TABLE I

VANILLIC ACID ESTERS

Ester	Method of prepn.	Yield, %	B. p., °C.	Mm.	Solv.[a]	M. p., °C. (cor.)	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Inhibiting concentrations,[e] % *Bacillus mycoides*	*Aspergillus niger*
Methyl[b]	I	97	118	2	A	63–64						0.21	0.21
	II	82											
Ethyl[b]	I	96	138	3	B	44						.15	.09
	II	92											
n-Propyl[b]	I	95	160	7	C	42–43						.09	.09
	II	85											
i-Propyl[b]	I	84			A	112–113						.09	.09
	II	80											
n-Butyl[b]	I	88	146–147	2	B	48–49						.015	.09
	II	89											
i-Butyl	II	88	125–126	2	B	56–57	$C_{12}H_{16}O_4$	64.27	64.24	7.19	7.07	.021	.03
s-Butyl	II	91	134	3	B	73–74	$C_{12}H_{16}O_4$	64.27	64.53	7.19	7.25	.09	.09
t-Butyl	III	60[c]			A	79–80	$C_{12}H_{16}O_4$	64.27	64.25	7.19	7.03	.09	.09
n-Amyl	I	91	165	4	B	35–36	$C_{13}H_{18}O_4$	65.53	65.38	7.61	7.49	.009	.15
i-Amyl	II	92	184	8	B	61–62	$C_{13}H_{18}O_4$	65.53	65.76	7.61	7.48	.009	.15
s-Butylcarbinyl	II	48	119–121	2			$C_{13}H_{18}O_4$	65.53	65.60	7.61	7.64	.03	.15
Diethylcarbinyl	II	23	112–114	2			$C_{13}H_{18}O_4$	65.53	65.62	7.61	7.63	.015	.09
n-Hexyl	II	59	129–130	2			$C_{14}H_{20}O_4$	66.64	66.36	7.99	7.97	.003	> .21
2-Ethylbutyl	I	78	166	1	A	37–38	$C_{14}H_{20}O_4$	66.64	66.37	7.99	7.92	.003	> .21
Benzyl[b]	IV	60	150–151	2	C	34–35						.015	.21
Phenyl	V	50[d]	185–186	3	D	93–94	$C_{14}H_{12}O_4$	68.84	68.75	4.95	5.03	.03	.15
Guaiacyl	V	10[f]	199–200	2	A	86–87	$C_{15}H_{14}O_5$	65.68	65.66	5.14	5.18	.03	> .21

[a] For recrystallization: A = petroleum ether (b. p. 65–110°); B = petroleum ether (b. p. 30–60°); C = dilute ethanol; D = dilute methanol. [b] This is a previously reported compound. See Sabalitschka and Tietz.[5] [c] 10% yield by Method IV. [d] 50% yield by Method III. [e] The inhibiting concentration against *Aerobacter aerogenes* was 0.21% in the case of *i*-butyl and *s*-butyl but was greater than this for every other ester in the table. [f] 60% yield by Method III.

Acknowledgment.—The authors are indebted to Virginia West Martin for the analyses reported in this paper.

Summary

A number of old and new esters of vanillic acid have been prepared. The inhibiting concentrations of these esters have been determined for three representative aerobic micro-organisms. Most of the esters effectively inhibited *Bacillus mycoides* and *Aspergillus niger* in low concentration.

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[CONTRIBUTION FROM THE DIVISION OF MEDICINAL CHEMISTRY, THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

Substituted Sulfanilamidopyrimidines[1]

BY WILLIAM BRAKER, EDWARD J. PRIBYL, JOHN T. SHEEHAN, ERVIN R. SPITZMILLER AND W. A. LOTT

The success of the heterocyclic derivatives[2,3,4,5] of sulfanilamide as antibacterial agents, especially those of the pyrimidine type such as sulfadiazine, sulfamerazine and sulfamethazine, prompted the present investigation.

It was considered possible that by introducing various substituents such as alkoxy, alkoxyalkyl, β-alkoxyalkoxy, dialkoxymethyl or dialkylamino groups into one or more of the 4-, 5- and 6-positions of the pyrimidine moiety of the 2-sulfanilamidopyrimidine type, a chemotherapeutic agent more efficacious than the aforementioned might result. In particular it was hoped that a compound would be found possessing more desirable pharmacological properties with respect to absorption, persistence in the blood, degree of acetylation, tendency to combine with blood plasma and solubility of both the conjugated and unconjugated drug.

The synthesis of these compounds required the preparation of a variety of substituted acetoacetic

(1) Presented before the Division of Medicinal Chemistry of the American Chemical Society, Atlantic City, N. J., April 8–12, 1946.

(2) Ewins, Phillips and Newberry, British Patent 516,288.

(3) Lott and Bergeim, THIS JOURNAL, **61**, 3593 (1939).

(4) Roblin, Williams, Winnek and English, *ibid.*, **62**, 2002 (1940).

(5) Northey, *Chem. Rev.*, **27**, 85 (1940).

TABLE I

SUBSTITUTED 2,4-PENTANEDIONES

Compound, 2,4-pentanedione	Prepared by condensation of	Yield, %	B. p., (uncor.) °C.	Mm.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Used in prepn. of SD[a]
1,1-Diethoxy-	Ethyl diethoxyacetate and acetone	70	78–82	3	$C_9H_{16}O_4$	57.45	57.70	8.62	8.76	9
1,5-Dimethoxy-	Methyl methoxyacetate and methoxyacetone	30	81–84	3	$C_7H_{12}O_4$	52.49	52.18	7.55	7.94	33
1,1-Dimethoxy-	Methyl dimethoxyacetate and acetone	55	67–70	4	$C_7H_{12}O_4$	52.49	52.31	7.55	7.69	7
1-Methoxy-5,5-diethoxy-	Ethyl diethoxyacetate and methoxyacetone	40	105–106	4	$C_{10}H_{18}O_5$	55.03	55.40	8.31	8.76	28

[a] In this and subsequent tables, SD refers to the sulfanilamidopyrimidine listed in Table V derived from this compound.

TABLE II

SUBSTITUTED HYDROXYPYRIMIDINES

2-Amino-( )-pyrimidine[a]	Method of prepn.	Yield, %	M. p., °C. (uncor.)	Formula	Analyses % Calcd. N	Analyses % Found N	Used in prepn. of SD
	Condensation of guanidine carbonate with—						
4,6-Dihydroxy-5-ethoxy	Ethyl ethoxymalonate[b]	60	>320	$C_6H_9N_3O_3$	24.55	24.28	41
4,6-Dihydroxy[c]	Ethyl malonate	52	>330	$C_4H_5N_3O_2$	33.10	33.30	30,31, 34, 38, 43, 44, 45
4,5-Dimethyl-6-hydroxy	Ethyl α-methylacetoacetate	83	330	$C_6H_9N_3O$	30.20	30.47	18, 19
4-Methyl-6-hydroxy[d]	Ethyl acetoacetate	79	299–300	$C_5H_7N_3O$	...	...	1, 2, 3, 4, 5, 10, 15, 16, 17
4-Methoxymethyl-6-hydroxy	Methyl γ-methoxyacetoacetate[e]	..	266–267	$C_6H_9N_3O_2$	27.08	27.36	23, 25, 27
4-Hydroxy-5,6-trimethylene	Ethyl cyclopentanone-2-carboxylate[f]	..	346	$C_7H_9N_3O$	27.83	27.80	22
4-Ethoxymethyl-5-ethoxy-6-hydroxy	Ethyl α,γ-diethoxyacetoacetate[g]	70	221	$C_9H_{15}N_3O_3$	19.71	19.89	35
4-Methyl-5-β-ethoxyethyl-6-hydroxy	Ethyl (β-ethoxyethyl)-acetoacetate[h]	45	238–239	$C_9H_{15}N_3O_2$	21.30	21.34	12, 14
4-Diethoxymethyl-6-hydroxy	Ethyl γ,γ-diethoxyacetoacetate[i]	71	195	$C_9H_{15}N_3O_3$	19.71	19.64	39, 40
4-Methoxymethyl-5-methoxy-6-hydroxy	Ethyl α,γ-dimethoxyacetoacetate[j]	63	196	$C_7H_{11}N_3O_3$	22.70	22.79	24, 26, 29
4-Methyl-5-methoxyethyl-6-hydroxy	Ethyl (β-methoxyethyl)-acetoacetate[k]	48	230–232	$C_8H_{13}N_3O_2$	22.93	22.40	13
4-Hydroxy-5-ethoxy	Ethyl formylethoxyacetate (sodium salt)	45	245–246	$C_6H_9N_3O_2$	27.08	26.80	37
4,6-Dihydroxy-5-ethyl[l]	Ethyl ethylmalonate	80	320	$C_6H_9N_3O_2$	...	...	32

[a] All compounds reported were purified by reprecipitation from aqueous alkaline solution. [b] Wislicenus and Scheidt, *Ber.*, **24**, 432 (1891); *ibid.*, **31**, 552 (1898). [c] Traube, *Ber.*, **26**, 2553 (1893). [d] Behrend and Kohler, *ibid.*, 19, 220 (1878). [e] Sommelet, *Bull. Soc. Chim.*, [4] **29**, 553 (1921). [f] Dobson, Ferns and Perkins, *J. Chem. Soc.*, **95**, 2015 (1909). [g] Conrad, *Ber.*, 11, 58 (1878). [h] Clark and Gurin, THIS JOURNAL, **57**, 1876 (1936). [i] Dakin and Dudley, *J. Chem. Soc.*, **105**, 2455 (1914); Johnson and Cretcher, THIS JOURNAL, **37**, 2149 (1915); Johnson and Mikeske, *ibid.*, **41**, 812 (1919). [j] Pratt and Robinson, *J. Chem. Soc.*, **127**, 168 (1925). [k] Palomaa and Kenetti, *Ber.*, **64**, 800 (1931). [l] von Merkatz, *Ber.*, **52**, 869 (1919).

esters, malonic esters and β-diketones. The α-substituted acetoacetic esters were prepared in the conventional manner by alkylation of the sodium salt of the ester; the γ-substituted acetoacetic esters, by the Reformatsky reaction; the α,γ-di-substituted acetoacetic esters by self-condensation of substituted alkyl acetates; and the β-diketones by condensation of esters with acetone or its derivatives.

Several unreported β-diketones are described in Table I. The structures assigned to the second and fourth compounds in this table and, hence, to the derived 2-sulfanilamidopyrimidines are believed to be as designated. Consideration has been given to the possible formation of isomers depending upon whether the reaction takes place at the methyl group or the methylene group in methoxyacetone. The probability of the structures as indicated is based on the observation that condensation of the methoxypentanedione obtained from methyl methoxyacetate and acetone when reacting with guanidine carbonate yields the same pyrimidine as does the β-diketone formed in the condensation of methyl acetate with methoxyacetone. This indicates that the point of attack is at the methyl group of the ketone and is the basis for the structures assigned.

TABLE III

SUBSTITUTED CHLOROPYRIMIDINES

2-Amino-( )-pyrimidine	M. p., °C. (uncor.)	Formula	Cl Analyses % Calcd.	Found	Used in prepn. of SD
4-Methoxy-6-chloro[a]	165–166	$C_5H_6N_3OCl$	...	...	21, 45
4,5-Dimethyl-6-chloro	215–216	$C_6H_8N_3Cl$	22.57	22.06	18, 19
4-Diethoxymethyl-6-chloro	100–101	$C_9H_{14}N_3O_2Cl$	15.30	15.70	39, 40
4-Methyl-5-methoxyethyl-6-chloro	134–135	$C_8H_{12}N_3OCl$	17.58	17.86	13
4-Methoxymethyl-5-methoxy-6-chloro	99–100	$C_7H_{10}N_3O_2Cl$	17.41	17.59	24, 26, 29
4-Methyl-5-β-ethoxyethyl-6-chloro	147–148	$C_9H_{14}N_3OCl$	16.43	16.58	12, 14
4-Chloro-5,6-trimethylene	196–197	$C_7H_8N_3Cl$	20.90	21.24	22
4-Methoxymethyl-6-chloro	131–132	$C_6H_8N_3OCl$	20.42	20.72	23, 25, 27
4-Ethoxymethyl-5-ethoxy-6-chloro	79–80	$C_9H_{14}N_3O_2Cl$	15.30	15.67	35
4-Methyl-6-chloro[b]	181–182 (dec.)	$C_5H_6N_3Cl$	...	...	1, 2, 3, 4, 5, 10, 15, 16, 17
4,6-Dichloro-5-ethoxy	181–182	$C_6H_7N_3OCl_2$	34.14	33.88	41
4-Chloro-5-ethoxy	166–167 (dec.)	$C_6H_8N_3OCl$	20.43	20.72	37
4-Chloro[c]	165–167 (dec.)	$C_4H_4N_3Cl$	...	...	42
4,6-Dichloro[d]	223–225	$C_4H_3N_3Cl_2$	43.25	43.23	30, 31, 34, 38, 43, 44
4,6-Dichloro-5-ethyl[e]	190–191	$C_6H_7N_3Cl_2$	...	...	32
4-Diethylamino-6-chloro	104–105	$C_8H_{13}N_4Cl$	[f]	[f]	21, 45

[a] Gabriel and Colman, *Ber.*, **36**, 3381 (1903). [b] Gabriel and Colman, *ibid.*, **32**, 2924 (1899). [c] Roblin, *et al.*, THIS JOURNAL, **62**, 2002 (1940). [d] Büttner, *Ber.*, **36**, 2227 (1903). [e] von Merkatz, *ibid.*, **52**, 869 (1919). [f] Calcd. for $C_8H_{13}N_4Cl$: N, 27.88. Found: N, 27.96.

Reaction of the various substituted acetoacetic and malonic esters with guanidine carbonate led to the formation of the pyrimidones and pyrimidinediones described in Table II, while the β-diketones and guanidine carbonate formed pyrimidines (Table IV) which could be directly condensed with acetylsulfanilyl chloride.

The treatment of the pyrimidones and pyrimidinediones with phosphorus oxychloride yielded the corresponding chloro derivatives described in Table III. By reducing these chloro compounds or reacting them with suitable reagents a variety of substituents was introduced in place of the chlorine atoms, resulting in the formation of the substituted aminopyrimidines which are described in Table IV.

In the utilization of the intermediate aminodichloropyrimidines for the preparation of the appropriate derivatives, it was observed that both chlorine groups could be replaced by treating with an excess of the reagent employed. However, one chlorine atom could be replaced by treating with only one equivalent of the substituting reagent or by controlling the temperature of the reaction as in the case of the introduction of the diethylamino radical. The second chlorine atom could then be replaced by a different radical or, through catalytic reduction, by hydrogen. This stepwise replacement of the chlorine atoms afforded a convenient method of obtaining substituted 2-aminopyrimidines containing dissimilar substituents in the 4- and 6-positions. The sequence of substitution does not seem material. For example, practically identical yields of 2-amino-4-methoxy-6-diethylaminopyrimidine were obtained whether 2-amino-4,6-dichloropyrimidine was first reacted with sodium methoxide and then with diethylamine or *vice versa*. It is noteworthy that where one alkoxy substituent was already present, attempts to introduce a second dissimilar alkoxyl group resulted in the replacement not only of the second chlorine atom but also of the original alkoxyl group. Rose and Tuey[6] reported a similar observation but were able to introduce dissimilar alkoxyl groups by employing different conditions for the reaction.

All the 2-acetylsulfanilamidopyrimidines described in Table V, except SD 36, were prepared by condensing the substituted aminopyrimidines with acetylsulfanilyl chloride. The substituted 2-sulfanilaminopyrimidines (Table V) were then obtained by hydrolyzing the acetyl derivatives with 10% sodium hydroxide.

Pharmacology

The pharmacological properties of most of these sulfanilamidopyrimidines[7] have been reported by van Dyke, *et al.*[8] It should be noted, however, that in many cases the substituents containing oxygen in the pyrimidine ring produced an increased solubility of the sulfanilamidopyrimidine and its acetyl derivative and that in some instances they produced drugs which were excreted entirely in the unconjugated form.

Experimental

Substituted 2,4-Pentanediones

The following specific example was generally applicable to the preparation of this type of compound.

(6) Rose and Tuey, *J. Chem. Soc.*, 81 (1946).

(7) The chemotherapeutic investigation of these drugs in bacterial infections was made under the direction of Dr. G. W. Rake in the Division of Microbiology and will be reported elsewhere.

(8) van Dyke, Tupikova, Chow and Walker, *J. Pharm. Exptl. Therap.*, **83**, 203 (1945).

TABLE IV

SUBSTITUTED AMINOPYRIMIDINES

2-Amino-( )-pyrimidine	Method of prepn.	Formula	M. p., °C. (uncor.)	N Analyses % Calcd.	Found	Used in prepn. of SD
4-Methyl-6-methoxy	(*f*)	$C_6H_9N_3O$	153–154	30.21	30.46	1
4-Methyl-6-ethoxy[a]	(*f*)	$C_7H_{11}N_3O$	89–90	...	...	2
4-Methyl-6-propoxy	(*f*)	$C_8H_{13}N_3O$	59–61	25.13	24.97	3
4-Methyl-6-amoxy	(*f*)	$C_{10}H_{17}N_3O$	51–52	21.52	21.62	4
4-Methyl-6-phenoxy	(*f*)	$C_{11}H_{11}N_3O$	194–195	20.88	20.87	5
4-Methyl-6-methoxymethyl[b]	(*b*)	$C_7H_{11}N_3O$	114–116	27.45	27.61	6
4-Methyl-6-dimethoxymethyl	(*j*)	$C_8H_{13}N_3O_2$	74–75	22.94	22.54	7
4-Methyl-6-ethoxymethyl[c]	(*c*)	$C_8H_{13}N_3O$	106–107	25.13	24.98	8
4-Methyl-6-diethoxymethyl	(*j*)	$C_{10}H_{17}N_3O_2$	87.5–88.5	19.89	19.85	9
4-Methyl-6-β-methoxyethoxy	(*f*)	$C_8H_{13}N_3O_2$	82–83	22.94	22.84	10
4-Methyl-5-β-hydroxyethyl	(*k*)	$C_7H_{11}N_3O$	159–160	27.45	27.01	11
4-Methyl-5-β-ethoxyethyl	(*g*)	$C_9H_{15}N_3O$	138–139	23.19	23.45	12
4-Methyl-5-β-methoxyethyl-6-methoxy	(*f*)	$C_9H_{15}N_3O_2$	82–83	21.30	21.48	13
4-Methyl-5-β-ethoxyethyl-6-methoxy	(*f*)	$C_{10}H_{17}N_3O_2$	94–95	19.87	19.86	14
4-Methyl-6-dimethylamino	(*h*)	$C_7H_{12}N_4$	169–170	36.75	37.03	15
4-Methyl-6-diethylamino	(*h*)	$C_9H_{16}N_4$	112–113	31.08	31.14	16
4-Methyl-6-β-diethylaminoethoxy	(*f*)	$C_{11}H_{20}N_4O$	42–43	24.93	24.69	17
4,5-Dimethyl-6-methoxy	(*f*)	$C_7H_{11}N_3O$	154–155	27.45	27.30	18
4,5-Dimethyl-6-methoxyethoxy	(*f*)	$C_9H_{15}N_3O_2$	108–109	21.32	20.80	19
4,5,6-Trimethyl[c]	(*c*)	$C_7H_{11}N_3$	203–204	30.63	30.34	20
4-Methoxy-6-diethylamino	(*h*)	$C_9H_{16}N_4O$	84–85	28.55	27.60	21
4-Methoxy-5,6-trimethylene	(*f*)	$C_8H_{11}N_3O$	119–120	25.43	25.72	22
4-Methoxymethyl	(*g*)	$C_6H_9N_3O$	123–124	30.20	29.97	23
4-Methoxymethyl-5-methoxy	(*g*)	$C_7H_{11}N_3O_2$	137–138	24.84	24.85	24
4-Methoxymethyl-6-methoxy	(*f*)	$C_7H_{11}N_3O_2$	116–117	24.84	24.50	25
4-Methoxymethyl-5,6-dimethoxy	(*f*)	$C_8H_{13}N_3O_3$	132–133	21.11	20.97	26
4-Methoxymethyl-6-ethoxy	(*f*)	$C_8H_{13}N_3O_2$	90–91	22.95	22.93	27
4-Methoxymethyl-6-diethoxymethyl	(*j*)	$C_{11}H_{19}N_3O_3$	65–66	17.42	17.97	28
4-Methoxymethyl-5-methoxy-6-ethoxy	(*f*)	$C_9H_{15}N_3O_3$	113–114	19.71	20.00	29
4-β-Methoxyethoxy	(*g*)	$C_7H_{11}N_3O_2$	104–105	24.84	25.22	30
4,6-Dimethoxy[d,i]	(*d*)	$C_6H_9N_3O_2$	94–95	27.10	27.23	31
4,6-Dimethoxy-5-ethyl[i]	(*f*)	$C_8H_{13}N_3O_2$	90–91	22.95	22.94	32
4,6-Dimethoxymethyl	(*j*)	$C_8H_{13}N_3O_2$	133–134	22.95	22.99	33
4,6-Di-β-methoxyethoxy	(*f*)	$C_{10}H_{17}N_3O_4$	85–86	17.30	17.47	34
4-Ethoxymethyl-5-ethoxy	(*g*)	$C_9H_{15}N_3O_2$	106–107	21.32	21.57	35
4-Ethoxymethyl-5-ethoxy-6-hydroxy	(*l*)	$C_9H_{15}N_3O_3$	219–220	19.71	19.89	36[e]
4,5-Diethoxy	(*g*)	$C_8H_{13}N_3O_2$	94–95	22.95	22.89	37
4,6-Diethoxy[i]	(*f*)[l]	$C_8H_{13}N_3O_2$	99.5–100	22.95	22.67	38
4-Diethoxymethyl	(*g*)	$C_9H_{15}N_3O_2$	134–135	21.31	20.92	39
4-Diethoxymethyl-6-methoxy	(*f*)	$C_{10}H_{17}N_3O_3$	84–85	18.49	18.25	40
4,5,6-Triethoxy	(*f*)	$C_{10}H_{17}N_3O_3$	76–78	18.49	18.32	41
4-Ethylmercapto	(*f*)	$C_6H_9N_3S$	156–157	27.07	27.35	42
4,6-Diethylmercapto	(*f*)	$C_8H_{13}N_3S_2$	52–53	19.51	19.33	43
4,6-Di-diethylamino	(*h*)	$C_{12}H_{23}N_5$	73–74	29.51	29.82	44

[a] Sprague, *et al.*, THIS JOURNAL, **63**, 3028 (1941). [b] Price, Leonard and Curtin, *J. Org. Chem.*, **10**, 318–326 (1945). [c] Clark, *et al.*, THIS JOURNAL, **68**, 98 (1946). [d] Fischer and Johnson, *ibid.*, **54**, 727 (1932). [e] SD # 36 was not prepared from this intermediate but was obtained by condensing acetylsulfanilylguanidine with ethyl α,γ-diethoxyacetoacetate. [f] Reaction of corresponding chloro compound with appropriate sodium alkoxide, phenoxide or mercaptide. [g] Catalytic reduction of 6-chloro analog. [h] Reaction of chloro analog with appropriate dialkylamine. [i] Rose and Tuey, *J. Chem. Soc.*, 81 (1946). [j] Reaction of corresponding β-diketone with guanidine carbonate. [k] Refer to experimental section. [l] Reaction of ethyl α,γ-diethoxyacetoacetate with guanidine carbonate.

1,1-Diethoxy-2,4-pentanedione.—Sodium shot (6.9 g.) was suspended in 150 cc. of benzene. Ethyl diethoxyacetate (67.2 g.) was added to this stirred suspension at 0°, followed by 20 g. of dry acetone, over a period of thirty minutes while the temperature was maintained at −5 to 0°. The mixture was further stirred at 0 to 5° for three hours and then stored in a refrigerator (10°) for eighteen hours. The benzene was removed under diminished pressure and the residue mixed with 75 cc. of water and acidified with acetic acid. The mixture was extracted with five 150-cc. portions of ether, the extracts combined, washed with saturated salt solution and dried over magnesium sulfate. After evaporating the ether, the residual oil was fractionated and 50.3 g. of 1,1-diethoxy-2,4-pentanedione was obtained as a colorless oil boiling at 78–82° (3 mm.).

TABLE V

SULFANILAMIDOPYRIMIDINES

SD	2-Sulfanilamido-( )-pyrimidine	M. p., °C. (uncor.)	Yield, %	Formula	Analyses: % Nitrogen Calcd.	% Nitrogen Found	% Sulfur Calcd.	% Sulfur Found	Acetyl derivative: M. p., °C. (uncor.)	Yield, %	% Nitrogen Calcd.	% Nitrogen Found
1	4-Methyl-6-methoxy	201–202	50	$C_{12}H_{14}N_4O_3S$	19.04	19.14	10.89	10.75	253–254 (dec.)	53	16.65	16.96
2	4-Methyl-6-ethoxy[a]	103–104	40	$C_{13}H_{16}N_4O_3S$	...	...	...	...	244.5–245[a]	72	...	...
3	4-Methyl-6-propoxy	153–154	75	$C_{14}H_{18}N_4O_3S$	17.38	17.57	9.94	9.90	211–212	55	15.38	15.20
4	4-Methyl-6-*n*-amoxy	146–147	67	$C_{16}H_{22}N_4O_3S$	15.99	15.77	9.18	9.07	167–168	80	14.28	14.04
5	4-Methyl-6-phenoxy	181–182	33	$C_{17}H_{16}N_4O_3S$	15.73	15.60	8.99	8.88	212–213	82	14.06	14.04
6	4-Methyl-6-methoxymethyl[b]	169–170	90	$C_{13}H_{16}N_4O_3S$	18.17	17.87	10.38	10.15	193.5–194.5[b]	65	15.99	16.23
7	4-Methyl-6-dimethoxymethyl	172–173	35	$C_{14}H_{18}N_4O_4S$	16.56	16.43	9.46	9.46	200–201	50	14.73	14.98
8	4-Methyl-6-ethoxymethyl[c]	153–154	75	$C_{14}H_{18}N_4O_4S$	...	...	...	...	215–216[c]	80	15.37	15.06
9	4-Methyl-6-diethoxymethyl	146–147	30	$C_{16}H_{22}N_4O_4S$	15.28	14.84	8.75	8.44	187–189	70	13.71	13.58
10	4-Methyl-6-β-methoxyethoxy	184–185	50	$C_{14}H_{18}N_4O_4S$	16.56	16.50	9.46	9.51	189–190	55	14.73	14.66
11	4-Methyl-5-β-hydroxyethyl	160–162	70	$C_{13}H_{16}N_4O_3S$	18.17	17.87	10.38	10.61	181–182	27	15.99	15.93
12	4-Methyl-5-β-ethoxyethyl	194–195	74	$C_{15}H_{20}N_4O_3S$	16.66	16.99	9.53	9.74	200–201	78	14.81	14.42
13	4-Methyl-5-methoxyethyl	189–190	72	$C_{15}H_{20}N_4O_4S$	15.90	16.12	9.09	9.40	213–214	60	14.21	14.06
14	4-Methyl-5-β-ethoxyethyl-6-methoxy	150–151	65	$C_{16}H_{22}N_4O_4S$	15.29	15.26	8.75	8.93	204–205	64	13.71	13.68
15	4-Methyl-6-dimethylamino	310–311	75	$C_{13}H_{17}N_5O_2S$	22.79	22.68	10.41	10.32	321–322	54	20.05	20.03
16	4-Methyl-6-diethylamino	249–250	71	$C_{15}H_{21}N_5O_2S$	20.88	20.90	9.56	9.46	306–307	42	18.56	18.81
17	4-Methyl-6-β-diethylamino-ethoxy	197–198	40	$C_{17}H_{26}N_5O_3S$	18.46	18.11	8.44	8.44	[d]	..	...	...
18	4,5-Dimethyl-6-methoxy	249–250	89	$C_{13}H_{16}N_4O_3S$	18.17	18.01	10.40	10.29	253–254	60	15.99	15.88
19	4,5-Dimethyl-6-β-methoxy-ethoxy	122–123	68	$C_{15}H_{20}N_4O_4S$	15.90	15.80	9.09	8.86	202–203	60	14.32	14.21
20	4,5,6-Trimethyl[c]	237–238	80	$C_{13}H_{16}N_4O_2S$	19.16	19.23	10.97	10.90	285–286[c]	93	16.76	16.96
21	4-Methoxy-6-diethylamino	150–151	60	$C_{16}H_{21}N_5O_3S$	19.93	19.91	9.12	9.02	168–169	82	17.89	17.55
22	4-Methoxy-5,6-trimethylene	228–229	62	$C_{14}H_{16}N_4O_3S$	17.46	17.81	10.00	9.99	249–250	63	15.46	15.27
23	4-Methoxymethyl	196–197	60	$C_{12}H_{14}N_4O_3S$	19.04	19.32	10.89	10.84	220–221	72	16.66	16.41
24	4-Methoxymethyl-5-methoxy	158–159	75	$C_{13}H_{16}N_4O_4S$	17.27	17.17	9.88	9.49	211–212	80	15.29	14.98
25	4-Methoxymethyl-6-methoxy	162–163	80	$C_{13}H_{16}N_4O_4S$	17.27	17.37	9.88	9.81	160–161	50	15.29	15.21
26	4-Methoxymethyl-5,6-dimethoxy	167–168	76	$C_{14}H_{18}N_4O_4S$	15.81	16.16	9.05	9.13	174–175	50	14.13	14.30
27	4-Methoxymethyl-6-ethoxy	144–145	87	$C_{14}H_{18}N_4O_4S$	16.56	16.57	9.46	9.61	164–165	50	14.73	15.06
28	4-Methoxymethyl-6-diethoxy-methyl	113–114	50	$C_{17}H_{24}N_4O_5S$	14.13	14.22	8.08	8.13	125–127	64	12.86	12.51
29	4-Methoxymethyl-5-methoxy-6-ethoxy	111–112	50	$C_{15}H_{20}N_4O_5S$	15.21	15.05	8.70	8.50	153–153.5	75	13.65	13.58
30	4-β-Methoxyethoxy	234–235	50	$C_{13}H_{16}N_4O_4S$	17.27	17.57	9.88	9.95	242–243	45	15.29	15.69
31	4,6-Dimethoxy[e]	177–178	50	$C_{12}H_{14}N_4O_4S$	18.06	17.74	10.33	10.26	240–241	83	15.90	15.65
32	4,6-Dimethoxy-5-ethyl[e]	229–230	83	$C_{14}H_{18}N_4O_4S$	16.56	16.89	9.46	9.16	198–199	77	14.73	14.66
33	4,6-Dimethoxymethyl	160–161	52	$C_{14}H_{18}N_4O_4S$	16.56	16.28	9.46	9.12	166–168	80	14.73	14.59
34	4,6-Di-β-methoxyethoxy	104–105	60	$C_{16}H_{22}N_4O_6S$	14.06	13.92	8.05	8.04	156–157	60	12.72	12.86
35	4-Ethoxymethyl-5-ethoxy	167–169	40	$C_{15}H_{20}N_4O_4S$	15.90	15.88	9.10	8.68	170–171	85	14.21	14.34
36	4-Ethoxymethyl-5-ethoxy-6-hydroxy	192–193	86	$C_{15}H_{20}N_4O_5S$	15.21	15.21	8.69	8.99	206–207	25	13.65	13.66
37	4,5-Diethoxy	203.5–204.5	68	$C_{14}H_{18}N_4O_4S$	16.56	16.89	9.46	9.29	196–197	68	14.73	14.45
38	4,6-Diethoxy[e]	158–159	72	$C_{14}H_{18}N_4O_4S$	16.56	16.61	9.46	9.27	222–223	80	14.73	15.13
39	4-Diethoxymethyl	200–201	86	$C_{15}H_{20}N_4O_4S$	15.90	15.77	9.10	9.01	192	60	14.21	13.46
40	4-Diethoxymethyl-6-methoxy	84–85	75	$C_{16}H_{22}N_4O_6S$	14.65	14.40	8.37	7.94	163–164	40	13.21	13.29
41	4,5,6-Triethoxy	117–118	72	$C_{15}H_{22}N_4O_5S$	14.65	14.96	8.37	8.37	188–189	84	13.21	13.22
42	4-Ethylmercapto	263–264	40	$C_{12}H_{14}N_4O_2S_2$	18.05	18.22	20.66	20.48	268–269	50	15.96	16.04
43	4,6-Diethylmercapto	161–162	28	$C_{14}H_{18}N_4O_2S_3$	15.13	15.00	25.93	26.01	191–192	30	13.58	13.58
44	4,6-Di-diethylamino	178–179	72	$C_{18}H_{28}N_6O_2S$	21.42	21.46	8.17	8.12	197–198	45	19.35	19.40
45	4-Diethylamino-6-chloro[f]	.....	..	$C_{14}H_{18}N_5O_2SCl$	...	...	...	...	221–222	74	17.62	17.50

[a] Sprague, Kissinger and Lincoln, THIS JOURNAL, **63**, 3029 (1941). [b] Price, Leonard and Curtin, *J. Org. Chem.*, **10**, 318–326 (1945). [c] Clark, *et al.*, THIS JOURNAL, **68**, 96 (1946). [d] Acetyl derivative could not be isolated. [e] In a paper which appeared after the completion of this work, Rose and Tuey, *J. Chem. Soc.*, 81 (1946), described this compound. [f] All attempts to deacetylate the acetyl derivative led to the recovery of 2-amino-4-diethylamino-6-chloropyrimidine or starting material.

Substituted Pyrimidones and Pyrimidinediones

The following typical preparations are illustrative of the general procedure employed.

2-Amino-4-methyl-5-β-ethoxyethyl-6-hydroxypyrimidine.—Ethyl (β-ethoxyethyl)-acetoacetate (10 g.) and guanidine carbonate (10 g.) were heated together in an oil-bath at 175° for six hours. The reaction mixture was cooled, dissolved in dilute hydrochloric acid and precipitated by neutralizing with 5% ammonium hydroxide. The solid was filtered, washed with water and dried. After recrystallization from methanol, the purified pyrimidone melted at 238–239°; yield 45%.

2-Amino-4,6-dihydroxy-5-ethoxypyrimidine.—A mixture of 42.3 g. of ethyl ethoxymalonate, 37.3 g. of guanidine carbonate and 100 cc. of absolute ethanol was refluxed for sixty hours. The alcohol insoluble solid was filtered, washed and dried. After purification by solution in 5% sodium hydroxide and reprecipitation by 5% acetic acid three times, the product was filtered, washed and dried. The yield of the pyrimidinedione which did not melt up to 320° was 21.4 g. (60%).

Substituted Chloropyrimidines

Pyrimidones and pyrimidinediones were converted to

mono- and dichloro derivatives as in the following preparations.

2-Amino-4-diethoxymethyl-6-chloropyrimidine.—A mixture of 2-amino-4-diethoxymethyl-6-hydroxypyrimidine (10 g.) and phosphorus oxychloride (30 cc.) was allowed to stand at 25° for four hours. A higher temperature results in a splitting of the acetal. The solution was poured into finely crushed ice and the mixture neutralized with concentrated ammonium hydroxide. The crude solid was filtered, washed with water and dried. After recrystallization from ether–hexane mixture, 4.5 g. of product, m. p. 100–101°, was obtained; yield 41%.

2-Amino-4,6-dichloro-5-ethoxypyrimidine.—A mixture of 14 g. of 2-amino-4,6-dihydroxy-5-ethoxypyrimidine and 80 cc. of phosphorus oxychloride was refluxed for ninety minutes. The solution was cooled and poured while stirring on 500 g. of cracked ice. After making alkaline with concentrated ammonium hydroxide, the mixture was extracted with five 100-cc. portions of ether, the extracts combined, washed with saturated salt solution and dried over magnesium sulfate. The ether was then evaporated and the residue recrystallized from a mixture of ether and hexane, whereupon 7.2 g. (42%) of product, m. p. 181–182°, was obtained.

2-Amino-4-methoxymethyl-5-methoxy-6-chloropyrimidine.—A mixture of 100 g. of 2-amino-4-methoxymethyl-5-methoxy-6-hydroxypyrimidine and 500 cc. of phosphorus oxychloride was refluxed for one hour. After cooling, the excess phosphorus oxychloride was removed under reduced pressure and the residual sirupy material poured on 500 g. of cracked ice. Water (500 cc.) was added and after rubbing, the oily product solidified. It was filtered, washed and dried and recrystallized from hexane. The yield of chloro compound was 86 g. (71%), m. p. 99–100°.

2-Amino-4-diethylamino-6-chloropyrimidine.—Five grams of 2-amino-4,6-dichloropyrimidine and 20 cc. of diethylamine were heated in a sealed tube for three hours at 120–130°. After cooling, the tube was opened and the contents washed out with 100 cc. of water and the mixture made alkaline with 30 cc. of 10% sodium hydroxide, then extracted three times with 25 cc. of ether. The combined ether extract after drying was evaporated and the residue recrystallized from hexane, yielding 2-amino-4-diethylamino-6-chloropyrimidine, m. p. 104–105°; yield 82%. This product also could be obtained when the dichloropyrimidine was refluxed on a steam-bath for twenty hours with diethylamine in the presence of a trace of copper–bronze.

When the above experiment was carried out in a sealed tube at 200° 2-amino-4,6-di-diethylaminopyrimidine, m. p. 73–74°, was obtained in a yield of 78%.

Substituted Pyrimidines

The following examples illustrate the different routes employed in the synthesis of this type of compound.

2-Amino-4-diethoxymethyl-6-methylpyrimidine.—A mixture of 1,1-diethoxy-2,4-pentanedione (7.5 g.) and guanidine carbonate (5.4 g.) was heated in an oil-bath at 120° for two hours. The reaction mixture was cooled, 30 cc. of water added and the suspension acidified with acetic acid. The reaction product was filtered, washed with water and dried. After recrystallization from hexane, 5.7 g. of the product was obtained, m. p. 87.5–88.5°; yield 70%.

2-Amino-4,6-dimethoxy-5-ethylpyrimidine.—Five grams of sodium metal was dissolved in 150 cc. of absolute methanol. To this solution 13 g. of 2-amino-4,6-dichloro-5-ethylpyrimidine was then added and the mixture refluxed on a steam-bath for six hours. The reaction mixture was cooled and the salt which separated was filtered off and washed with a small amount of methanol. The combined filtrate and washings were taken to dryness *in vacuo*. The residue was treated with 200 cc. of water and the insoluble material filtered off, washed with water and then dried. After recrystallization from hexane, 11.5 g. of the product was obtained, melting at 90–91°. The yield was 93%.

2-Amino-4-methoxy-6-diethylaminopyrimidine.—Forty grams of 2-amino-4-methoxy-6-chloropyrimidine was heated with 30 cc. of diethylamine in a sealed tube at 110° for four hours. The contents were then removed, made slightly alkaline with dilute sodium hydroxide and extracted several times with ether. After removal of the ether, the residue was recrystallized from hexane; yield 32.1 g. (65%), m. p. 84–85°.

Substituted Pyrimidines by Dehalogenation

2-Amino-4-methyl-5-β-ethoxyethylpyrimidine.—Ten grams of 2-amino-4-methyl-5-β-ethoxyethyl-6-chloropyrimidine was dissolved in 150 cc. of 95% ethanol and one gram of 5% palladium-on-charcoal catalyst added. The mixture was shaken with hydrogen at atmospheric pressure until just slightly more than the theoretical amount of hydrogen was absorbed. The mixture was then filtered and the filtrate concentrated to dryness. The residue was dissolved in water and the solution made alkaline, the precipitated product filtered, washed and dried. After recrystallization from water, 5.5 g. of 2-amino-4-methyl-5-β-ethoxyethylpyrimidine, m. p. 138–139°, was obtained; yield 65%.

2-Amino-4-methoxymethyl-5-methoxypyrimidine.—Five grams of 2-amino-4-methoxymethyl-5-methoxy-6-chloropyrimidine was dissolved in 50 cc. of 2% hydrochloric acid. In this preparation the use of 2% hydrochloric acid in lieu of 95% ethanol as employed above leads to better yields. One gram of 5% palladium-on-charcoal catalyst was added and the mixture shaken with hydrogen at atmospheric pressure until slightly more than the theoretical amount of hydrogen was absorbed. The mixture was filtered and the filtrate alkalinized with an equal volume of 50% sodium hydroxide and then extracted with three 100-cc. portions of ether. The ether extracts were combined, washed with saturated salt solution and dried over magnesium sulfate. After evaporating the ether, the residue was recrystallized from benzene. The yield of the desired pyrimidine, m. p. 137–138°, was 3.5 g. (84%).

2-Amino-4-diethoxymethylpyrimidine.—Eight grams of 2-amino-4-diethoxymethyl-6-chloropyrimidine was dissolved in 80 cc. of normal methanolic ammonia. The ammonia is present to neutralize the hydrogen chloride formed in the course of reduction and thereby prevent cleavage of the acetal group. Two grams of 5% palladium-on-charcoal catalyst was added and the mixture shaken with hydrogen at atmospheric pressure. When the required quantity of hydrogen was absorbed, the mixture was filtered and the filtrate evaporated. The residue was taken up in 50 cc. of water and the solid filtered off. After recrystallization from methanol, 3.5 g. (53%) of the pyrimidine, m. p. 134–135°, was obtained.

Substituted 2-Acetylsulfanilamidopyrimidines

The following specific preparations are exemplary of the general procedures employed.

2-Acetylsulfanilamido-4-methyl-5-β-methoxyethyl-6-methoxypyrimidine.—2-Amino-4-methyl-5-β-methoxyethyl-6-methoxypyrimidine (11.5 g.) was dissolved in pyridine (35 cc.). The solution was cooled to 15° and while stirring acetylsulfanilyl chloride (16.5 g.) was added over a period of thirty minutes. The reaction mixture was allowed to remain at 25° for eighteen hours. The pyridine was then removed by distillation under reduced pressure. The residue was mixed with water and the solid filtered and washed with water. After recrystallization from 95% ethanol, the product was obtained as a white crystalline material, m. p. 213–214°; yield 60%.

2-Acetylsulfanilamido-4-methyl-6-diethylaminopyrimidine.—A solution of 25 g. of 2-amino-4-methyl-6-diethylaminopyrimidine in 75 cc. of pyridine was cooled to 10–15° and while stirring vigorously 36 g. of acetylsulfanilyl chloride was added over a period of thirty minutes. The mixture was then allowed to stand at room temperature for twenty-four hours. The pyridine was removed by distilling under reduced pressure. Water (500 cc.) was added to the oily residue which then solidified. After filtration, the product was purified by dissolving in dilute sodium hydroxide, followed by precipitation with dilute hydrochloric acid, the latter being added until the *p*H of the

mixture was 7.0. After purification by dissolving in dilute alkali and reprecipitating with dilute acid three times, the product was filtered, washed and dried, m. p. 306–307°; yield 22 g. (42%).

2-Acetylsulfanilamido-4-ethoxymethyl-5-ethoxy-6-hydroxypyrimidine: Acetyl Derivative of SD 36.—The procedure used was essentially that described by K. Ganapathi, *et al.*,[9] for analogous compounds. Three and one-half grams of sodium was dissolved in 200 cc. of absolute ethanol. Twenty-one and eight-tenths grams of ethyl α,γ-diethoxyacetoacetate in 400 cc. of absolute ethanol was added with stirring, followed by 25.6 g. of acetylsulfanilylguanidine. The mixture was stirred and refluxed for ten hours after which it was cooled and the insoluble material filtered, washed and dried. The crude solid was stirred with 100 cc. of 5% sodium hydroxide solution. The alkali insoluble material which was filtered off weighed 10 g. and was identified as unreacted acetylsulfanilylguanidine. The filtrate containing the alkali soluble fraction was acidified with acetic acid and the precipitate filtered, washed and dried. After crystallization from absolute ethanol, 9.0 g. (25%) of product of m. p. 206–207° was obtained.

2-Acetylsulfanilamido-4-diethylamino-6-chloropyrimidine.—To a solution of 7.3 g. of 2-amino-4-diethylamino-6-chloropyrimidine in 15 cc. of pyridine maintained at 0°, there was added over a period of fifteen minutes 7.7 g. of acetylsulfanilyl chloride. After the addition the temperature was allowed to rise to room temperature and the stirring continued for two hours. After standing overnight the pyridine was removed under vacuum from the reaction mixture and the sticky residue treated successively with three 50-cc. portions of water. The water was removed each time under vacuum until finally the residue became solid. The crude product, weighing 11 g., was crystallized twice from absolute alcohol and a material melting at 221–222° was obtained.

Attempts to deacetylate the above substance by acid hydrolysis were unsuccessful. When shaken for twelve hours at room temperature with about 15% alcoholic hydrogen chloride the starting material was recovered. When refluxed for twenty minutes with 5 *N* hydrochloric acid or for five minutes with 34% methylsulfonic acid, cleavage of the $-SO_2NH-$ group occurred and 2-amino-4-diethylamino-6-chloropyrimidine was obtained along with some unchanged starting material. Alkaline hydrolysis was not tried because of the lability of the chloro group.

Substituted 2-Sulfanilamidopyrimidines

The hydrolysis of the acetyl derivatives was effected by boiling with 10% sodium hydroxide. The following preparations are typical.

2-Sulfanilamido-4,5-diethoxypyrimidine.—2-Acetylsulfanilamido-4,5-diethoxypyrimidine (8.0 g.) was dissolved in 30 cc. of 10% sodium hydroxide and the solution refluxed for two and one-half hours, the progress of hydrolysis being followed by nitrite titration. At the end of this period, the solution was cooled and acidified with acetic acid. The solid was filtered, washed and dried. After recrystallizing from 95% ethanol, the product was obtained as a white crystalline solid, m. p. 203.5–204.5°; yield 68%.

(9) Ganapathi, Deliwala and Shirsat, *Proc. Indian Acad. Sci.*, **16A**, 115 (1942).

2-Sulfanilamido-4-methyl-5-β-hydroxyethylpyrimidine, SD 11.—This compound was obtained by the following route.

2-Amino-4-methyl-5-β-bromoethylpyrimidine.—Twenty grams of 2-amino-4-methyl-5-β-ethoxyethylpyrimidine was heated on the steam-bath for two hours with 600 cc. of 10% hydrogen bromide in acetic acid. The acid was removed under reduced pressure and the residue dissolved in 75 cc. of water and filtered. The filtrate was neutralized with sodium bicarbonate and the solid filtered off, washed and dried to give 17 g. of product, m. p. 166–169°, which could not be obtained analytically pure. To establish the identity of this compound, a sample was converted by heating with 5% potassium carbonate to 2-amino-4-methyl-5-β-hydroxyethylpyrimidine, m. p. 159–160°, after crystallization from absolute ethanol.

Anal. Calcd. for $C_7H_{11}N_3O$: C, 54.85; H, 7.24; N, 27.43. Found: C, 54.83; H, 7.18; N, 27.01.

2-Acetylsulfanilamido-4-methyl-5-β-hydroxyethylpyrimidine.—A solution of 5.4 g. of 2-amino-4-methyl-5-β-bromoethylpyrimidine in 50 cc. of dry pyridine was warmed with 6.4 g. of acetylsulfanilyl chloride at 40° for three hours. The pyridine was removed *in vacuo* and the product dissolved in dilute ammonium hydroxide, treated with charcoal, filtered and the filtrate acidified with acetic acid. The solid was filtered off and recrystallized from aqueous alcohol, m. p. 245–246°. Four grams of this material was heated on the steam-bath with 4.5 g. of potassium carbonate dissolved in 90 cc. of water. On cooling, the insoluble material was filtered off and the filtrate acidified with acetic acid. After crystallization from aqueous alcohol, 2.4 g. of product, melting at 181–182°, was obtained; yield 27.3%.

2-Sulfanilamido-4-methyl-5-β-hydroxyethylpyrimidine.—Two grams of the acetyl body was hydrolyzed by boiling with 10% sodium hydroxide solution for one and one-half hours. The solution was filtered and acidified with acetic acid. The solid was filtered off, redissolved in dilute alkali, treated with carbon, filtered and reacidified. The material was recrystallized from aqueous alcohol to give 1.2 g. of product, m. p. 160–162°; yield 70%.

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Summary

A number of new substituted β-diketones are reported and described.

The compounds produced by the reaction of various β-diketones, acetoacetic esters and malonic esters with guanidine carbonate are reported and described, as well as their mono- and dichloro analogs.

A number of substituted aminopyrimidines have been prepared and are described.

A variety of substituted 2-sulfanilamidopyrimidines were obtained from the described aminopyrimidines.

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