TABLE I

N-(2-ACETOXYETHYL)-AMIDES OF ALIPHATIC ACIDS

N-(2-Acetoxyethyl)-	Reaction product Yield, %	Reaction product M.p., °C.	Crystallized product Yield, %	Crystallized product M.p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Saponification No.[a] Calcd.	Saponification No.[a] Found
Acetamide[b]	..	.....	71[c]	.....	49.6	49.8	7.64	7.35	9.65	9.33	386.5	393.8
Caproamide	99	<24	62	26.5–27.4	59.7	59.5	9.52	9.75	6.96	6.87	278.8	277.1
Lauramide	97	65.1–66.0	30	70.0–70.5	67.3	67.2	11.0	10.7	4.91	5.01	196.6	193.8
Palmitamide	99	78.4–79.0	95	79.5–80.0	70.3	70.8	11.5	11.7	4.10	4.08	164.3	164.5
Stearamide	99	83.1–84.0	92	84.1–84.4	71.5	72.0	11.7	11.7	3.79	3.82	151.8	151.8
Oleamide	99	34.5–35.2	77[d]	39.0–39.3	71.9	71.9	11.2	11.0	3.81	3.83	152.6	153.3

[a] Refluxed 1/2 hour with 0.2 *N* KOH. [b] Reference 3 gives b.p. 147–154° (8 mm.); $n^{24}D$ 1.4511; d^{24}_4 1.1015. [c] Distilled once through a 3′ Vigreux column; b.p. 142.0–142.5° (5.1 mm.); $n^{25}D$ 1.4500. [d] Iodine number; calcd. 69.1; found 70.0.

N-(2-Acetoxyethyl)-lauramide, -palmitamide and -stearamide reaction mixtures were repeatedly washed by vigorous mechanical stirring with hot water until acid-free. The acetoxyethyl amides were allowed to solidify and the cakes were dried and crystallized: N-(2-acetoxyethyl)-lauramide, once from acetone, 5 ml./g., at 0°, once from ethanol, 10 ml./g., at 0° and once from ether, 12 ml./g., at 24°; N-(2-acetoxyethyl)-palmitamide, once from ethanol, 8 ml./g., at −20°; N-(2-acetoxyethyl)-stearamide, twice from ethanol, 8 ml./g., at −20°.

The crude reaction mixture of N-(2-acetoxyethyl)-oleamide was dissolved in approximately ten times its volume of petroleum naphtha and washed repeatedly with warm water until free of acid. The petroleum naphtha was then distilled off under vacuum and the residue of crude amide was crystallized twice from ethanol, 10 ml./g., at −20°.

Results are summarized in Table I.

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CONTRIBUTION FROM THE
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Some 2,4,6-Triamino-5-alkyl- and 5-Benzylpyrimidines

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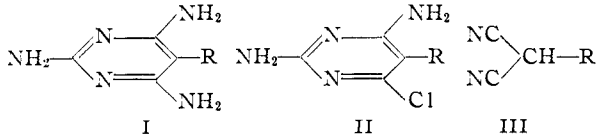
In connection with studies on 2,4-diaminopyrimidine antimalarials at present being conducted in these laboratories[1–4] it seemed desirable to prepare and test some 2,4,6-triaminopyrimidines with alkyl, benzyl and aryl substituents at the 5-position (I, R = alkyl, benzyl or aryl).



I II III

v. Merkatz[5] found that 2,4,6-trichloro-5-ethylpyrimidine reacted readily with ammonia to give 2,4-diamino-6-chloro-5-ethylpyrimidine (II, R = Et) but that further amination of this compound required vigorous treatment. This resistance to amination is general for 2,4-diamino-6-chloropyrimidines. Thus the amination of 2-amino-4,6-dichloro-5-benzylpyrimidine gives II (R = CH_2Ph)[6] while treatment of 2,4,6-trichloro-5-phenyl- and 4,6-dichloro-2-methylanilino-5-phenylpyrimidine with ammonia at elevated temperatures gives II (R = Ph) and 4-amino-6-chloro-2-methylanilino-5-phenylpyrimidine, respectively.[7] In view of these findings it seemed more profitable to prepare the triaminopyrimidines (I) by the condensation of guanidine with the substituted malonitrile (III).[8,9] The malonitriles (III) were prepared by distillation of the corresponding readily available malondiamides[10] with phosphorus pentoxide. Heretofore it has been more usual to employ the corresponding cyanacetamides.[11] The yields of III by the new method are quite satisfactory (45–90%). The nitriles (III, R = alkyl or benzyl) on refluxing with guanidine gave good yields of the triaminopyrimidines (I). Phenylmalononitrile, however, with guanidine in alcohol gave a compound which is believed to arise from the condensation of two molecules of guanidine with one of nitrile. The failure of III (R = Ph) to yield a pyrimidine with guanidine is reminiscent of the failures of phenylmalondialdehyde[12] and α-formylphenylacetonitrile[4] to condense with the same base.

The triaminopyrimidines (I, R = *n*-C_4H_9, $CH_2C_6H_5$ and $CH_2C_6H_4Cl$-*p*) were tested for antimalarial activity against *Plasmodium gallinaceum* in chicks and *P. berghei* in mice.[1] All these compounds showed antimalarial activity at doses between 10 and 100 mg./kg. (*i.e.*, between 0.1 and 0.05 the activity of N^1-*p*-chlorophenyl-N^5-isopropylbiguanide (chlorguanide)).

When tested against Sarcoma 180 by Stock and associates[13] at the Sloan–Kettering Institute four of the triaminopyrimidines (I, R = C_2H_5, $CH_2C_6H_5$, $CH_2C_6H_4Cl$-*p* and $CH_2C_6H_3Cl_2$-3,4) showed some signs of activity. Only the 2,4,6-

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TABLE I

MALONDIAMIDES

Malondiamides	M.p., °C.	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
p-Chlorobenzyl	244	$C_{10}H_{11}O_2N_2Cl$	..	...	12.4	..	...	12.5
p-Bromobenzyl	245	$C_{10}H_{11}O_2N_2Br$	..	...	10.3	..	...	9.9
p-Methoxybenzyl	216-217	$C_{11}H_{14}O_3N_2$	..	...	12.6	..	...	12.9
3,4-Dichlorobenzyl	212	$C_{10}H_{10}O_2N_2Cl_2$	46.0	3.8	10.7	46.4	3.9	10.2
Phenyl	226-228	$C_9H_{10}O_2N_2$	60.7	5.6	15.7	60.7	5.8	16.0

TABLE II

MALONONITRILES (III)

R	Yield, %	M.p. or b.p., °C.	Formula	Analyses, % Calcd. N	Found N
CH_2CH_3	80	b. 100 (20 mm.)[a]	$C_5H_6N_2$	..	..
$(CH_2)_3CH_3$	70	b. 120 (20 mm.)	$C_7H_{10}N_2$	23.0	23.0
$CH_2C_6H_5$	47	m. 79[b]	$C_{10}H_8N_2$	..	..
$CH_2C_6H_4Cl$-*p*	55	89	$C_{10}H_7N_2Cl$	14.7	14.4
$CH_2C_6H_4Br$-*p*	50	90-91	$C_{10}H_7N_2Br$	11.9	11.6
$CH_2C_6H_3Cl_2$-3,4	60	[c]	$C_{10}H_6N_2Cl_2$	..	..
$CH_2C_6H_4(OCH_3)$-*p*	48	70-72	$C_{11}H_{10}ON_2$	15.1	14.7
C_6H_5	47	67[d]	$C_9H_6N_2$	..	..

[a] J. C. Hessler, *Am. Chem. J.*, **22**, 185 (1899), gives b.p. 90–91° (20 mm.). [b] J. C. Hessler[a] gives m.p. 91°; E. Hantzsch and G. Osswald, *Ber.*, **32**, 649 (1899), give 78–79°. [c] Viscous oil, did not crystallize. [d] J. C. Hessler, *Am. Chem. J.*, **32**, 123 (1904), gives 68–69°.

TABLE III

2,4,6-TRIAMINO-5-SUBSTITUTED PYRIMIDINES (I)

R	Yield, %	M.p., °C.	Formula	Analyses, % Calcd. C	H	N	Found C	H	N
C_2H_5	92	190[a]	$C_6H_{11}N_5$	..	...	..	..	...	..
C_4H_9-*n*	90	199	$C_8H_{15}N_5$	53.0	8.3	..	53.4	8.3	..
$CH_2C_6H_5$	85	191–192	$C_{11}H_{13}N_5$	61.4	6.0	32.6	61.6	6.0	32.6
$CH_2C_6H_4Cl$-*p*	98	218	$C_{11}H_{12}N_5Cl$	..	...	28.1	..	...	28.4
$CH_2C_6H_4Br$-*p*	85	235	$C_{11}H_{12}N_5Br$	..	...	23.8	..	...	24.1
$CH_2C_6H_4(OCH_3)$-*p*	80	218-219	$C_{12}H_{15}ON_5$	..	...	28.6	..	...	28.5
$CH_2C_6H_3Cl_2$-3,4	92	255	$C_{11}H_{11}N_5Cl_2$	46.5	3.9	24.6	46.5	3.9	24.6

[a] Merck (ref. 9) and v. Merkatz (ref. 5) give m.p. 190°.

triamino-5-*p*-chlorobenzylpyrimidine (I, R = $CH_2C_6H_4Cl(p)$), however, gave consistent results of a ± grade on repeated trials.

Experimental

Malonic Esters.—The malonic esters, where not commercially available, were prepared by the action of the halide on sodium malonic ester in ethanol. They were distilled to separate any disubstituted ester and then converted to the amides directly as shown below. It should be noted that any of the disubstituted ester present would not be converted to the amide under the conditions used.[10] Ethyl *p*-methoxybenzylmalonate was prepared by reduction of ethyl *p*-methoxybenzalmalonate.[14]

Malondiamides.—The malondiamides were prepared by the previously described method.[10] They are listed in Table I.

Malononitriles.—The malononitriles were prepared by the distillation of the corresponding diamides with phosphorus pentoxide. The preparation of benzyl malononitrile is given as an example. The properties of these compounds are given in Table II.

Benzylmalononitrile.—Benzylmalondiamide[10] (30 g.) was mixed well with phosphorus pentoxide (60 g.) and the mixture distilled at 250° (bath temp.) (20 mm.). The distillate solidified on cooling. It was redistilled to give a colorless oil (17 g.) b.p. 220–225° (23 mm.) which solidified to colorless crystals, m.p. 79°.

2,4,6-Triaminopyrimidines (I).—These compounds were prepared by refluxing the malononitriles (III) with guanidine in alcohol. The preparation of 2,4,6-triamino-5-benzylpyrimidine (I, R = $CH_2C_6H_5$) is given as an example. The compounds are listed in Table III.

To a solution of sodium ethoxide prepared by dissolving sodium (3.4 g.) in ethanol (100 ml.) was added guanidine hydrochloride (9.5 g.) and benzylmalononitrile (14 g.) and the mixture was refluxed for three hours. After filtration the solution was allowed to cool when the pyrimidine (15 g.) crystallized as plates. Recrystallization from ethanol gave colorless plates, m.p. 191–192°.

Reaction of Phenylmalononitrile (III, R = C_6H_5) **with Guanidine.**—The nitrile (6 g.) was added to a solution of guanidine (from the hydrochloride (4.0 g.)) in ethanol (75 ml.) and the solution refluxed for 5 hours. On cooling and standing crystals separated which after recrystallization from ethanol–ether melted at 139–140° (Found: N, 41.6%).

Acknowledgment.—Thanks are due S. W. Blackman, N. Martinez, Jr., and Pauline Kulka for the analyses recorded in this paper.

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The Halogenation of 3,5-Dimethyl-1-(2′-quinolyl)-pyrazole

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The behavior of the 1-substituted pyrazoles varies from the very stable aryl (or alkyl) types to the relatively unstable carbamyl class.