method permits only partial recovery of the red antioxygenic substances, it was of some value in detecting their presence in highly pigmented vegetable oils.

Chemical and Biological Properties.—The absorption spectrum of the concentrates in the visible region, as measured in alcoholic solution by a Bausch and Lomb spectrophotometer, is identical with that of authentic chroman-5,6-quinones[9] and shows maximal absorption in the range 560–570 mμ.

The quinone concentrates are efficient stabilizers for lard and other fat substrates (Table II). They are instantly decolorized by reducing agents but quickly regain their initial color after separation from the reducing agent and re-exposure to air. Reductive acetylation, however, yields stable colorless oils which possess no antioxygenic properties. When the quinone concentrates react with *o*-phenylenediamine, they form products whose ether solutions exhibit the greenish fluorescence in daylight and in ultraviolet light, characteristic of the phenazines of authentic chroman-5,6-quinones.[9] The antioxygenic quinoid substances are destroyed when the concentrates are saponified. Their lability to alkali, first noted by John and Emte[15] with the authentic compounds, is markedly diminished when sodium hydrosulfite is present. However, when the quinone concentrates were saponified in the presence of this reducing agent, only a small proportion of the total quinone was isolated from the unsaponifiable matter. The greater proportion of it appeared to remain in the saponified fraction. Likewise, only partial recovery of the chroman-5,6-quinone oxidation product of α-tocopherol was secured when it was subjected to the same treatment.

(15) John and Emte, *Z. physiol. Chem.*, **261**, 24 (1939).

Conflicting statements have appeared regarding the vitamin E activity of the chroman-5,6-quinone derived from α-tocopherol. Evans, as reported in a paper of Smith and co-workers,[9] found that it was inactive in doses up to 6 mg. whereas Ridgway, Drummond and Wright[16] reported that it showed some activity in amounts of 5 mg. In our hands, the red oxidation product of α-tocopherol as well as its hydroquinone diacetate and the red quinoid substances obtained from vegetable oils were devoid of biological activity in doses of 10–15 mg. (eight animals).

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Summary

Cottonseed and soybean oils and mixed hydrogenated vegetable fats contain alkali-labile antioxygenic substances other than the tocopherols. The chemical behavior of these fat antioxidants showed that they are similar to, if not identical with, the chroman-5,6-quinones and occur in fresh vegetable fats in a colorless, possibly quinol form. Their isolation and concentration were accomplished by chromatographic adsorption and the use of selective solvents. These antioxygenic quinoid substances, like the chroman-5,6-quinone product of α-tocopherol, were devoid of vitamin E activity.

(16) Ridgway, Drummond and Wright, *Biochem. J.*, **34**, 1569 (1940).

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[CONTRIBUTION FROM THE DERMATOLOGICAL RESEARCH LABORATORIES, DIVISION OF ABBOTT LABORATORIES]

N¹-Sulfanilylamino-alkyl-pyrimidines

BY GEORGE W. RAIZISS AND MORRIS FREIFELDER

The substitution of an amide hydrogen in sulfanilamide by some heterocyclic nuclei has resulted in compounds with increased therapeutic activity. In continuing our work[1] in this field, we have synthesized a series of sulfanilylamino alkylpyrimidines. Some of these were prepared concurrently by other investigators and have been described[2]; in addition, we have mentioned herewith several which were previously unpublished.

The 4-alkyl and 4,5-dialkyl substituted 2-aminopyrimidines reacted readily with *p*-acetsulfanilyl chloride, forming the acetsulfanilyl derivatives which were subsequently hydrolyzed to the sulfanilylaminoalkylpyrimidines. Our attempts to combine the acid chloride with amino hydroxypyrimidines, such as isocytosine (2-amino-4-hydroxypyrimidine) or divicine (2,5-diamino-4,6-dihydroxypyrimidine), and purines such as adenine or guanine, failed.

Most of the aminopyrimidines used were prepared according to Benary's method[3] by treating guanidine carbonate with sodium oxymethylene ketones; these were obtained by condensation of methyl alkyl ketone and ethyl formate in presence of sodium methylate. 2-Amino-4-ethyl-5-methylpyrimidine was prepared from sodium oxymethylene-α-methyl-methyl ethyl ketone (derived from diethyl ketone and ethyl formate); 2-amino-4-isobutylpyrimidine from sodium oxy-

(1) (a) Raiziss, Clemence and Freifelder, THIS JOURNAL, **63**, 2739 (1941); (b) Raiziss and Clemence, *ibid.*, **63**, 3124 (1941).

(2) (a) Roblin, Williams, Winnek and English, *ibid.*, **62**, 2003 (1940); (b) Caldwell, Kornfeld and Donnell, *ibid.*, **63**, 2189 (1941); (c) Sprague, Kissinger and Lincoln, *ibid.*, **63**, 3028 (1941).

(3) Benary, *Ber.*, **63**, 2601 (1930).

methylene methyl isobutyl ketone (derived from methyl isobutyl ketone), 2-amino-4-*n*-amylpyrimidine from sodium oxymethylenemethyl-*n*-amyl ketone (derived from methyl *n*-amyl ketone). 2,5-Diaminopyrimidine was prepared in excellent yield by catalytic reduction of 5-nitro-2-aminopyrimidine[4] using platinum oxide catalyst; 2-amino-4-hexylpyrimidine was prepared by combining guanidine carbonate with the sodium oxymethylene alkyl ketone derived from ethyl formate and methyl *n*-hexyl ketone. A product was obtained which melted at 92–93° (after several recrystallizations). This is in agreement with the melting point reported by Caldwell, Kornfeld and Donnell[2b] (named as 2-amino-4-methyl-5-*n*-amylpyrimidine) and the melting point reported by Sprague, Kissinger and Lincoln[2c] (named as 2-amino-4-hexylpyrimidine). Oxidation with nitric acid was performed by Caldwell,[2b] with the result that some material was obtained which he considered to be 2-amino-4-carboxy-5-*n*-amylpyrimidine. We carried out a number of oxidations with the hexylpyrimidine, which we obtained, and never had yields above 2–3% of the carboxy compound. It is our belief that the 2-amino-4-methyl-5-*n*-amylpyrimidine reported by Caldwell is essentially 2-amino-4-hexylpyrimidine (as reported by Sprague) containing a small amount of the isomeric 4-methyl-5-*n*-amyl derivative. Employing the same technique we were unable to obtain any oxidation of either 2-amino-4-isobutylpyrimidine or 2-amino-4-*n*-amylpyrimidine.

In Table II, it is interesting to note the solubilities of acetsulfanilylpyrimidines in urine, which may have some relationship to the deposition of crystals in the kidneys and the genito-urinary tract with the formation of urinary concretions. The acetyl-4,5-dimethylpyrimidine derivative is considerably more soluble in urine than any of the compounds. Next in solubility was the monomethyl product. Other acetyl products were very slightly soluble. The study of the therapeutic

TABLE I

AMINOPYRIMIDINES

-Pyrimidines	M. p., (uncor.) °C.	Formula	Nitrogen, % Calcd.	Found
2-Amino-4-isobutyl-[a]	119	$C_8H_{13}N_3$	27.8	27.2
2-Amino-4-amyl-[b]	90	$C_9H_{15}N_3$	25.55	25.39
2-Amino-4-ethyl-5-methyl-[c]	157	$C_7H_{11}N_3$	30.6	30.4
2,5-Diamino-[a,c]	200	$C_4H_6N_4$	50.9	50.3

[a] Recrystallized from hot water. [b] Recrystallized from petroleum ether. [c] Prepared as intermediate but not isolated by Roblin, Winnek and English, THIS JOURNAL, **64**, 567 (1942).

TABLE II

2-(N⁴-ACETYLSULFANILYLAMINO)-PYRIMIDINES

Compound[c]	Yield, %	Melting point, °C.	Solubility at 37°C., mg./100 cc. Water	Urine	Formula	Nitrogen, % Calcd.	Found
2-(N⁴-Acetylsulfanilylamino)-4-methylpyrimidine[a]	59	244 .	24.7	27.0	$C_{13}H_{14}N_4O_3S$	18.03	18.36
2-(N⁴-Acetylsulfanilylamino)-4-ethylpyrimidine	76	274	0.78	1.0	$C_{14}H_{16}N_4O_3S$	17.5	17.41
2-(N⁴-Acetylsulfanilylamino)-4-*n*-propylpyrimidine	82	258	.64	0.8	$C_{15}H_{18}N_4O_3S$	16.76	17.02
2-(N⁴-Acetylsulfanilylamino)-4-isobutylpyrimidine	68	233	.38	.825	$C_{16}H_{20}N_4O_3S$	16.09	15.67
2-(N⁴-Acetylsulfanilylamino)-4-*n*-amylpyrimidine	84	222–223	.44	.5	$C_{17}H_{22}N_4O_3S$	15 46	15.7
2-(N⁴-Acetylsulfanilylamino)-4-hexylpyrimidine[b]	55	216	.35	.7	$C_{18}H_{24}N_4O_3S$	14.89	14.56
2-(N⁴-Acetylsulfanilylamino)-4,5-dimethylpyrimidine[b]	78	272–273	11.25	43.5	$C_{14}H_{16}N_4O_3S$	17.5	17.3
2-(N⁴-Acetylsulfanilylamino)-4-ethyl-5-methylpyrimidine	84	286	0.36	0.65	$C_{15}H_{18}N_4O_3S$	16.76	16.6
2-(N⁴-Acetylsulfanilylamino)-4-phenylpyrimidine	95	287	.36	.51	$C_{18}H_{16}N_4O_3S$	15.21	14.95
2-(N⁴-Acetylsulfanilylamino)-5,6,7,8-tetrahydroquinazoline[b]	78	259	.76	.97	$C_{16}H_{18}N_4O_3S$	16.18	15.93
2,5-Di-(N⁴-acetylsulfanilylaminopyrimidine	56	295 dec.	.5	1.4	$C_{20}H_{20}N_6O_6S_2$	16.66	16.46

[a] Ref. 2a. [b] Ref. 2b. [c] The above 2-(N⁴-acetylsulfanilylamino) derivatives were crystallized at least twice from 50% alcohol.

(4) Hale and Brill, THIS JOURNAL, **34**, 91 (1912).

TABLE III

2-SULFANILYLAMINOPYRIMIDINES

	Yield, %[d]	Melting point, °C.	Solubility in H_2O, 37°C., mg./100 cc.	Formula	Nitrogen, % Calcd.	Found
2-Sulfanilylamino-4-methylpyrimidine[a,c]	45	235–236	40	$C_{11}H_{12}N_4O_2S$	20.82	20.72
2-Sulfanilylamino-4-ethylpyrimidine	51	242	17.2	$C_{12}H_{14}N_4O_2S$	20.14	20.16
2-Sulfanilylamino-4-propylpyrimidine[c]	50	212–214	25	$C_{13}H_{16}N_4O_2S$	19.1	18.89
2-Sulfanilylamino-4-isobutylpyrimidine	40	232	10	$C_{14}H_{18}N_4O_2S$	18.3	18.08
2-Sulfanilylamino-4-amylpyrimidine	46	226	20	$C_{15}H_{20}N_4O_2S$	17.5	17.21
2-Sulfanilylamino-4-hexylpyrimdine[b,c]	40	204	20	$C_{16}H_{20}N_4O_2S$	16.7	16.52
2-Sulfanilylamino-4,5-dimethylpyrimidine[b]	60	222	20	$C_{12}H_{14}N_4O_2S$	20.14	20.05
2-Sulfanilylamino-4-ethyl-5-methylpyrimidine	60	215	25	$C_{13}H_{16}N_4O_2S$	19.18	19.3
2-Sulfanilylamino-4-phenylpyrimidine[e]	45	264	0.9	$C_{16}H_{14}N_4O_2S$	17.17	16.85
2-Sulfanilylamino-5,6,7,8-tetrahydroquinazoline[b,c]	50	247	2.5	$C_{14}H_{16}N_4O_2S$	18.4	18.2
2,5-Disulfanilylaminopyrimidine[e]	42	241–242	5.4	$C_{16}H_{16}N_4O_2S$	20.00	20.04

[a] Ref. 2a. [b] Ref. 2b. [c] Ref. 2c. [d] Yields based on aminopyrimidines. [e] Roblin, *et al.*, THIS JOURNAL, **64**, 568 (1942), reported 231–232° for this compound.

effect in mice infected with pneumococcus type II (method described in publication)[5] disclosed good therapeutic results for sulfanilylamino 4,5-dimethyl- and 4-monomethylpyrimidines. The ethyl derivative showed slight therapeutic effect, while higher homologs and other derivatives were found to be inactive.

Experimental

The compounds in Table I were prepared according to Benary's method as has been previously mentioned.

2,5-Diamino-pyrimidine: 5.6 g. of 2-amino-5-nitropyrimidine (4) was suspended in 150 cc. alcohol and reduced in presence of 0.2 g. of platinum oxide by hydrogen at 3 atmospheres pressure. The reduction was complete in one hour and the almost clear solution was filtered and evaporated to dryness. The yield was quantitative. After two recrystallizations from water the yield was 3.5 g. (80%).

The acet-sulfanilylaminopyrimidines were all prepared and subsequently hydrolyzed according to the method described in the following example. All of the compounds were recrystallized from 50% alcohol.

2-Sulfanilylamino-4-*n*-amylpyrimidine: 3.3 g. (0.02 mole) of 2-amino-4-*n*-amylpyrimidine was dissolved in 4.8 cc. (0.06 mole) of pyridine and 4.7 g. (0.02 mole) of *p*-acetsulfanilyl chloride added gradually with mixing, keeping temperature below 60°. The mixture was then warmed at 60° for one hour and then stirred into 50 cc. of ice-water. The precipitate was filtered and washed with water and dried; yield 6.2 g. (84%). This material can be recrystallized from 50% alcohol, but for further hydrolysis to the amino compound, recrystallization was not necessary. The acetyl product was hydrolyzed by refluxing in ten volumes of 5% sodium hydroxide for two hours. The solution was cooled and neutralized by the addition of dilute hydrochloric acid. The precipitate was filtered, washed with water and dried. After two recrystallizations from 50% alcohol, the yield was 3 g. (48%).

(5) Raiziss, Severac and Moetsch, *Proc. Soc. Exp. Biol. Med.*, **40**, 434 (1939).

Summary

1. We have prepared and described the chemical and biological properties of various sulfanilylamino-mono- and dialkylpyrimidines and their corresponding acetyl products.

2. The sulfanilylamino-methyl and dimethylpyrimidine derivatives proved to have good therapeutic effect in the treatment of mice infected with Type II pneumococcus.

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