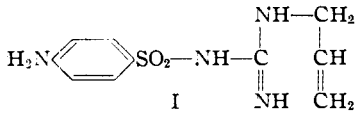
[CONTRIBUTION FROM THE DANIEL SIEFF RESEARCH INSTITUTE]

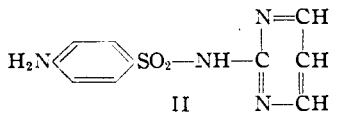
Alkyl Derivatives of Sulfaguanidine

BY FELIX BERGMANN

The resemblance between the formulas of sulfanilylakylisothioureas and sulfathiazole on one hand, and of alkyl substituted sulfaguanidines and sulfadiazine on the other, suggests that in each case the first-named compound may be considered as an open-chain homolog of the second. Thus sulfanilylallylguanidine (I) is probably one of the most interesting members of such an homologous series because of its similarity to sulfadiazine (II).

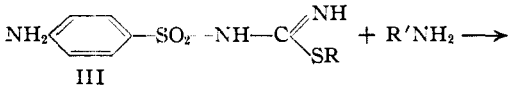


I

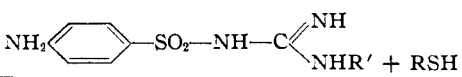


II

Roblin and co-workers[1] have prepared the ethyl, *n*-propyl and *n*-butyl members of the series, and the present paper describes the preparation of the methyl, allyl and benzyl compounds. Identical products were obtained both from the action of acetylsulfanilyl chloride on the free alkylguanidine bases, and by the interaction of N^4-acetylsulfanilylmethylisothiourea and the appropriate alkylamines, thereby suggesting that the alkylguanidines condense by means of their unsubstituted amino group. We have found that the replacement of the RS-group of the isothiourea derivatives by alkylamines can be carried out advantageously as follows, without acetylating the para amino group of sulfanilylisothioureas

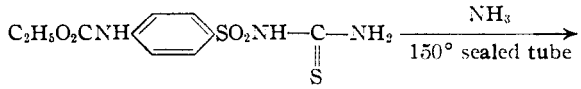


III

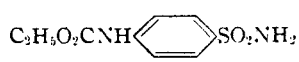


This method gives excellent yields and avoids subsequent deacetylation with hydrochloric acid, as was necessary in the older procedure.[1]

It is surprising to find that ammonia itself does not react appreciably with any of the sulfanilylisothioureas studied. Even under drastic reaction conditions there was obtained only a trace of sulfaguanidine or its acetyl derivative. Wilm and Wischin[2] found that phenylurethan is split into aniline and urea by the action of ammonia at elevated temperatures. It was hoped that the observed resistance of the alkylthio radical to ammonolysis could be utilized in the selective elimination of the carbethoxy group from N^4-carbethoxysulfanilyl-*t*-butylisothiourea[3] to give sulfanilyl-*t*-butylisothiourea (III, R = *t*-butyl). The carbethoxy-*t*-butyl compound was recovered unchanged after heating in a sealed tube with a 15% solution of ammonia in alcohol for six hours at 150°. Under the same conditions, however, N^4-carbethoxysulfanilylthiourea (IV) was converted into N^4-carbethoxysulfanilamide (V) identical with a specimen prepared according to the procedure of Adams, Long and Johanson.[4]



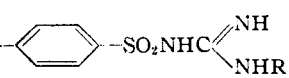
IV



V

This reaction is paralleled by the fission of phenylthiourea into aniline and ammonium isothiocyanate when heated in a sealed tube with ammonia.[5]

TABLE I

PROPERTIES AND ANALYSES OF SULFANILYL-ALKYLGUANIDINES, 

R =	M. p., °C.	Recrystallized from	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
CH_3[a]	170	Ethanol	$C_8H_{12}O_2N_4S \cdot 0.5\ H_2O$	40.5	5.5		40.6	5.5	
C_2H_5	160[1]								
n-C_3H_7	147[1]								
n-C_4H_9	185[1]								
Allyl	155	Ethanol	$C_{10}H_{14}O_2N_4S$	47.2	5.5	22.0	46.9	5.5	22.0
Benzyl[b]	223	Acetic acid	$C_{14}H_{16}O_2N_4S$	55.3	5.3		54.9	5.3	

[a] The acetyl derivative was recrystallized from dilute acetic acid; m. p. 252°. *Anal.* Calcd. for $C_{10}H_{14}O_3N_4S$: C, 44.4; H, 5.2; N, 20.7. Found: C, 44.3; H, 5.0; N, 21.0. [b] In this case, the reactants were dissolved in 50% dioxane.

(1) Winnek, Anderson, Marson, Faith and Roblin, THIS JOURNAL, **64**, 1682 (1942); U. S. Patent 2,301,000.

(2) Wilm and Wischin, *Ann.*, **147**, 157 (1868).

(3) F. Bergmann, THIS JOURNAL, **68**, 761 (1946).

(4) Adams, Long and Johanson, *ibid.*, **61**, 2342 (1939).

(5) de Clermont, *Bull. soc. chim.*, [2] **25**, 242 (1876); *Ber.*, **9**, 446 (1876).

Experimental Details[6]

General Procedure.—Sulfanilyl-methylisothiourea (0.01 mole) and the appropriate amine (0.03 mole) were mixed with water (4 cc.), whereupon usually an exothermic reaction set in and methyl mercaptan was evolved. After standing at room temperature for twenty-four hours, the mixture was heated on a water-bath for one hour. On cooling, the reaction product crystallizes in almost quantitative yield (see Table I). Three of the products are new compounds.

From Table I, it can be seen that in contrast to the homologous series of the isothiourea derivatives,[3] the butyl- and benzyl-sulfaguanidine derivatives show much higher melting points, than would be expected from comparison with the isothiourea derivatives.

N^4-Carbethoxysulfanilamide (V).—N^4-Carbethoxysulfanilylthiourea[3] (1 g.) and 10 cc. of a 15% solution of ammonia in ethanol were heated in a sealed tube for four hours at 150°. On cooling, the reaction product crystallized spontaneously. After two crystallizations from butanol, the substance was obtained as twinned leaflets, m. p. 235–236°; mixed m. p. with N^4-carbethoxysulfanilamide,[4] was 236°. *Anal.* Calcd. for $C_9H_{12}O_4N_2S$: C, 44.3; H, 4.9. Found: C, 44.2; H, 5.1.

(6) With the assistance of Z. Weinberg.

Summary

Aminolysis of sulfanilylalkylisothioureas gives excellent yields of alkylated sulfaguanidines by replacement of the alkylthio group. Three new members of the series have been prepared. Ammonolysis of the isothiourea derivatives, on the other hand, was unsuccessful, and N^4-carbethoxysulfanilyl-A, butylisothiourea was attacked neither on the isothiourea group nor on the ethoxyl by ammonia. N^4-Carbethoxysulfathiourea is split by ammonia to N^4-carbethoxysulfanilamide.

REHOVOTH, PALESTINE RECEIVED MARCH 15, 1945

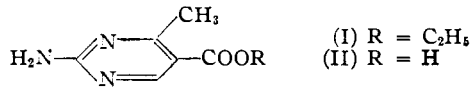
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

An Isomer of Thiamin[1]

BY CHARLES C. PRICE,[2] NELSON J. LEONARD AND ROBERT H. REITSEMA

In order to define further the limits of variation in structure of thiamin type compounds which would permit retention of antineuritic activity, an isomer of thiamin has been prepared in which the positions of the amino and methyl groups on the pyrimidine ring are reversed.

Syntheses of the requisite 2-amino-4-methyl-5-aminomethyl- or halomethylpyrimidine were suggested by the numerous preparations of the pyrimidine portion of thiamin itself. Two of these methods,[3,4] used to produce properly-substituted pyrimidines directly by ring closure, did not appear feasible due to the difficulty of obtaining the necessary dicarbonyl compound. Another approach to the preparation of the desired pyrimidine had been conversion of the ester group of a 5-carbethoxypyrimidine to the nitrile by dehydration of the amide.[5] However, the amide of the readily available 2-amino-4-methyl-5-carbethoxypyrimidine could not be prepared by ammonolysis of the ester (I).



(I) R = C_2H_5
(II) R = H

Unchanged ester was recovered after five days shaking with concentrated ammonium hydroxide at room temperature or after twelve hours heating at 130° with liquid ammonia. Addition of ammonium chloride as a catalyst[6] was of no avail. Hydrolysis to the acid was the main reaction occurring when I was heated at 150° with concentrated ammonium hydroxide, whereas no reaction was observed after heating the ester at 75° for fifteen hours. Intermediate temperatures were used, but in no instance was the desired amide produced in even moderate amounts. The difficulty of preparing amides of 5-carbethoxypyrimidines possessing an adjacent methyl group was also noted by Grewe.[3]

The ester group of ethyl 2-methyl-4-amino-5-pyrimidinecarboxylate has been converted to an aldehyde group by application of a McFadyen–Stevens reaction.[7] An attempted application of this synthesis failed for the isomeric ester (I) since the necessary intermediate in the reaction, the hydrazide of I, could not be prepared.

Further attempts to convert the ester group of I to a hydroxymethyl group by reduction at high temperature and pressure with a copper chromite catalyst resulted in decomposition of the pyrimidine ring. Electrolytic reduction of the corresponding acid II yielded a resin which could not be purified.

Since conversion of the ester group of I to a useful derivative proved impracticable, the corresponding nitrile (IX) has been prepared by the application of the Rosenmund–von Braun nitrile synthesis to 2-amino-4-methyl-5-bromopyrimidine (VI). The latter was obtained by bromination[8] of 2-amino-4-methylpyrimidine (V). The prepa-

(1) The work described in this paper was done in part under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Illinois.

(2) Present address: Department of Chemistry, University of Notre Dame, Notre Dame, Indiana.

(3) Grewe, *Z. physiol. Chem.*, **242**, 89 (1936).

(4) Williams and Cline, THIS JOURNAL, **58**, 1504 (1936).

(5) Todd and Bergel, *J. Chem. Soc.*, 364 (1937).

(6) Fellinger and Audrieth, THIS JOURNAL, **60**, 579 (1938).

(7) Price, May and Pickel, *ibid.*, **62**, 2818 (1940).

(8) Benary, *Ber.*, **63B**, 2601 (1930).