpyrimido[1,2-*a*]benzimidazoles (Va-e, VII, and IX) and the 11-[[(dialkylamino)alkyl]-amino]-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]-benzimidazoles (XVIa and b) lacked appreciable effects against *Plasmodium berghei* in the mouse (9, 10). Therefore, compounds XII-XIV were not converted to the

corresponding diamine derivatives.

Although compounds Va-e, VII, IX, and XVIa and b were devoid of antimalarial properties, it was of interest to provide evidence confirming their structures. The initial condensation of 2-aminobenzimidazole with a β-keto ester could give III and/or the isomer XVII. Compound XVII upon chlorination and treatment with an



XVII

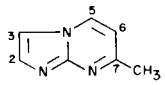


XVIII

aliphatic diamine would then give XVIII. The mode of addition of β-keto esters and aromatic amines is known to be influenced by the reaction conditions (11).

Numerous attempts have been made to obtain an isomeric product from the condensation of a β-keto ester and 2-aminobenzimidazole. Unfortunately, for our purposes, these reactions appear to proceed with great facility, and lead only to a single isolable product. Thus in addition to the fusion procedure described in the Experimental Section, wherein the components were heated briefly in an oil bath at 130°, the reaction of ethyl acetoacetate and 2-aminobenzimidazole in ethanol under reflux for 45 hours, in dimethylformamide at 100° for 3 hours, or in ethanol in the presence of sodium ethoxide under reflux for 18 hours led only to III in 20, 40, and 73% yield, respectively. Similarly heating 2-aminobenzimidazole with ethyl 3-aminocrotonate at 130° for 0.2 hour gave III in 14% yield; 2-aminobenzimidazole and *t*-butyl acetoacetate at 135° for 1.5 hours gave III in 38% yield; and 2-aminobenzimidazole heated under reflux in benzene for 20 hours with *t*-butyl acetoacetate and a trace of *p*-toluenesulfonic acid afforded III in 60% yield. Several attempts to condense 2-chlorobenzimidazole with ethyl 3-aminocrotonate led either to the recovery of starting material or to intractable mixtures.

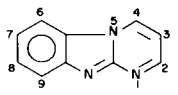
Definitive assignment of the condensation product of 2-aminobenzimidazole with ethyl acetoacetate as III rather than the isomeric XVII was made on the basis of NMR spectroscopy. The NMR spectra (12) of III, X, and XIII-XV showed a shift of one proton downfield about 1 ppm from the multiplet containing the other three aromatic protons. This proton is assigned as H-6 (in III) in agreement with the deshielding effect observed in similar "angular" proton interactions (13), as well as that recorded for the proton *ortho* to the acylamino group of *ortho*-substituted acylanilines (14, 15). Deshielding of H-6 of a smaller magnitude is also observed in the chloro compound IV (0.4 ppm) (13) and in the (dialkylamino)-alkylamino derivatives Va-e (0.7 ppm). Paudler (16, 17), Robins (18), and co-workers have made detailed assignments in the NMR spectra of the imidazo[1,2-*a*]pyridines based on the use of known models. Extending this work to the imidazo[1,2-*a*]pyrimidines, Paudler and Kuder (19) assigned the product of the condensation of 2-amino-4-methylpyrimidine and 2-bromoacetaldehyde as the 7-methyl isomer XIX. The signals of H-2 and H-3 were



XIX

TABLE I

NMR Spectral Data of Pyrimido[1,2-*a*]benzimidazoles

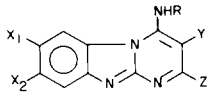


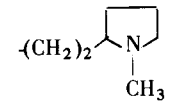
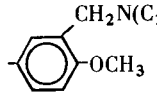
Substituent	Chemical Shifts 2	3	4	6	7 and 8	9	J Values cps $J_{2,3}$	$J_{3,4}$	$J_{2,4}$
None	8.89d (a)	7.20d (a)	9.49d (a)	8.3 or 7.9	7.5	7.9 or 8.3	4.0	6.5	2.0
2-CH_3	2.62s	7.00d	9.33d	8.3 or 7.9	7.5	7.9 or 8.3	0.0	6.5	0.0
2,4-$(CH_3)_2$	2.53s	6.76s	2.97d	8.1 or 7.8	7.4	7.8 or 8.1	0.0	0.9	0.0
2-CH_3-4-Cl	2.32s	5.85s	----	7.9	7.5 (7,8,9)	-------	0.0	--	--
2-CH_3-4-OH	2.32d (b)	5.81s	----	8.4	7.4 (7,8,9)	-------	0.6	--	--
2-CH_3-4-$NHCH_2CH_2N(C_2H_5)_2$	2.42s	6.05s	----	8.2	7.5 (7,8,9)	-------	0.0	--	--

d = doublet, s = singlet, m = multiplet; (a) pairs of doublets; (b) using normal sweep width (500 cps) this appears as a singlet but spreading the peak using sweep width of 50 cps clearly reveals the doublet. This treatment also splits the singlet at 8.4 into a multiplet.

TABLE II

4-[[(Dialkylamino)alkyl]amino]-2-methylpyrimido[1,2-*a*]benzimidazoles
and 11-[[(Dialkylamino)alkyl]amino]-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazoles



No.	X_1	X_2	Y	Z	R	M.p., °C	Yield Purified %	Purification solvent	Formula	Analyses Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Va	H	H	H	CH_3	$-(CH_2)_3N(CH_3)_2$	198-200	60	Ethyl acetate	$C_{16}H_{21}N_5$	67.81	67.88	7.47	7.41	24.72	24.91
VII	Cl	H	H	CH_3	$-(CH_2)_2N(C_2H_5)_2$	158-160	10	Aqueous ethanol	$C_{17}H_{22}ClN_5$	61.53	61.54	6.67	6.55	21.11	21.02
IX	H	Cl	H	CH_3	$-(CH_2)_2N(C_2H_5)_2$	209-211	16	Ethyl acetate	$C_{17}H_{22}ClN_5$	61.53	61.89	6.67	6.59	21.11	21.19
Vb	H	H	H	CH_3	$-(CH_2)_2N(C_2H_5)_2$	180-181	45	Ethyl acetate	$C_{17}H_{23}N_5$	68.65	68.73	7.80	7.59	23.55	23.89
Vd	H	H	H	CH_3		181-182	65	Ethyl acetate	$C_{18}H_{23}N_5$	69.87	70.17	7.49	7.37	22.64	22.79
Vc	H	H	H	CH_3	$-(CH_2)_3N(C_2H_5)_2$	100-102	45	*n*-Heptane	$C_{18}H_{25}N_5$	69.42	69.13	8.09	7.90	22.49	22.63
Ve	H	H	H	CH_3		230-232	24	Ethyl acetate or ethanol	$C_{23}H_{27}N_5O$	70.92	71.11	6.99	7.13	17.98	18.25
XVIb	H	H	$-(CH_2)_3-$		$-(CH_2)_3N(CH_3)_2$	183-185	23	Ethyl acetate	$C_{18}H_{23}N_5$	69.87	69.90	7.49	7.67	22.64	22.93
XVIa	H	H	$-(CH_2)_3-$		$-(CH_2)_2N(C_2H_5)_2$	220-222	30	Ethyl acetate	$C_{19}H_{25}N_5$	70.56	70.59	7.79	7.83	21.65	21.42

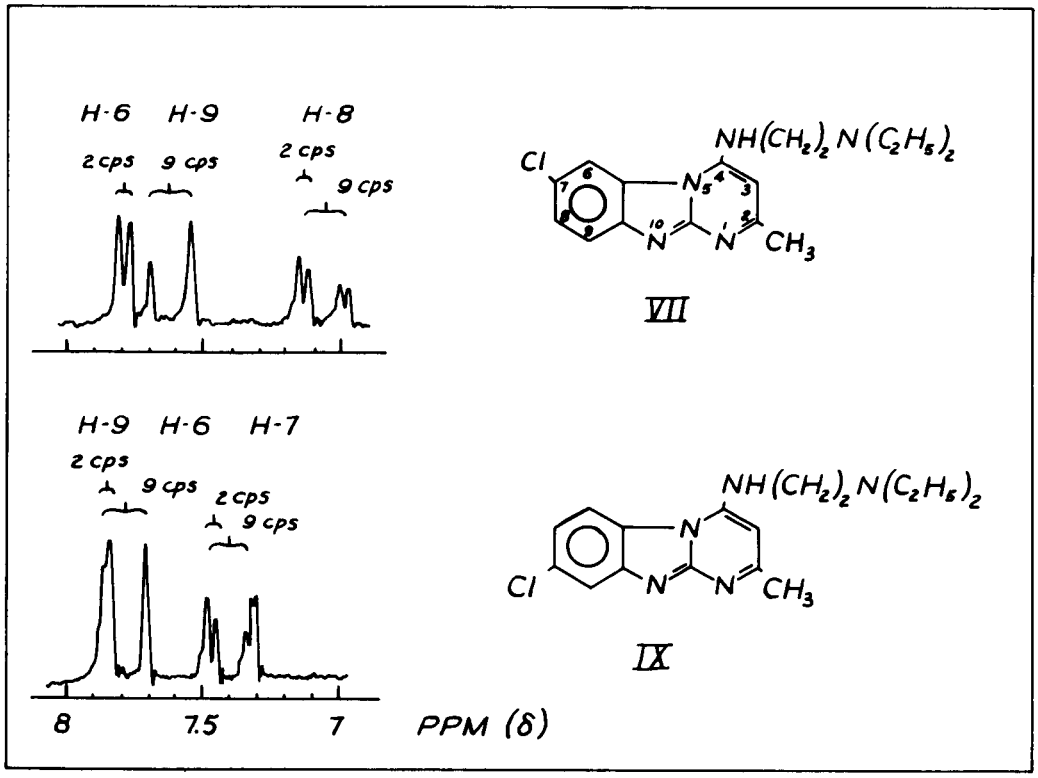
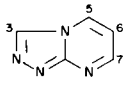


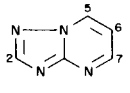
Figure 1. NMR of 7(and 8)-Chloro-4-[[2-(diethylamino)ethyl]amino]-2-methylpyrimido[1,2-*a*]benzimidazole in deuteriochloroform.

assigned by analogy with their earlier work on the imidazo[1,2-*a*]pyridines. Thus in 5,7-dimethylimidazo-[1,2-*a*]pyrimidine, whose structure is unequivocal, it was anticipated that H-3 would appear at a more shielded position than in the unsubstituted compound. This additional shielding of H-3 ($\Delta\tau$ 0.24) was clearly visible. In the 5-methyl compound H-3 would be expected to resonate at essentially the same frequency as in the 5,7-dimethyl derivative. The condensation product of 2-amino-4-methylpyrimidine was assigned the 7-Me structure because H-3 resonance was closer to that of the parent than that of the 5,7-dimethyl analog. In addition they showed that a methyl at C-5 appears as a doublet JH-6, Me-5 = 1.0 while Me-7 is a singlet, and that J5,6 was 6.9 for the H-5–H-6 AB system while J6,7 was about 4.5.

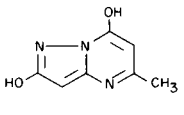
Their investigations were further extended to the 1,2,4-triazolo[4,3-*a*]pyrimidines (XX) and the 1,2,4-triazolo-[1,5-*a*]pyrimidines (XXI) (20), and these observations, as well as those of Makisumi (21), appear to confirm both the larger J value for J5,6 (6-7 cps) than for J6,7 (4 cps) and the fact that only the Me-5 couples with the adjacent H-6 to give a doublet. Vidal (22) has also utilized a similar difference in J values to assign structures to the pyrazolo[1,5-*a*]pyrimidines (XXII) and [3,4-*b*]-pyridines (XXIII) obtained from the condensation of ethyl acetoacetate with 2-aminopyrazol-4-ol.



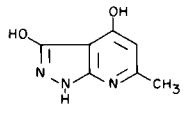
XX



XXI

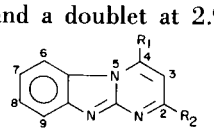


XXII



XXIII

To enable structure assignment *via* NMR spectroscopy several simple pyrimido[1,2-*a*]benzimidazoles were prepared. Spectral data is tabulated for these materials in Table I. 2,4-Dimethylpyrimido[1,2-*a*]benzimidazole (5) (XXIV, $R_1 = R_2 = CH_3$) showed a methyl singlet at 2.53 assigned as Me-2; and a doublet at 2.97 assigned Me-4

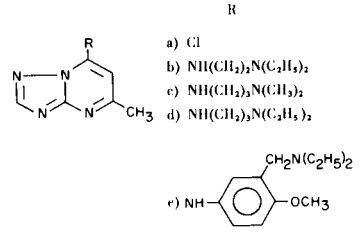


XXIV

which is split as expected by coupling with H-3. The monomethyl derivative prepared from 2-aminobenzimidazole and acetoacetaldehyde dimethyl acetal (23) was assigned the 2-methyl orientation (XXIV, R_1 = H, R_2 = CH_3) on the basis of the absence of splitting of the methyl peak and the high J value (6.5) indicative of H3,4 coupling. The parent compound (XXIV, R_1 = R_2 = H), prepared from 2-aminobenzimidazole and 1,1,3,3-tetraethoxypropane, confirmed the lower value for H2,3 coupling (4.0) and revealed in addition the small H2,4 coupling (2.0), in accord with the earlier work. Positions for the other peaks in these materials reported in Table I are also consistent with the data reported for related systems by Paudler, Vidal, and Makisumi. The 2-methyl group in XXIV (R_2 = CH_3, R_1 = OH) is split into a doublet, but this is due to coupling with H-3 on the C2,3 fixed double bond of the keto form. H-3 is also split into a multiplet in this system. In contrast, XXIV (R_2 = CH_3, R_1 = Cl) and XXIV [R_2 = CH_3, R_1 = $NHCH_2CH_2N(C_2H_5)_2$] confirm the absence of coupling between the CH_3-2 and H-3 in the aromatic system (and also defines the existence of the amine as written rather than in the tautomeric imino form). Finally catalytic hydrogenolysis of IV gave a compound identical in all respects with XXIV (R_1 = H, R_2 = CH_3). Thus it is concluded that condensation of 2-aminobenzimidazole with both acetoacetaldehyde and ethyl acetoacetate proceeds to give the 2-methylpyrimido[1,2-*a*]benzimidazoles. It has been presumed without further verification that the condensations with other β-ketoesters proceed similarly.

The use of 2-amino-5-chlorobenzimidazole in this procedure led after chlorination and replacement with *N,N*-diethylethylenediamine to the isomeric VII and IX. The 2-methyl orientation is assumed in both cases. The assignments proposed, *i.e.* the low-melting isomer as VII and the high-melting isomer as IX, are based on analyses of the aromatic region of the NMR spectra. In the NMR of VII (Figure 1) the absorption farthest downfield is a doublet at 7.80. This is assigned as H-6 (J6,8 = 2 cps *meta* coupling) and its position results from the deshielding effect of the angular proton interaction with the NH at C-4. H-8 appears as a pair of doublets centered at 7.05 (J8,9 = 9 cps *ortho* coupling), and H-9 appears as a doublet centered at 7.62. The NMR of IX contains a broadened singlet at 7.85 which can be shown by utilizing a smaller sweep width to be composed of a doublet assigned to H-9 (at approximately 7.85 with J7,9 = 2 cps *meta* coupling) and half of the doublet centered at 7.80 assigned to H-6 (J6,7 = 9 cps *ortho* coupling). A pair of doublets centered at 7.42 is assigned as H-7. This data does not offer unequivocal proof for the structures of VII and IX, but does allow the assignments to be made with some measure of rationality. Further confirmation for the structures of VII and IX is provided by the high field position of H-8 in VII compared with H-7 in IX since one might predict increased electron density at H-8 in VII but not at H-7 in IX.

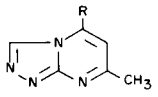
It was also of interest to prepare similarly constituted 7-[[[(dialkylamino)alkyl]amino]]-5-methyl-*s*-triazolo[1,5-*a*]-pyrimidines. Chlorination of 5-methyl-*s*-triazolo[1,5-*a*]-pyrimidin-7-ol (24) (XXV, R = OH) gave the corresponding



XXV

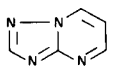
chloro compound (XXVa) (73%) (25). Displacement with amines then provided XXVb-e in 12-52% yield.

The structures of XXVa-e may remain open to some question. The past literature on this ring system provided a rather uncertain picture. None of the available synthetic routes leads to unequivocal structures, and may provide either the triazolo[1,5-*a*]pyrimidines XXV or the isomeric triazolo[4,3-*a*]pyrimidines XXVI.

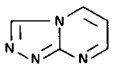


XXVI

Early structure assignments in this field utilized ultraviolet spectroscopy and were somewhat less than adequate (23, 25-29). More recent work using NMR spectroscopy (20, 30, 31) seems to have eliminated most of the confusion. Particularly the work of Paudler and Helmick (20) has established the structures of the dimethyl derivatives of both ring systems XXV and XXVI (R = CH_3) as well as the parent compounds XXVII and XXVIII, and confirmed



XXVII



XXVIII

the assignments proposed earlier.

There appears to be ample data in the recent literature (27, 30, 31) to support the triazolo[1,5-*a*]pyrimidine XXV as the more stable isomer. Since our starting material (XXV, R = OH) was prepared by cyclization in refluxing acetic acid (36), conditions which are known to favor the more stable isomer, the ring system is almost certainly that depicted in XXV. The appearance of the methyl group as a sharp singlet in all the compounds prepared

by us further supports the orientation of methyl with respect to R as shown in XXV.

Compounds III, Va-e, VI (R = OH), VII, VIII (R = OH), IX-XVI, XXIV (R_1 = H, R_2 = CH_3), XXIV (R_1 = R_2 = CH_3), and XXVb-e were administered subcutaneously in a single dose to mice infected with *P. berghei* (9, 10). None of these compounds caused a significant prolongation of the mean survival time of mice even at the highest dose level employed, namely 640 mg./kg. Further when representative compounds Va-e, VII, IX, XVIa and b, and XXVb-e) were given continuously in the diet for 6 days to mice infected with another strain of *P. berghei* in daily doses ranging from 77 to 368 mg./kg., no significant reduction in parasitemia was observed among the treated groups (32, 33).

EXPERIMENTAL (34)

2-Methylpyrimido[1,2-*a*]benzimidazol-4-ol (III).

A mixture of 2-aminobenzimidazole (6.7 g., 0.05 mole) and ethyl acetoacetate (6.5 g., 0.05 mole) was heated under reflux with stirring in an oil bath at 130° for 1.25 hours. The reaction mixture became solid when the oil bath temperature reached 120°. The reaction mixture was cooled and the crude solid was recrystallized from ethanol to give 3.2 g. (32%) of the desired product, m.p. 292-296° dec.

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.09. Found: C, 66.25; H, 4.41; N, 21.04.

4-Chloro-2-methylpyrimido[1,2-*a*]benzimidazole (IV).

A mixture of 8.8 g. (0.044 mole) of 2-methylpyrimido[1,2-*a*]-benzimidazol-4-ol (III) and 140 ml. of phosphorus oxychloride was heated on a steam bath for 3 hours. The reaction mixture was filtered and the red solid obtained was dissolved in 350 ml. of water. The aqueous solution was made alkaline with concentrated ammonium hydroxide and 7.0 g. (73%) of the product was collected by filtration. This material does not melt but undergoes a thermal transformation at about 165° when it changes color from yellow-orange to a deep purple. Thin layer chromatography showed this material to be homogeneous. The phosphorus oxychloride solution was decomposed over ice and water and made basic with concentrated ammonium hydroxide to yield 2.3 g. of a solid which was shown by thin layer chromatography to be a mixture and was discarded.

4-[[2-(Diethylamino)ethyl]amino]-2-methylpyrimido[1,2-*a*]benzimidazole (Vb).

To a solution of 7.0 g. (0.032 mole) of 4-chloro-2-methylpyrimido[1,2-*a*]benzimidazole in 100 ml. of chloroform, 8.1 g. (0.07 mole) of *N,N*-diethylethylenediamine was added and the mixture was stirred at room temperature for 21 hours. The reaction mixture was evaporated to dryness, and the resulting solid was recrystallized from ethyl acetate to give 4.3 g. (45%) of the desired product, m.p. 180-181°.

Compounds Va and c-e were prepared by a similar procedure (Table II).

7(and 8)-Chloro-2-methylpyrimido[1,2-*a*]benzimidazol-4-ol (VI and VIII, R = OH).

A mixture of 2-amino-5-chlorobenzimidazole (10.0 g., 0.06 mole) and 8.8 g. (0.06 mole) of ethyl acetoacetate was heated in an oil bath to 135°. The solution thus obtained solidified on further heating. The cooled solid was recrystallized from dimethylformamide to yield 3.4 g. (21%) of pure product, m.p. 305-310°.

Anal. Calcd. for $C_{11}H_8ClN_3O$: C, 56.54; H, 3.45; N, 17.98; Cl, 15.17. Found: C, 56.52; H, 3.38; N, 18.12; Cl, 15.39.

4,7(and 8)-Dichloro-2-methylpyrimido[1,2-*a*]benzimidazole (VI and VIII, R = Cl).

A mixture of 4.6 g. (0.02 mole) of 7(and 8)-chloro-2-methylpyrimido[1,2-*a*]benzimidazol-4-ol and 100 ml. of phosphorus oxychloride was heated on the steam bath for 4 hours. The reaction mixture was cooled to room temperature and filtered, and the solid obtained was suspended in water and stirred for 2 hours. The aqueous solution was filtered and made alkaline to *p*H 8 with concentrated ammonium hydroxide. The solid which formed was collected by filtration and dried, 2.4 g. The original phosphorus oxychloride filtrate was poured into ice and water and filtered. The filtrate was made alkaline with concentrated ammonium hydroxide and filtered to yield 3.5 g. Neither of these two fractions was homogeneous nor could they be purified. The crude chloro compound was used directly in the next step.

7(and 8)-Chloro-4-[[2-(diethylamino)ethyl]amino]-2-methylpyrimido[1,2-*a*]benzimidazole (VII and IX) (Table II).

To a solution of 7.1 g. (0.028 mole) of crude 4,7(and 8)-dichloro-2-methylpyrimido[1,2-*a*]benzimidazole in 200 ml. of chloroform was added 6.6 g. (0.057 mole) of *N,N*-diethylethylenediamine. The reaction mixture was stirred at room temperature for 3 days, and filtered to remove 0.5 g. of starting material. The filtrate was washed with 200 ml. of 5% sodium hydroxide solution and 200 ml. of water and dried over potassium carbonate. The chloroform solution was evaporated to dryness. The solid residue was recrystallized from ethyl acetate to give 2 g. of solid, m.p. 192-198°. After 3 additional recrystallizations from ethyl acetate and an acid-base reprecipitation to remove some silicone grease, 0.9 g. of the high-melting isomer, m.p. 209-211° (IX) was obtained. All of the mother liquors from the ethyl acetate recrystallizations were combined and evaporated to dryness. Three recrystallizations from aqueous ethanol and an acid-base reprecipitation yielded 1.5 g. of the low-melting isomer, m.p. 158-160° (VII).

2-(Trifluoromethyl)pyrimido[1,2-*a*]benzimidazol-4-ol (X).

A mixture of 2-aminobenzimidazole (6.7 g., 0.05 mole) and ethyl trifluoroacetoacetate (9.2 g., 0.05 mole) was heated in an oil bath at 130° for 1.25 hours. The reaction mixture was dry in appearance but turned pasty as the reaction temperature was reached. After 1 hour at 130° the reaction mixture again became dry. The reaction was cooled and the crude solid was recrystallized from ethanol and slurried in ether to give 3.7 g. (14%) of the desired product, m.p. 315-318°.

Anal. Calcd. for $C_{11}H_6F_3N_3O$: C, 52.18; H, 2.39; N, 16.60. Found: C, 52.13; H, 2.58; N, 16.49.

2,2′-(Trifluoromethyl)[1,4′-bipyrimido[1,2-*a*]benzimidazol]-4(1*H*)-one (XI).

A solution of 2-(trifluoromethyl)pyrimido[1,2-*a*]benzimidazol-4-ol (X) (5.0 g., 0.0179 mole) and 100 ml. of phosphorus oxychloride was stirred at reflux temperature for 4 hours. The reaction mixture was then cautiously added with stirring to 2500 ml. of ice and water made strongly basic with 50% aqueous sodium hydroxide. A bright yellow solid precipitated which was collected by filtration, washed with water, slurried with ether, and

recrystallized from methanol to give 1.2 g. (36%) of the product, m.p. 325°.

Anal. Calcd. for $C_{22}H_{10}F_6N_6O$: C, 54.10; H, 2.06; N, 17.21. Found: C, 54.10; H, 1.80; N, 17.63.

2,7,8-Trimethylpyrimido[1,2-*a*]benzimidazol-4-ol (XII).

A solution of 25.0 g. (0.155 mole) of 2-amino-5,6-dimethylbenzimidazole and 20.1 g. (0.155 mole) of ethyl acetoacetate in 100 ml. of dimethylformamide was heated on a steam bath for 6 hours. The cooled mixture was poured into 3 l. of iced water. The precipitate which formed was removed by filtration and recrystallized from ethanol to give 7.6 g. (36%) of the product, m.p. 291-294°.

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.76; N, 18.49. Found: C, 68.57; H, 5.54; N, 18.92.

2-Benzyl-1,2,3,4-tetrahydropyrido[4',3':4,5]pyrimido[1,2-*a*]benzimidazol-12-ol (XIII).

To a warm solution of 14.9 g. (0.05 mole) of ethyl 1-benzyl-4-oxonipecotate monohydrochloride in 150 ml. of dimethylformamide was added 6.7 g. (0.05 mole) of 2-aminobenzimidazole. The mixture was heated on a steam bath for 6 hours. The solid which formed on cooling was removed by filtration and recrystallized from dimethylformamide to yield 1.0 g. (6%) of the product, m.p. 325-327° dec.

Anal. Calcd. for $C_{20}H_{18}N_4O$: C, 72.70; H, 5.49; N, 16.96. Found: C, 72.39; H, 5.32; N, 16.98.

1,2,3,4-Tetrahydrobenzimidazo[2,1-*b*]quinazolin-12-ol (XIV).

A mixture of 2-aminobenzimidazole (6.7 g., 0.05 mole) and 7.7 g. (0.05 mole) of ethyl 2-oxocyclohexanecarboxylate was heated in an oil bath to 120°. The resulting solution was then heated to 150° for 0.5 hour. The solid which resulted was recrystallized from 25% ethanol in benzene and dried *in vacuo* at 60° to yield 4.2 g. (35%) of product, m.p. 297-299°.

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.28; H, 5.47; N, 17.56. Found: C, 70.03; H, 5.53; N, 17.69.

2,3-Dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazol-11-ol (XV).

A mixture of 2-aminobenzimidazole (67.0 g., 0.5 mole) and 78.0 g. (0.5 mole) of ethyl 2-oxocyclopentanecarboxylate was heated in an oil bath to 125°. The resulting solution solidified upon further heating. The mixture was held at 140-150° for an additional hour. The cooled mass was recrystallized from ethanol-benzene to yield 38.5 g. (34%) of pure product, m.p. 307-312°.

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.45; H, 5.05; N, 18.84.

11-Chloro-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazole.

A mixture of 5.6 g. (0.025 mole) of 2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazol-11-ol (XV), 3.0 g. (0.025 mole) of *N,N*-dimethylaniline, and 100 ml. of phosphorus oxychloride was heated on a steam bath for 10 minutes. During the heating period the reaction mixture gradually became red and then purple. The reaction mixture was stirred for an additional 3.5 hours without heating and filtered. The solid was dissolved in water and the crude product (2.9 g.) was precipitated by the addition of concentrated ammonium hydroxide. The filtrate from the original reaction mixture was poured into ice and water and made basic with concentrated ammonium hydroxide to give 2.2 g. of a solid which could not be purified. Thin layer chromatography of this material revealed two major components neither of which was the starting material.

11-[[2-(Diethylamino)ethyl]amino]-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazole (XVIa) (Table II).

To a solution of 5.1 g. (0.021 mole) of crude 11-chloro-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazole in 100 ml. of chloroform was added 4.9 g. (0.042 mole) of *N,N*-diethylethylenediamine. The solution was stirred at room temperature for 22 hours, washed first with 200 ml. of 5% sodium hydroxide solution, and then with 200 ml. of water. The chloroform solution was dried over anhydrous potassium carbonate and evaporated to dryness. The residue was recrystallized from ethyl acetate and then from acetonitrile to yield 2.0 g. (30%) of the desired product, m.p. 220-221°. Thin layer chromatography showed this material to be homogeneous.

11-[[3-(Dimethylamino)propyl]amino]-2,3-dihydro-1*H*-cyclopenta[4,5]pyrimido[1,2-*a*]benzimidazole (XVIb) (Table II) was prepared similarly.

Pyrimido[1,2-*a*]benzimidazole (XXIV, $R_1 = R_2 = H$).

A solution of 13.3 g. (0.1 mole) of 2-aminobenzimidazole, 33.0 g. (0.15 mole) of 1,1,3,3-tetraethoxypropane, 10 drops of concentrated hydrochloric acid, and 50 ml. of glacial acetic acid was heated under reflux for 2 hours. The reaction mixture was concentrated *in vacuo* to a semisolid which was extracted with two 300-ml. portions of boiling benzene. The solid which crystallized from the extracts was isolated by filtration, recrystallized first from benzene (decolorizing charcoal) and then from 2-propanol to yield 1.8 g. (11%) of the desired product, m.p. 197-200°.

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.85. Found: C, 71.03; H, 4.33; N, 24.60.

2-Methylpyrimido[1,2-*a*]benzimidazole (XXIV, $R_1 = H$, $R_2 = CH_3$).

Method A.

A mixture of 6.7 g. (0.05 mole) of 2-aminobenzimidazole and 6.6 g. (0.05 mole) of acetoacetaldehyde, dimethyl acetal was heated at 130-140° (oil bath temp.) for 5.3 hours. After cooling, the solid reaction mixture was recrystallized from ethanol to give 2.2 g. (24%) of the desired product, m.p. 230-232°.

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 71.79; H, 4.91; N, 23.05.

Method B.

Crude 4-chloro-2-methylpyrimido[1,2-*a*]benzimidazole (IV) (2.0 g.) was chromatographed on neutral alumina with chloroform to obtain 1.2 g. of nearly homogeneous material.

To a solution of 1.2 g. (0.0056 mole) of purified 4-chloro-2-methylpyrimido[1,2-*a*]benzimidazole, 0.46 g. of sodium acetate, and 250 ml. of absolute ethanol was added 0.7 g. of 5% palladium-on-carbon catalyst. The mixture was hydrogenated on a Parr shaker at an initial pressure of 52.0 p.s.i.g. and temperature of 24° for 0.3 hour. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to dryness. The residue was suspended in 200 ml. of water and extracted with 150 ml. of chloroform. The chloroform extract was dried over anhydrous sodium sulfate and concentrated *in vacuo* to dryness. The residue was recrystallized from benzene to yield 0.5 g. (49%) of the desired product, m.p. 229-232°, identical with that obtained by Method A.

2,4-Dimethylpyrimido[1,2-*a*]benzimidazole (XXIV, $R_1 = R_2 = CH_3$).

A mixture of 6.7 g. (0.05 mole) of 2-aminobenzimidazole and 30 ml. of 2,4-pentanedione was heated on the steam bath for 2

hours. The pasty reaction mixture was diluted with 45 ml. of 2-propanol and heated under reflux for 18 hours. The reaction mixture was filtered hot to isolate 4.2 g. (43%) of the desired product, m.p. 239-241°.

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.31. Found: C, 72.80; H, 5.50; N, 21.58.

7-Chloro-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (XXVa).

A mixture of 30.0 g. (0.20 mole) of 5-methyl-*s*-triazolo[1,5-*a*]-pyrimidin-7-ol (24) and 250 ml. of phosphorus oxychloride was heated under reflux for 2 hours. The excess phosphorus oxychloride was removed *in vacuo*, and the residue was poured into ice and water, adjusted to *p*H 8 with ammonium hydroxide, and extracted with chloroform. The chloroform extract was dried over anhydrous potassium carbonate and evaporated to dryness. Recrystallization of the residual solid from ethanol gave 22.1 g. of product, m.p. 149-152°, and a second crop of 2.5 g., m.p. 148-150° [Lit. (25) m.p. 150-152°]. Total yield, 73%.

The ultraviolet spectrum agreed with the data reported in the literature (25), but a satisfactory analysis was not obtained.

7-[[2-(Diethylamino)ethyl]amino]-5-methyl-*s*-triazolo[1,5-*a*]-pyrimidine Dihydrochloride (XXVb).

To a solution of 6.7 g. (0.04 mole) of 7-chloro-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (XXVa) in 100 ml. of chloroform was added 9.3 g. (0.08 mole) of *N,N*-diethylethylenediamine. An exothermic reaction resulted which caused the reaction mixture to reflux for a few minutes. The reaction mixture was stirred without external heating for 2 hours and was washed first with 200 ml. of 5% sodium hydroxide solution and then with 200 ml. of water. The chloroform solution was dried over potassium carbonate and then evaporated to dryness *in vacuo*. Recrystallization from cyclohexane yielded 6.9 g. of a low-melting solid which was recrystallized again to give a waxy solid, m.p. 49-51° which became oily on drying. The oil was dissolved in ether and hydrogen chloride was passed into the solution. The hydrochloride salt that formed was collected by filtration, dried, and recrystallized from ethanol to yield 5.0 g. (39%) of the title compound, m.p. 226-228° dec.

Anal. Calcd. for $C_{12}H_{20}N_6 \cdot 2HCl$: C, 44.86; H, 6.90; N, 26.16; Cl^-, 22.07. Found: C, 45.02; H, 6.75; N, 25.89; Cl^-, 21.60.

7-[[3-(Dimethylamino)propyl]amino]-5-methyl-*s*-triazolo[1,5-*a*]-pyrimidine (XXVc).

To a solution of 6.7 g. (0.04 mole) of 7-chloro-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (XXVa) in 100 ml. of chloroform was added 8.2 g. (0.08 mole) of *N,N*-dimethyl-1,3-propanediamine. An exothermic reaction resulted which caused the reaction mixture to reflux for a few minutes. The reaction mixture was stirred without external heating for 16.5 hours. It was washed successively with 200 ml. of 5% sodium hydroxide solution and 200 ml. of water. The chloroform solution was dried over potassium carbonate and evaporated to dryness. The residue was crystallized twice from cyclohexane to give 4.9 g. (52%) of the desired product, m.p. 91-93°.

Anal. Calcd. for $C_{11}H_{18}N_6$: C, 56.39; H, 7.74; N, 35.87. Found: C, 56.42; H, 7.65; N, 36.18.

7-[[3-(Diethylamino)propyl]amino]-5-methyl-*s*-triazolo[1,5-*a*]-pyrimidine Dihydrochloride Monohydrate (XXVd).

To a solution of 6.7 g. (0.04 mole) of 7-chloro-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (XXVa) in 100 ml. of chloroform was added 10.4 g. (0.08 mole) of *N,N*-diethyl-1,3-propanediamine. The reaction was analogous to (a) and worked up in the same manner. Recrystallization from ethanol yielded 1.7 g. (12%) of the title compound, m.p. 220-222°.

Anal. Calcd. for $C_{13}H_{22}N_6 \cdot 2HCl \cdot H_2O$: C, 44.19; H, 7.42; N, 23.79; Cl^-, 20.07; H_2O, 5.10. Found: C, 44.31; H, 7.40; N, 24.00; Cl^-, 19.89; H_2O, 4.67.

7-[[3-[(Diethylamino)methyl]-*p*-anisidino]-5-methyl-*s*-triazolo-[1,5-*a*]pyrimidine (XXVe).

To a solution of 6.0 g. (0.0356 mole) of 7-chloro-5-methyl-*s*-triazolo[1,5-*a*]pyrimidine (XXVa) in 50 ml. of chloroform was added 14.8 g. (0.071 mole) of N^{α},N^{α}-diethyl-6-methoxytoluene-α,3-diamine (generated from 20 g. of the dihydrochloride salt) (35) in 100 ml. of chloroform. The solution was heated under reflux for 3 days. The solvent was removed *in vacuo*, and the residual oil was washed with water and recrystallized from *n*-heptane to give 1.7 g. (14%) of the product, m.p. 127-129°.

Anal. Calcd. for $C_{18}H_{24}N_6O$: C, 63.50; H, 7.11; N, 24.69. Found: C, 63.46; H, 7.18; N, 24.79.

N^{α},N^{α}-Diethyl-6-methoxytoluene-α,3-diamine Dihydrochloride.

A solution of 97.5 g. (0.0355 mole) of *N,N*-diethyl-2-methoxy-5-nitrobenzylamine (35) in 700 ml. of methanol was hydrogenated over 5 g. of 20% palladium on carbon at an initial pressure of 50.5 p.s.i.g. at room temperature. After two days 10 g. of Raney Nickel was added and the reduction was completed. The reaction mixture was filtered into a solution of 2-propanol containing 1.5 moles of hydrogen chloride and the solvents were then removed *in vacuo*. The oil was taken up in 2-propanol and treated with ether to give a solid which was collected and dried *in vacuo* to give 76.5 g. (76%) of the product, m.p. 209-210°.

Anal. Calcd. for $C_{12}H_{20}N_2O \cdot 2HCl$: C, 51.25; H, 7.89; N, 9.96. Found: C, 51.06; H, 7.95; N, 9.85.

Acknowledgment.

The authors are indebted to Dr. Leo Rane of the University of Miami and to Dr. Paul E. Thompson of these laboratories for the antimalarial testing, Mr. C. E. Childs and associates for the microanalyses, Dr. J. M. Vandenbelt and coworkers for the spectral determinations, and Mr. W. M. Pearlman for the hydrogenations reported herein. We also acknowledge helpful discussions with Dr. Glenn A. Berchtold and Mr. Donald F. Worth at various stages of this research.

REFERENCES

(1) This investigation was supported by U. S. Army Medical Research and Development Command Contract DA-49-193-MD-2754. This is Contribution No. 675 to the Army Research Program on Malaria.

(2) This is Contribution XIX of a series of potential antimalarial substances. For previous paper, see E. F. Elslager, F. H. Tendick, L. M. Werbel, and D. F. Worth, *J. Med. Chem.*, 12, 000 (1969).

(3) F. L. Rose, *J. Chem. Soc.*, 2770 (1951).

(4) For recent reviews, see: (a) E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1965," C. K. Cain, Ed., Academic Press, New York, N. Y., 1966, p. 136; (b) E. F. Elslager in "Annual Reports in Medicinal Chemistry, 1966," C. K. Cain, Ed., Academic Press, New York, N. Y., 1967, p. 131.

(5) H. Henecka, German Patent 641,598; *Frdl.*, 23, 270 (1940).

(6) A. DeCat and A. von Dormael, *Bull. Soc. Chim. Belges*, 59, 573 (1950).

(7) H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951).

(8) A. R. Katritzky and J. M. Lagouski, *Advances in Heterocyclic Chem.*, 1, 339 (1963), Academic Press, New York, N. Y.

(9) The antimalarial screening was carried out by Dr. Leo Rane of the University of Miami, and test results were supplied through the courtesy of Dr. David P. Jacobus of the Walter Reed Army Institute of Research.

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

(11) C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.*, 70, 2402 (1948).

(12) Unless otherwise specified all NMR spectra described were run in deuterated dimethylsulfoxide using tetramethylsilane as an internal standard on a Varian A60 instrument. Chemical shifts are recorded as δ (p.p.m.) downfield from TMS, and coupling constants as c.p.s.

(13) W. W. Paudler and T. J. Kress, *J. Org. Chem.*, 32, 2616 (1967).

(14) M. Zanger, W. W. Simons, and A. R. Gennaro, *ibid.*, 33, 3673 (1968).

(15) S. C. Bell and G. Conklin, *J. Heterocyclic Chem.*, 5, 179 (1968).

(16) W. W. Paudler and H. L. Blewitt, *J. Org. Chem.*, 30, 4081 (1965).

(17) W. W. Paudler and H. L. Blewitt, *Tetrahedron*, 21, 353 (1965).

(18) J. P. Paolini and R. K. Robins, *J. Heterocyclic Chem.*, 2, 53 (1965).

(19) W. W. Paudler and J. E. Kuder, *J. Org. Chem.*, 31, 809 (1966).

(20) W. W. Paudler and L. S. Helmick, *J. Heterocyclic Chem.*, 3, 269 (1966). To avoid confusion the reader should note the errors in the melting points which are corrected in W. W. Paudler and L. S. Helmick, *J. Org. Chem.*, 33, 1087 (1968).

(21) Y. Makisumi, H. Watanabe, and K. Tori, *Chem. Pharm. Bull. Japan*, 12, 204 (1964).

(22) J. L. Vidal, Ph.D. Thesis, Université de Montpellier, 1968.

(23) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. Van Allan, *J. Org. Chem.*, 24, 796 (1959).

(24) Purchased from Alfred Bader Chemicals, Milwaukee, Wis.

(25) Y. Makisumi, *Chem. Pharm. Bull. Japan*, 9, 808 (1961).

(26) Y. Makisumi, *ibid.*, 9, 801 (1961).

(27) J. A. Bee and F. L. Rose, *J. Chem. Soc.* (C), 2031 (1966).

(28) K. Shirakawa, *J. Pharm. Soc. Japan*, 79, 903 (1959) and references therein.

(29) Y. Makisumi, H. Watanabe, and K. Tori, *Chem. Pharm. Bull. Japan*, 12, 204 (1964).

(30) R. G. W. Spickett and S. H. B. Wright, *J. Chem. Soc.* (C), 498 (1967).

(31) R. G. W. Spickett and S. H. B. Wright, *ibid.*, 503 (1967).

(32) Selected compounds were kindly evaluated by drug-diet against *P. berghei* in mice by Dr. Paul E. Thompson and coworkers, Research Laboratories, Parke, Davis and Co., Ann Arbor, Michigan.

(33) For a description of antimalarial test methods, see P. E. Thompson, A. Bayles, and B. Olszewsky, *Exp. Parasitol.*, in press.

(34) Melting points (corrected) were taken in open capillary tubes in a Thomas-Hoover capillary melting point apparatus. Water determinations are by the Karl Fischer method.

(35) J. H. Burckhalter, F. H. Tendick, E. M. Jones, P. A. Jones, W. F. Holcomb, and A. L. Rawlins, *J. Am. Chem. Soc.*, 70, 1363 (1948).

(36) Personal communication from Dr. Alfred Bader, Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.

Received July 1, 1969 Ann Arbor, Michigan 48106