2. The quantum yield of hydrogen formation has not been precisely determined but is very low.

3. Attempts to produce photochemical exchange reactions between benzene and deuterium were unsuccessful.

4. While definite conclusions concerning mechanism are not possible, the best explanation of the data is based on a small amount of primary dissociation of benzene molecules into acetylene.

ROCHESTER, NEW YORK RECEIVED AUGUST 19, 1941

[CONTRIBUTION FROM THE MEDICAL-RESEARCH DIVISION, SHARP AND DOHME, INC.]

Sulfonamido Derivatives of Pyrimidines

BY JAMES M. SPRAGUE, L. W. KISSINGER AND ROBERT M. LINCOLN

The substitution of pyridyl and thiazolyl radicals into the N^1 position of sulfanilamide has resulted in compounds of improved therapeutic value. In continuing our study[1] of heterocyclic derivatives of sulfanilamide a number of sulfonamidopyrimidines[2] have been synthesized and a preliminary evaluation of their therapeutic activity in experimental infections has been made.

These compounds are 2- and 4-sulfonamidopyrimidines (Table I) and, in general, were prepared by the reaction of a sulfonyl chloride on 2- or 4-aminopyrimidines. 4-Alkyl or 4,5-dialkyl substituted 2-aminopyrimidines are conveniently prepared, although in low yields, from the reaction of guanidine with α-formyl, or hydroxymethylene ketones which are obtained by the condensation of methyl alkyl ketones with ethyl formate.[3] However, ketones of the type RCH_2COCH_3 may give rise to isomeric formyl derivatives, RCH_2COCH_2CHO I or $RCH(CHO)COCH_3$ II, depending on whether the ethyl formate condenses with the methyl or methylene group.[4] On condensing with guanidine these isomeric formyl derivatives would produce 4-alkyl- and 5-alkyl-4-methyl-2-aminopyrimidines, respectively. Benary[5] has shown that methyl ethyl ketone on condensation with ethyl formate, gives a mixture of the two formyl derivatives, I and II ($R = CH_3$), while methyl *n*-propyl ketone and methylheptenone[6] give only the methyl condensation product (I, $R = C_3H_7$, $(CH_3)_2C{=}CH(CH_2)_2{-}$). Recently, Tracy and Elderfield[7] have shown that, insofar as the structure of pyridine derivatives may be taken as evidence, the formyl methyl ethyl ketone has the structure II ($R = CH_3$) and point out that it is difficult to reconcile this fact with the report[5] that the next higher homolog, methyl *n*-propyl ketone, gives exclusively a formyl derivative of structure I.

Since, in the present study, the formyl derivatives of methyl *n*-propyl and methyl *n*-hexyl ketone were used in the preparation of 4-propyl and 4-*n*-hexyl-2-aminopyrimidine, respectively, it was desirable to prove the structures of these pyrimidines. Proof was obtained in two ways. 2-Amino-4-methyl-5-ethyl- and 2-amino-4-methyl-5-*n*-amylpyrimidine, which would arise if the formyl derivatives of methyl *n*-propyl ketone and methyl *n*-hexyl ketone had structure II, were synthesized from ethyl ethylacetoacetate and ethyl *n*-amylacetoacetate, respectively. These pyrimidines were found to be entirely different from the products derived from the formyl ketones. Further evidence was obtained by the synthesis of 2-amino-4-*n*-hexylpyrimidine from *n*-propyl heptanoylacetate. This product was found to be identical with the pyrimidine obtained from formyl methyl *n*-hexyl ketone. Therefore, from the structure of the aminopyrimidines, it is concluded that the formyl derivatives of methyl *n*-propyl ketone and methyl *n*-hexyl ketone have the structure I resulting from condensation on the methyl group.

Since the conclusion of this work, Caldwell, Kornfeld and Donnell[2b] have reported on the condensation of methyl *n*-hexyl ketone with ethyl formate and the 2-aminopyrimidine derived from the resulting formyl derivative. From the results of a nitric acid oxidation they concluded that the pyrimidine was 2-amino-4-methyl-5-*n*-amylpyrimidine and, therefore, that the formyl methyl *n*-hexyl ketone had the structure II resulting from reaction at the methylene group. This conclusion is not in agreement with our results.

(1) Sprague and Kissinger, THIS JOURNAL, **63**, 578 (1941).

(2) Since this work was started some sulfanilamidopyrimidines have been reported by (a) Roblin, Williams, Winnek and English, *ibid.*, **62**, 2002 (1940), and by (b) Caldwell, Kornfeld and Donnell, *ibid.*, **63**, 2188 (1941).

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

(4) Benary, Meyer and Charisius, *ibid.*, **59**, 108 (1926).

(5) Benary, *ibid.*, **59**, 2198 (1926).

(6) Leser, *Compt. rend.*, **128**, 108, 371 (1899).

(7) Tracy and Elderfield, *J. Org. Chem.*, **6**, 63 (1941).

TABLE I

SULFONAMIDOPYRIMIDINES

( )-Pyrimidine	M. p., °C. (uncor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found	Acetyl derivative M. p., °C. (uncor.)	Acetyl derivative Nitrogen, % Calcd.	Acetyl derivative Nitrogen, % Found
2-Sulfanilamido-[a]	251–252	$C_{10}H_{10}O_2N_4S$	22.39	22.45	12.81	12.86	254–255	19.17	18.74
2-Sulfanilamido-4-methyl-[a]	230–231	$C_{11}H_{12}O_2N_4S$	21.20	21.02	12.13	12.26	245–246	18.29	18.15
2-Sulfanilamido-4,6-dimethyl-[b]	175.5–176.5	$C_{12}H_{14}O_2N_4S$	20.13	20.07	11.52	11.59	240–241.5	17.49	17.48
2-*p*-Nitrobenzenesulfonamido-4-methyl-	260–261	$C_{11}H_{10}O_4N_4S$	19.04	19.09	10.90	11.05	.....	...	...
2-Sulfanilamido-4-methyl-5-bromo-	231–232	$C_{11}H_{11}O_2N_4BrS$	16.33	16.36	...	...	261–262	14.57	14.45
2-Sulfanilamido-4-methyl-5-*n*-amyl-	215–216	$C_{16}H_{22}O_2N_4S$	16.76	16.85	...	...	182–183	14.86	14.94
2-Sulfanilamido-4-*n*-hexyl-	206–207	$C_{16}H_{22}O_2N_4S$	16.76	16.69	9.59	9.70	214–215	14.88	14.90
2-Sulfanilamido-4-*n*-propyl-	217–218	$C_{13}H_{16}O_2N_4S$	19.17	19.20	10.97	11.05	253.5–254	16.76	16.62
2-Sulfanilamido-4-phenyl-	268–269	$C_{16}H_{14}O_2N_4S$	17.15	17.01	9.82	9.72	274–275	15.20	15.15
2-Sulfanilamido-5-methyl-	262–263	$C_{11}H_{12}O_2N_4S$	21.20	21.12	12.13	12.02	271–272	18.29	18.06
2-Sulfanilamido-5-*n*-butyl-	205–206	$C_{14}H_{18}O_2N_4S$	18.29	18.27	10.46	10.49	241–242	16.08	15.98
2-Sulfanilamido-tetrahydrobenzo-[b]	252–253	$C_{14}H_{16}O_2N_4S$	18.41	18.48	10.53	10.41	255–256	16.16	16.02
2-Sulfanilamido-4-methyl-6-ethoxy-[c]	151–152	$C_{13}H_{16}O_3N_4S$	18.18	18.11	...	...	244.5–245[f]	15.99	15.90
2-Sulfanilamido-4-methyl-6-oxy-	253.5–254	$C_{11}H_{12}O_3N_4S$	19.99	19.94	11.44	11.63	.....	...	...
4-Sulfanilamido-2-ethoxy-6-methyl-[d]	186–187	$C_{13}H_{16}O_3N_4S$	18.18	18.11	10.41	10.49	200–201	15.20[g]	15.22
4-Sulfanilamido-2-ethylmercapto-6-methyl-	188–189	$C_{13}H_{16}O_2N_4S_2$	17.28	17.35	...	...	208–209[h]	15.30	15.44
4-*p*-Nitrobenzenesulfonamido-2-ethoxy-[e]	202	$C_{12}H_{12}O_5N_4S$	17.27	17.11					
4-Sulfanilamido-2-ethoxy-[i]	256–257	$C_{12}H_{14}O_3N_4S$	19.03	19.00	...	...	278–279[j]	16.66	16.55

[a] Roblin, Williams, Winnek and English, THIS JOURNAL, **62**, 2002 (1940). [b] Caldwell, Kornfeld and Donnell, *ibid.*, **63**, 2188 (1941). [c] Ethoxy, calcd. 14.61%, found 14.49%, hydrate from dilute alcohol, m. p. 104–105°. [d] Ethoxy, calcd. 14.61%, found 14.60%. [e] Ethoxy, calcd. 13.89%, found 13.63%. [f] Ethoxy, calcd. 12.87%, found 12.93%. [g] Analysis on monohydrate, m. p. 161–162° dec. [h] Also prepared by heating 2-ethylmercapto-4-methyl-6-chloropyrimidine with N^4-acetylsulfanilamide in the presence of anhydrous sodium carbonate and copper powder, *cf.* Phillips, *J. Chem. Soc.*, 9 (1941). [i] Ethoxy, calcd. 15.30%, found 15.36%. [j] Ethoxy, calcd. 13.40%, found 13.31%.

TABLE II

AMINOPYRMIDINES

( )-Pyrimidine	M. p., °C. (uncor.)	Formula	Nitrogen, % Calcd.	Nitrogen, % Found
2-Amino-5-*n*-butyl-4,6-dioxy-	330 dec.[b]	$C_8H_{13}O_2N_3$	22.95	23.04
2-Amino-5-*n*-butyl-4,6-dichloro-	170–171	$C_8H_{11}N_3Cl_2$	19.09	18.96
2-Amino-5-*n*-butyl-	127–128	$C_8H_{13}N_3$	27.81	27.77
2-Amino-4-methyl-5-*n*-amyl-6-oxy-	249–250	$C_{10}H_{17}ON_3$	21.53	21.64
2-Amino-4-methyl-5-*n*-amyl-6-chloro-	151.5–153	$C_{10}H_{16}N_3Cl$	19.67	19.82
2-Amino-4-methyl-5-*n*-amyl-	135–136	$C_{10}H_{17}N_3$	23.44	23.36
2-Amino-4-methyl-5-ethyl-6-oxy-	288–289	$C_7H_{11}ON_3$	24.45	24.21
2-Amino-4-methyl-5-ethyl-6-chloro-	156–157	$C_7H_{10}N_3Cl$	24.49	24.54
2-Amino-4-methyl-5-ethyl-	166–167.5	$C_7H_{11}N_3$	30.65	30.66
2-Amino-4-*n*-hexyl-6-oxy-	199	$C_{10}H_{17}ON_3$	21.53	21.23
2-Amino-4-*n*-hexyl-6-chloro-	61–62.5	$C_{10}H_{16}N_3Cl$	19.67	19.52
2-Amino-4-*n*-hexyl-	93–94	$C_{10}H_{17}N_3$	23.44	23.47
2-Amino-4-ethoxy-6-methyl-	89–90	$C_7H_{11}ON_3$	27.44	27.44
2-Ethoxy-4-amino-[a]	151–152	$C_6H_9ON_3$	30.21	30.18
2-Ethoxy-4-amino-6-methyl-	109–110	$C_7H_{11}ON_3$	27.44	27.50

[a] Ethoxy, calcd. 32.43%, found 32.33%. [b] From dilute acetic acid.

Results of preliminary pharmacological studies indicate that the sulfonamidopyrimidines, in general, exhibit a high order of activity in experimental infection. However, more extensive data will permit an exact, relative evaluation of individual compounds.

Experimental Part[8]

Most of the aminopyrimidines used in this study are recorded in the literature and were prepared by standard methods. The preparations of other aminopyrimidines are described below and the properties and analyses recorded in Table II.

Sulfonamidopyrimidines.—To a solution of the aminopyrimidine in dry pyridine, a slight excess of the required sulfonyl chloride was added slowly and the reaction completed either by warming on a steam-bath at 50–70° for one hour or by allowing to stand at room temperature for fifteen to twenty hours. The excess pyridine was removed under diminished pressure at 50–70°. Water was added to the residue and distilled under reduced pressure. The addition and distillation of water was repeated until the pyridine was completely removed. The products were purified as previously described.[1] The yields were generally 60% or above. The sulfanilamido pyrimidines were obtained from the N^4-acetyl derivatives by alkaline

(8) All melting points are uncorrected. The analyses were carried out, in part, by Mr. John P. Lutz and Mr. John R. Taylor of this Laboratory.

hydrolysis[1] or from the *p*-nitrobenzenesulfonamidopyrimidines by catalytic reduction with platinum oxide.

2-Sulfanilamido-4-methyl-6-oxypyrimidine was obtained by acid hydrolysis[1] of 2-N⁴-acetylsulfanilamido-4-methyl-6-ethoxypyrimidine.

2-Amino-4-*n*-hexylpyrimidine. (A) **From Formyl Methyl *n*-Hexyl Ketone.**—A mixture of 75 g. of dry ethyl formate and 128 g. of freshly distilled methyl *n*-hexyl ketone was added to a well-stirred suspension of 23 g. of powdered sodium in 2 liters of anhydrous ether. The addition required one to two hours and was adjusted so that the ether refluxed vigorously. The reaction mixture was allowed to stand for sixteen to eighteen hours and the sodium salt of the formyl derivative removed by filtration. The dried sodium salt and 90 g. of finely powdered guanidine carbonate were added to 300 cc. of anhydrous alcohol and the mixture shaken on a mechanical shaker for sixteen hours. After standing for forty-eight hours the mixture was filtered and the solid extracted with hot alcohol. The alcohol solutions were combined and distilled to dryness and the residue recrystallized from naphtha or alcohol and water; yield 19.4 g., 11%, m. p. 93–94°.

Under the same conditions methyl *n*-propyl ketone gave a 23% yield of 2-amino-4-*n*-propylpyrimidine (m. p. 124–125°), acetone 37% of 2-amino-4-methylpyrimidine, acetophenone 10% of 2-amino-4-phenylpyrimidine and cyclohexanone 39% of 2-amino-4,5-tetrahydrobenzopyrimidine.

(B) **From *n*-Propyl Heptanoylacetate.**—Thirteen grams of *n*-propyl heptanoylacetate,[9] 4.5 g. of guanidine carbonate and 20 cc. of anhydrous alcohol were heated under reflux for twelve hours at 130–150°. After cooling, the 2-amino-4-*n*-hexyl-6-oxypyrimidine was removed by filtration, dissolved in dilute potassium hydroxide solution and precipitated by acetic acid. Recrystallization from 50% alcohol gave 8.2 g., 84%. Five grams of the purified oxypyrimidine and 25 cc. of phosphorus oxychloride were heated on a steam-bath for five hours. The excess phosphorus oxychloride was removed under reduced pressure and the residue treated with 50 cc. of warm water. After vigorous agitation, the aqueous solution was decanted from insoluble gum and chilled. 2-Amino-4-*n*-hexyl-6-chloropyrimidine was obtained on making the aqueous solution basic with ammonia (yield 2.7 g., 50%, m. p. 60–62°) and was recrystallized from petroleum ether. One and seven-tenths grams of the recrystallized chloropyrimidine in alcohol solution was catalytically dehalogenated with palladium on charcoal catalyst. After removing the alcohol, the residue was treated with water. The insoluble 2-amino-4-*n*-hexylpyrimidine was separated (yield 1.25 g., 87%, m. p. 93–94°) and recrystallized from dilute alcohol, m. p. 93–94°. A mixed melting point with the 2-amino-4-*n*-hexylpyrimidine prepared from the formyl derivative of methyl hexyl ketone showed no depression.

2-Amino-4-methyl-5-*n*-amylpyrimidine.—Ethyl *n*-amylacetoacetate (1.1 moles) and guanidine carbonate (1 mole) were heated together under reflux at 140–160° for seventeen hours. The solid was washed with ether and dissolved in dilute sodium hydroxide. The 2-amino-4-methyl-5-*n*-amyl-6-oxypyrimidine was precipitated from the alkaline solution with acetic acid (yield 45%) and recrystallized from dilute alcohol. The oxypyrimidine was treated with phosphorus oxychloride (5 cc. per gram) on a steam-bath for six hours. The 2-amino-4-methyl-5-*n*-amyl-6-chloropyrimidine was isolated as described for the 2-amino-4-*n*-hexyl-6-chloropyrimidine (yield 47%) and recrystallized from alcohol or benzene. The chloropyrimidine was dehalogenated as previously described in an alcohol–dioxane solution and the 2-amino-4-methyl-5-*n*-amylpyrimidine recrystallized from alcohol or benzene, yield 70%.

2-Amino-4-methyl-5-ethylpyrimidine.—This compound was prepared from ethyl ethylacetoacetate in a manner similar to the corresponding 5-*n*-amyl derivative above. The yields on the three steps were 50–60, 42 and 94%, respectively.

2-Amino-5-*n*-butylpyrimidine.—2-Amino-4,6-dioxy-5-*n*-butylpyrimidine was prepared in a 78% yield from guanidine carbonate and ethyl *n*-butylmalonate with sodium in alcohol according to the standard procedure.[10] The product was purified by repeated solution in dilute alkali and precipitation with acid. The thoroughly dried dioxypyrimidine was refluxed with phosphorus oxychloride (4 cc. per gram) for four hours. Most of the phosphorus oxychloride was removed under reduced pressure and the residue poured into a large volume of cold water with vigorous agitation. The aqueous suspension was made alkaline with ammonia, the 2-amino-4,6-dichloro-5-*n*-butylpyrimidine removed by filtration and recrystallized from alcohol or toluene, yield 30–40%. Catalytic dehalogenation gave 2-amino-5-*n*-butylpyrimidine in 80–90% yield, m. p. 127–128° from naphtha.

2-Amino-5-methylpyrimidine[10] was prepared in a similar manner from ethyl methylmalonate.

Aminoethoxypyrimidines.—These compounds (Table II) were prepared from the corresponding aminochloropyrimidine and 1.25 moles of sodium in alcohol. The reaction mixture was heated gently or allowed to stand several hours at room temperature. After removal of the excess alcohol by distillation at low temperature under reduced pressure, the products were obtained by extraction or sublimation and recrystallized from naphtha or ethyl acetate. The yields were above 50%.

Summary

The synthesis of a number of sulfonamidopyrimidines is described.

The 2-aminopyrimidines derived from the formyl derivatives of methyl *n*-propyl ketone and methyl *n*-hexyl ketone are shown to be 2-amino-4-*n*-propylpyrimidine and 2-amino-4-*n*-hexylpyrimidine, respectively.

GLENOLDEN, PA. RECEIVED AUGUST 21, 1941

(9) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2252 (1941). We are indebted to Dr. V. H. Wallingford of the Research Laboratories of the Mallinckrodt Chemical Works for a supply of this ester.

(10) Gerngross, *Ber.*, **38**, 3399 (1905).