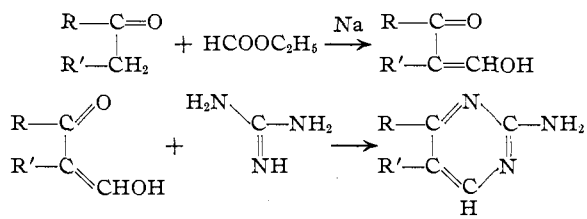
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF TEMPLE UNIVERSITY]

Substituted 2-Sulfanilamidopyrimidines

BY WILLIAM T. CALDWELL, EDMUND C. KORNFELD[1] AND CONARD K. DONNELL[1]

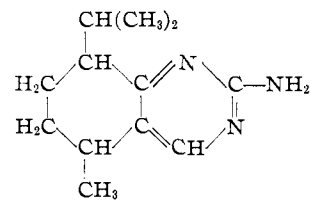
The pharmacological activity and low toxicity of sulfapyrimidine[2] have led us to continue[3] the preparation of a number of higher homologs and related derivatives, some of which we wish to describe at this time. Five of the requisite substituted 2-aminopyrimidines were prepared by refluxing the appropriate hydroxymethylene ketones with guanidine carbonate in alcohol.[4]



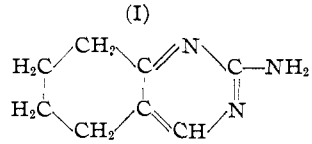
Although the pure hydroxymethylene ketones were not usually isolated, the yield from the Claisen condensation was good in all experiments attempted. On the other hand, yields obtained from the condensations of these hydroxymethylene ketones with guanidine carbonate left something to be desired. Thus, with hydroxymethylene menthone,[5] we obtained a 32% yield of 2-amino-5,6,7,8-tetrahydro-8-isopropyl-5-methylquinazoline (I); with hydroxymethylene cyclohexanone,[6] a 23% yield of 2-amino-5,6,7,8-tetrahydroquinazoline (II); with hydroxymethylene methyl ethyl ketone, a 6.1% yield of 2-amino-4,5-dimethylpyrimidine; finally, with hydroxymethylene cyclopentanone, the amount of 2-amino-4,5-trimethylenepyrimidine (III) formed was unpromisingly small.

The yield of 2-aminobornylenepyrimidine (IV) was increased to 64% (based on the pure hydroxymethylene ketone) by using a continuous water separator while refluxing hydroxymethylene camphor[5] with guanidine carbonate in amyl alcohol.

A new pyrimidine, 2-amino-4-methyl-5-*n*-amylpyrimidine, was prepared from methyl *n*-hexyl ketone in the usual manner in 4.4% yield. When diisopropyl ether was used with a water separator



(I)



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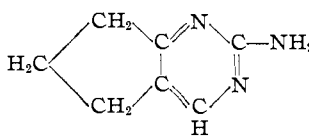

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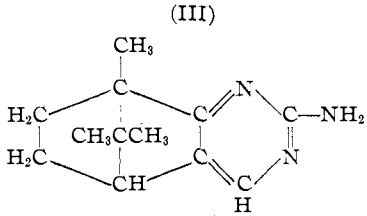
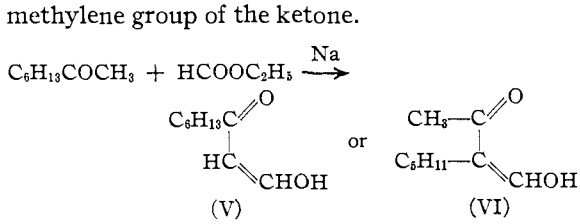


(IV)

in this condensation, a 20% yield of an amine was obtained, but this melted over a wide range and the melting point was not improved on successive recrystallizations.

As in the case of methyl ethyl ketone, two isomers are possible depending on whether the ethyl formate condenses with the methyl or the α-methylene group of the ketone.



Condensation of (V) with guanidine would yield 2-amino-4-*n*-hexylpyrimidine, while (VI) would give 2-amino-4-methyl-5-*n*-amylpyrimidine.

It has been established[7] that ethyl formate reacts with the methylene group of butanone to form a hydroxymethylene ketone; however, with higher homologs such as 2-pentanone[7] and 2-

(1) Submitted in partial fulfillment of the requirements for the degree of Master of Arts.

(2) Roblin, Williams, Winnek and English, THIS JOURNAL, **62**, 2002 (1940).

(3) Caldwell and Kime, *ibid.*, **62**, 2365 (1940).

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

(5) Bishop, Claisen and Sinclair, *Ann.*, **281**, 314 (1894).

(6) Auwers, Buschmann and Heidenreich, *ibid.*, **435**, 296 (1924).

(7) Benary, *Ber.*, **59**, 600 (1926).

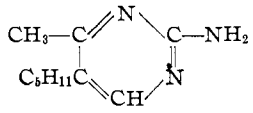
TABLE I

PROPERTIES OF SUBSTITUTED SULFANILAMIDOPYRIMIDINES

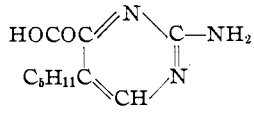
Compound	Water[a] soly. at 29°C.	M. p., °C., corr.	Formula	N Analyses, % Calcd.	Found
2-N^4-Acetylsulfanilamido-5,6,7,8-tetrahydroquinazoline		258–260[c]	$C_{16}H_{18}N_4O_3S$	16.18	16.01
2-Sulfanilamido-5,6,7,8-tetrahydroquinazoline	6.8	255–256[c]	$C_{14}H_{16}N_4O_2S$	18.41	18.40
2-N^4-Acetylsulfanilamido-4,5-dimethylpyrimidine		276–277[b]	$C_{14}H_{16}N_4O_3S$	17.49	17.55
2-Sulfanilamido-4,5-dimethylpyrimidine	20	225.7–226.3[b]	$C_{12}H_{14}N_4O_2S$	20.13	20.09
2-N^4-Acetylsulfanilamidobornylenepyrimidine		261.5–262.0[b]	$C_{20}H_{24}N_4O_3S$	13.99	13.88[e]
2-Sulfanilamidobornylenepyrimidine	3.0	276–277[b]	$C_{18}H_{22}N_4O_2S$	15.63	15.39
2-N^4-Acetylsulfanilamido-4-methyl-5-*n*-amylpyrimidine		208.3–209[c]	$C_{18}H_{24}N_4O_3S$	14.88	14.89
2-Sulfanilamido-4-methyl-5-*n*-amylpyrimidine	2.8	188–190[c]	$C_{16}H_{22}N_4O_2S$	16.75	16.67
2-N^4-Acetylsulfanilamido-5,6,7,8-tetrahydro-8-isopropyl-5-methylquinazoline		227.5–228.5[b]	$C_{20}H_{26}N_4O_3S$	13.92	13.92
2-Sulfanilamido-5,6,7,8-tetrahydro-8-isopropyl-5-methylquinazoline	2.4	185–187[c]	$C_{18}H_{24}N_4O_2S$	15.55	15.58
2-N^4-Acetylsulfanilamido-4,6-dimethylpyrimidine		246.8–247.4[c]	$C_{14}H_{16}N_4O_3S$	17.49	17.26
2-Sulfanilamido-4,6-dimethylpyrimidine	150	178–180[d]	$C_{12}H_{14}N_4O_2S$	20.13	20.03[f]
					20.17

[a] Mg./100 ml. [b] Recrystallized from dioxane–water. [c] Ethanol–water. [d] Water. [e] Dried at 150°. Forms trihydrate from dioxane–water. Calcd. for $C_{18}H_{22}N_4O_2S\cdot 3H_2O$: H_2O, 11.88. Found: 11.60. [f] Calcd. for $C_{12}H_{14}N_4O_2S$: C, 51.78; H, 5.07. Found: C, 51.78; H, 4.83.

methyl-2-heptenone-6[8] it is the methyl group adjoining the carbonyl that reacts. While it seemed probable, therefore, that methyl *n*-hexyl ketone would behave like these higher ketones, our results lead us to believe that it is the α-methylene group which reacts. If position 5 were unsubstituted, nitration should give a nitro derivative; however, we could obtain no such nitro compound, but did get a product whose analysis and chemical properties agreed with the assumption that a methyl group in position 4 had been oxidized to a carboxyl as indicated below



(VII)



(VIII)

The sixth intermediate, 2-amino-4,6-dimethylpyrimidine, was prepared in 78% yield by condensing acetylacetone with guanidine carbonate.[9]

Solubilities in water were determined by weighing the residue obtained by evaporating to dryness a known volume of solution saturated at 29°. All derivatives form somewhat soluble hydrochlorides and easily soluble sodium salts.

Pharmacological tests on these derivatives are being made by Dr. A. E. Livingston and Dr. E. J. Fellows of the Department of Pharmacology, Temple University Medical School. The results will be published in detail elsewhere.

(8) Leser, *Compt. rend.*, **128**, 109 (1900).

(9) Combes and Combes, *Bull. soc. chim.*, [3] **7**, 791 (1900).

Experimental

2-Amino-4-methyl-5-*n*-amylpyrimidine (VII).—A solution of 64 g. (0.5 mole) of methyl *n*-hexyl ketone and 39 g. (0.53 mole) of ethyl formate in 50 ml. of absolute ether was added over a period of two hours, with vigorous mechanical stirring, to 11.5 g. (0.5 mole) of sodium wire in 250 ml. of absolute ether, the temperature being kept at 10–15°. Stirring was continued for four to six hours and the buff-colored, pasty mass was allowed to stand overnight. The sodium salt was extracted with 350 ml. of ice water and the aqueous solution washed with 100 ml. of ether. The free hydroxymethylene ketone separated as an oil on acidification with 30% acetic acid and was extracted with 250 ml. of ether and dried over calcium sulfate.

The ether was distilled off and the red-brown residue was refluxed in 150 ml. of absolute alcohol with 22.5 g. (0.25 mole) of guanidine carbonate for two hours. The solution was diluted with 600 ml. of water, acidified with concentrated hydrochloric acid and extracted with ether to remove unchanged ketone. On addition of aqueous sodium hydroxide, the amine separated as a yellow flocculent precipitate which was dissolved in dilute hydrochloric acid, decolorized, and reprecipitated by addition of sodium hydroxide; yield 4 g. Recrystallization from dilute alcohol yielded colorless prisms, m. p. 92–93°. About one-third of the methyl *n*-hexyl ketone was recovered from the ether extracts.

Anal. Calcd. for $C_{10}H_{17}N_3$: N, 23.44. Found: N, 23.36.

2-Amino-5-*n*-amylpyrimidine-4-carboxylic acid (VIII).—Four grams of the amine (VII) was added slowly with mechanical stirring to 16 ml. of fuming nitric acid (sp. gr. 1.6), and then 16 ml. of concd. sulfuric acid was added dropwise. The temperature was maintained at 0° during both additions, and stirring was continued at that temperature for fifteen minutes. The solution was then poured with stirring into 250 g. of ice and water. Upon

neutralizing exactly with sodium hydroxide, a product was obtained which was soluble, however, in more alkali. This solid was filtered off and washed with water; yield 1 g. After several recrystallizations from dilute alcohol the product melted at 191–192° (dec., cor.).

Anal. Calcd. for $C_{10}H_{18}N_3O_2$: N, 20.09; C, 57.43; H, 7.18. Found: N, 20.14; C, 57.39; H, 8.19.

2-N^4-Acetylsulfanilamidopyrimidines.—The N^4-acetylsulfanilamides were prepared in 67–97% yields by adding a small excess of acetyl sulfanilyl chloride to the aminopyrimidine suspended in dry pyridine, the weight of the latter being equal to that of the total solids. Solution took place with evolution of heat and the reactions were completed by heating at 60° for one-half to one hour. The crude derivatives obtained by pouring the dark solutions into ice water or dilute hydrochloric acid were dissolved in one equivalent of aqueous sodium hydroxide, decolorized, and reprecipitated by addition of excess of hydrochloric acid.

Hydrolysis.—The N^4-acetyl group was hydrolyzed by refluxing 0.5–1.0 molar solutions containing 2.5 equivalents of sodium hydroxide for three hours. The solutions were decolorized and the free amines precipitated by acidification to *p*H 6. Yields of 80–99% were obtained.

Summary

The preparation of six new 2-sulfanilamidopyrimidines and their N^4-acetyl derivatives is reported.

The synthesis of 2-amino-4-methyl-5-*n*-amylpyrimidine is described and evidence for its structure is presented.

PHILADELPHIA, PENNA. RECEIVED APRIL 28, 1941

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

The Preparation of Certain 5-Acetates and 5-Acetamides of 5-Phenylhydantoin[1]

BY BURL G. ROGERS[2] WITH HENRY R. HENZE

Previous attempts in this Laboratory to prepare derivatives of hydantoin possessing valuable physiological activity have been restricted largely to variation in alkyl, alkoxyalkyl, aryl, or aryloxyalkyl groupings attached to the 5-position of the heterocycle. In broadening this investigation to include additional groups, it was with the knowledge that simple aliphatic acids exhibit scarcely any narcotic action and, therefore, the introduction of a carboxyl group into the molecular structure tends to diminish hypnotic effect. However, esterification of the carboxyl group, or conversion of the latter into an amide, restores or increases physiological activity. Hence it seemed desirable to synthesize certain hydantoin derivatives in which ester or amide groupings were present in addition to a phenyl grouping, which, in hydantoins such as Nirvanol and Dilantin, appears to be favorable for hypnotic effect and essential for maximum anticonvulsant activity.

Ethyl 5-Phenyl-5-hydantoinacetate.—A mixture of 19.2 g. of ethyl benzoylacetate[3] with 13 g. of potassium cyanide and 45.5 g. of ammonium carbonate cubes was dissolved in 350 cc. of 60% alcohol and warmed for ten hours at 58–62°. After chilling, the hydantoin derivative was precipitated with hydrochloric acid and on recrystallization from diluted alcohol gave fine white crystals; m. p. 139–140° (cor.) in 60% yield. The action of concentrated ammonium hydroxide solution at room temperature for one week converted this ester into the amide.

5-Phenyl-5-hydantoinacetic Acid.—Twenty grams of the ethyl ester was boiled for three hours with 50 cc. of 20% hydrochloric acid. Recrystallization from water yielded 16.5 g. (87%) of crystalline acid; m. p. 261.5–262.5° (cor.).

Esters of 5-Phenyl-5-hydantoinacetic Acid.—Additional esters were obtained by suspending the acid in an excess of an appropriate alcohol (methyl, *n*-propyl, allyl, benzyl) or ethylene glycol and saturating the mixture with dry hydrogen chloride until complete solution of the acid had occurred. The solution was heated under reflux for two to three hours, the excess alcohol removed by evaporation, and the solid residue was recrystallized from dilute alcohol. The phenyl ester was secured by interaction of the acid chloride and phenol in the presence of pyridine using dry tetrachloroethylene as solvent.

Substituted Amides of 5-Phenyl-5-hydantoinacetic Acid.—Contact of the ethyl ester for ten days at room temperature with a 33% aqueous solution of ethylamine gives rise to the ethyl amide which is insoluble in acetone, dioxane, ethanol, chloroform and benzene, but can be recrystallized from dilute alcohol. Attempts to crystallize the ethyl amide from glacial acetic acid give the hydantoinacetic acid. Attempts to prepare other substituted amides from the ethyl ester and the appropriate amine resulted in failure, but these amides were prepared by converting the hydantoinacetic acid compound into the acid chloride by means of thionyl chloride and by treating the latter, without purification, with 2 equivalents of an amine such as diethylamine, aniline and morpholine. The amides were recrystallized from diluted alcohol and are soluble in acetone and alcohol, but relatively insoluble in water

(1) Presented before the Division of Organic Chemistry at the 99th meeting of The American Chemical Society at Cincinnati, Ohio, April 8–12, 1940.

(2) From the Ph.D. dissertation of B. G. Rogers, June, 1940.

(3) Dorsch and McElvain, THIS JOURNAL, **54**, 2960 (1932).