PYRIMIDINE RESEARCH

THE ACTION OF AMINES AND HYDRAZINE ON ETHYL 2-METHYL-MERCAPTO-4-METHYL-PYRIMIDINE-5-CARBOXYLATE* **

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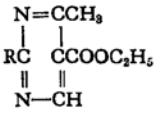
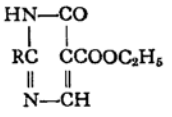
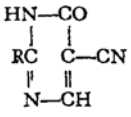
Wheeler, Johnson, and their coworkers[1, 2] condensed ethyl ethoxymethylene-malonate with ethyl psedothiourea to form 2-ethylmercapto15-carbethoxy-6-hydroxy-pyrimidine. Johnson[3] condensed ethyl ethoxymethylene-cyanoacetate with ethyl pseudothiourea to form 2-ethylmercapto-5-cyano-6-hydroxy-pyrimidine. In these two cases, cyclization took place in the carbethoxy group with the elimination of alcohol. Mitter and his coworkers[4, 5] condensed ethyl ethoxymethylene-acetoacetate or ethoxymethylene-acetylacetone with amidines or guanidine to form pyrimidine derivatives represented by formula I ($R=C_6H_5$, $CH_3C_6H_4$, p-$CH_3OC_6H_4$, β-$C_{10}H_7$, or NH_2). Here, cyclization took place at CH_3CO-grouping with the elimination of water. Mitter and Patit [5] condensed ethyl ethoxymethylene-malonate with amidines to form pyrimidine derivatives represented by formula II and condensed ethyl ethyoxymethylene-cyanoacetate with amidines to form pyrimidine derivatives represented by formula III.



I

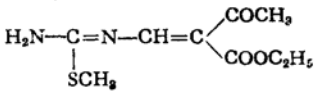


II



III

In this paper is described the experimental condition for the condensation between ethyl ethoxymethylene-acetoacetate and methylpseudothiourea. Claisen[6] described that ethyl ethoxymethylene-acetoacetate reacted with ethanol-ammonia to form ethyl amino-methylene-acetoacetate. Thus, the authors proposed the existence of an intermediate product, (IV), which could



VI

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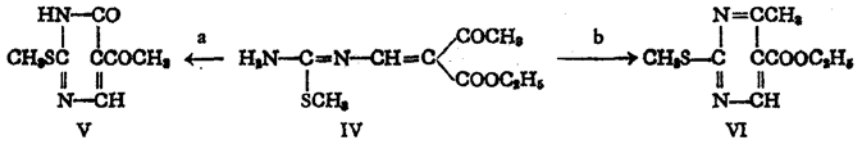
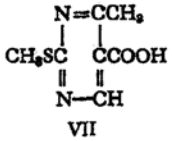
**The data of analyses recorded in this paper were made by Comrades Chou Chang-lin, Pang Shu-kuei and Fan Wen-chi, to whom the authors wish to express their heartiest thanks.

be cyclized in two directions, giving pyrimidine derivatives represented by formulas V and VI:



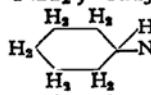
A compound, melting at 53-54°, was isolated in this condensation and recrystallized from anhydrous ethanol in colourless needles. The data of analyses (C, 50.77, 50.43%; H, 5.90, 5.96%) agreed better with ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate (VI) (Calcd.: C, 50.90%; H, 5.70%) than with ethyl methylpseudothiourea-methylene-acetoacetate (IV) (Calcd.: C, 46.92%; H, 6.13%) or 2-methylmercapto-5-acetyl-6-hydroxypyrimidine (V) (Calcd.: C, 45.62%; H, 4.38%). This experimental finding is in harmony with Mitter and his coworkers' work[4, 5] that ethyl ethoxymethylene-acetoacetate reacted with methyl pseudothiourea, giving ethyl methylpseudothiourea-methylene-acetoacetate (IV), which could be cyclised with elimination of water according to the direction (b). The formation of ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate (VI) was further proved by iodoform test, which was negative on short exposure with iodine and alkali at room temperature. However, this compound gave a positive iodoform test, when it was heated on a water bath with iodine and alkali for a somewhat longer time. This phenomenon can be explained as follows: The $COOC_2H_5$ grouping in the compound can be hydrolyzed in the presence of alkali with the liberation of ethyl alcohol, which will give a positive iodoform test.

The structure of compound VI was further substantiated by the following experiment: Ethyl 2-methylmercapto-4-methylpyrimidine-5-carboxylate (VI) was heated with alcoholic potash, when 2-methylmercapto-4-methyl-pyrimidine-5-carboxylic acid (VII), melting at 169-170°, was isolated and recry-



stallized from absolute alcohol in colourless needles. The data of analyses (C, 45.86, 45.71%; H, 4.57, 4.49%) agreed well with compound VII (Calcd.: C, 45.62%; H, 4.38%). Further evidence for supporting the structure of compound VII is as follows: (1) It dissolved in dilute sodium hydrogen carbonate solution with the evolution of carbon dioxide. (2) It gave a distinctly negative iodoform test. (3) Its neutralization equivalent was 193 or 195 (Calcd. 184). (4) Its silver salt reacted with ethyl iodide to give ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate (VI), being identified by its melting point and its mixed melting point.

Ethyl 2-phenyl-4-methyl-pyrimidine-5-carboxylate (I, R=C_6H_5) reacted with hydrazine hydrate in ethanol to form a carbohydrazide. When the ratio of hydrazine hydrate to ethanol was 1:1, the formation of carbohydrazide was smooth on heating on a water bath for one hour. When the ratio of hydrazine hydrate to ethanol was 1:10, the carbohydrazide was not formed, but the original pyrimidine derivative was recovered. Nevertheless, ethyl 2-methyl-mercapto-4-methyl-pyrimidine-5-carboxylate (VI) did not react with hydrazine hydrate in ethanol to form a carbohydrazide, but ethyl 2-hydrazino-4-methyl-pyrimidine-5-carboxylate (I, R=H_2N-NH-). To our surprise is an exceptional finding that the methylmercapto-grouping is so easily replaced by H_2N-NH-grouping in compound VI. It is very probable that the presence of $COOC_2H_5$ grouping at position 5 of the pyrimidine cycle will influence the easy replacement of CH_3S-grouping at position 2 by N_2H-NH-group and the presence of CH_3 grouping at position 4 will retard the formation of a carbohydrazide at position 5 due to steric hindrance. Compound VI reacted with hydrazine hydrate in ethanol at 70—80°. for several minutes to give a sulphur-free compound, which was shown to be ethyl 2-hydrazino-4-methyl-pyrimidine-5-carboxylate (I, R=H_2N-NH-), no carbohydrazide being formed. This finding was substantiated by the following experiment: 2-Methylmercapto-4-hydroxy-pyrimidine reacted with hydrazine hydrate in ethanol for a longer time to form 2-hydrazino-4-hydroxy-pyrimidine.

The replacement of ethylmercapto-grouping in the pyrimidine cycle by amino-grouping at a higher temperature was noticed by various workers[7—10]. Ethyl 2-methyl-mercapto-4-methyl-pyrimidine-5-carboxylate (VI) reacted with ammonia, methylamine, ethylamine, n-butylamine, cyclohexylamine, or benzylamine in ethanol in a sealed tube at 110° or 115-120° to give a sulphur-free compound, which was shown to be 2-amino-pyrimidine and 2-alkyl, aralkyl or cyclohexyl-amino-pyrimidine (I, R=NH_2^-, $CH_3NH_2^-$, C_2H_5NH-, $n-C_4H_9NH-$, $C_6H_5CH_2NH-$, or ); and at the same time, mercaptan was liberated. On the other hand, it did not react with dimethylamine, diethylamine, piperidine, isopropylamine, and aniline even at a higher temperature. Nor did it react with phenylhydrazine in a small volume of ethanol, when the molecular proportion of mercapto-pyrimidine VI to phenylhydrazine was 1:1. Russell and his coworkers[11] found that the limitations to the reaction between 2,4-dithiolpyrimidines and amines appeared to be determined by the steric factors. The authors proposed that the non-reactivity of certain amines, such as dimethyl amine, diethylamine, piperidene, and isopropylamine, toward mercapto-pyrimidine-carboxylic ester VI might be due to steric factors. However, the non-reactivity of aniline toward VI might be due to its aromatic character.

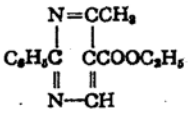
2-Phenyl-4-methyl-pyrimidine-5-carbohydrazide was converted into N,N′-benzenesulphonyl- (2-phenyl-4-methyl-pyrimidine-5-) -carbohydrazide, which

was attempted to be converted into an aldehyde by McFadyen and Stevens' method[12], but in vain.

Ethyl 2-hydrazino-4-methyl-pyrimidine-5-carboxylate (I, R=H_2N-NH-) and 2-phenyl-4-methyl-pyrimidine-5-carbohydrazide were sent out for testing their action as anti-tuberculous compounds.

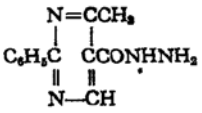
Experimental Part

Ethyl 2-Phenyl-4-methyl-pyrimidine-5-carboxylate,



This compound was prepared according to Mitter and Bardhan's direction[4], m.p. 95—96°; yield, 73%.

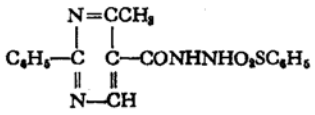
2-Phenyl-4-methyl-pyrimidine-5-carbohydrazide,



Ethyl 2-phenyl-4-methyl-pyrimidine-5-carboxylate (6g) and 70% hydrazine hydrate (10ml) were mixed in ethanol (10ml) and refluxed for one hour. Then, another volume of 50 ml of ethanol was added. On cooling, there crystallized out white needles; m.p. 185—187°. The yield was 4.1 g, or 74% of the theory. It was recrystallized from absolute alcohol in white needles, melting at 185-187°.

Analysis: Calcd. for $C_{12}H_{12}ON_4$: N, 24.56%.
Found: N, 24.42%.

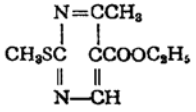
N, N' - Benzenesulphonyl- [2-phenyl-4-methyl-pyrimidine-5-] -Carbohydrazide



2-Phenyl-4-methyl-pyrimidine-5-carbohydrazide (1g) was dissolved in dry pyridine (20 ml), into which was introduced drop by drop benzene-sulphonyl chloride (0.88 g). It was stirred at room temperature for one hour. The solution was treated with ice-water and a little hydrochloric acid, whereupon there separated out a pale yellow solid, m.p. 216-219°. It was recrystallized from 90% ethanol in colourless fibres. It melted at 219-220°. The yield was 1 g. It was proved to contain nitrogen and sulphur by sodium fusion method.

Analysis: Calcd. for $C_{18}H_{16}O_2N_4S$: N, 15.22%.
Found: N, 15.44, 15.50%.

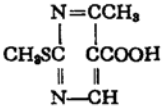
Ethyl 2-Methylmercapto-4-methyl-pyrimidine-5-carboxylate,



Sodium (1.5 g, or 0.05 gram-atom) was dissolved in 100 ml absolute alcohol. To the alcoholic solution containing sodium ethylate, which was cooled to 0°, were added gradually S-methyl pseudothioura sulfate (7g, or 0.025 mole) and ethyl ethoxymethylene-acetoacetate[6], b.p. 120-124°/4mm (9.3 g, or 0.05 mole). It was then refluxed on a water bath for two hours. The solution became reddish and was contaminated with a small quantity of insoluble solid. It was filtered while hot. The filtrate was diluted with water, whereupon there separated methylmercaptopyrimidine-carboxylic ester in colourless needles, m.p. 52-54°. The yield was 8 g, or 75% of the theory. For purification, it was recrystallized from absolute alcohol in colourless needles and melted at 53-54°. It was proved to contain nitrogen and sulphur by sodium fusion method. The compound was easily soluble in ethyl ether and petroleum ether, but not in water. The iodoform test was negative, if the reaction time for this reaction was short. In case the reaction mixture was heated on a water bath and the time for this reaction was longer, the iodoform test would be positive.

Analysis: Calcd. for $C_9H_{12}O_2N_2S$: C,50.90%; H, 5.70%.
Found: C, 50.77, 50.43%; H, 5.90, 5.96%.

2-Methylmercapto-4-methyl-pyrimidine-5-carboxylic acid,



Ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate (1.5 g) was mixed with 15 ml of 0.5 N 95% alcoholic potassium hydroxide. It was refluxed on a water bath for two hours. The solvent was removed from the colourless solution under diminished pressure, and the white residual solid remaining in the flask was dissolved in a small quantity of water and then acidified, when white solids separated out. The yield was lg. It melted at 164—167°. It was recrystallized from absolute alcohol in colourless needles, melting at 169—171°. It was proved to contain nitrogen and sulphur by sodium fusion method. The compound was insoluble in water. It dissolved in dilute sodium hydrogen carbonate solution with the evolution of carbon dioxide. The iodoform test was negative.

Analysis: Calcd. for $C_7H_8O_2N_2S$; C, 45.62%; H, 4.38%.
Found: C, 45.86, 45.71%; H, 4.57, 4.49%.

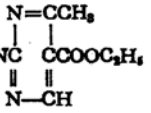
Neutralization equivalent: Calcd,: 184;
Found: 193, 195.

Esterification of -2-methylmercapto-4-methyl-pyrimidine-5-carboxylic acid

2-Methylmercapto-4-methyl-pyrimidine-5-carboxylic acid (0.92 g) was neutralized with 3N ammonium hydroxide and then treated with silver nitrate solution (containing 0.8 g of $AgNO_3$), whereupon there separated out white precipitate. It was filtered and dried in oven. The dried solid was suspended in anhydrous ethanol (5 ml), and then treated with ethyl iodide (3 g). It was refluxed on a water bath for 3 hours. When the insoluble silver iodide was filtered, the filtrate was diluted with water; whereupon there separated out an oil, which was solidified on cooling in an ice-box. It crystallized from anhydrous ethanol in colourless needles, melting at 53—54°. When it was mixed with the product obtained by condensing S-methyl-pseudothiourea sulphate with ethyl ethoxymethylene-acetoacetate in the presence of sodium ethylate in ethyl alcohol, the mixed melting point was not depressed.

The action of Ammonia, Amines and Hydrazine on Ethyl 2-Methylmercapto-4-methyl-pyrimidine-5-carboxylate

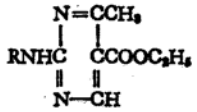
Ethyl 2-Amino-4-methyl-pyrimidine-5-carboxylate,



Ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate (0.5 g) was mixed with ice-cooled, saturated, anhydrous ethyl alcoholic ammonia solution (5 ml) and then heated in a sealed tube at 120°. On cooling, there separated out white needles. The tube was opened, and a strong odour of mercaptan was smelled. The crystalline solid was collected, and it melted at 220—222°. The yield was 0.35 g. For purification, it was crystallized from anhydrous ethanol in white, long, slender needles, melting at 220—220°. Mitter and Palit[5] reported that the compound (being crystallized from ethanol or acetone) melted at 222°. It was proved to contain nitrogen, but not sulphur by sodium fusion method.

Analysis: Calcd. for $C_8H_{11}O_2N_3$; N, 23.21%.
Found: N, 22.79%.

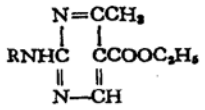
Ethyl 2-Alkylamino-, aralkyl-amino-, or cycloalkylamino-4-methyl pyrimidine-5-carboxylate,

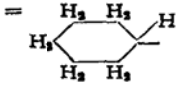


Ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate and various amines were heated in anhydrous ethanol in a sealed tube for several hours. When the tube was opened, there was smelled a strong odour of mercaptane. In some case, the solution was left over in air, when the solvent was removed

Table 1

Experimental Condition for Preparing Various Amino-pyrimidine-carboxylic Esters



(A) R = n-C_4H_9-
(B) R = CH_3-
(C) R = C_2H_5
(D) R = $C_6H_5CH_2$
(E) R = 

Compound	Reactants		Solvent Used in Reaction (ml)	Reaction Temperature (°C)	Solvent Used for Recrystallization	Crystal-form	Yield	
	Ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate g	Various Amines					g	%
A	0.5	n-Butylamine; 1 ml	anhydrous ethanol; 4 ml	115–120°	aq. ethyl alcohol	colourless rods	0.35	62
B	0.5	methylamine; 1 ml	anhydrous ethanol; 5 ml	110°	aq. ethyl alcohol	colourless fine needles	0.20	43
C	0.5	ethylamine; 1.5 ml	anhydrous ethanol; 4 ml	115–120°	anhydrous ethanol	colourless long needles	0.28	56
D	0.5	benzylamine; 1 ml	anhydrous ethanol; 4 ml	115–120°	anhydrous ethanol	colourless needles	0.20	36
E	0.5	Cyclohexylamine; 1.2 ml	anhydrous ethanol; 4 ml	115–120°	aq. ethanol	colourless rods	0.24	40

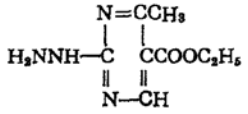
by spontaneous evaporation. The residual semi-solid was treated with ethanol and then recrystallized from the same solvent. In other cases, it was not necessary to evaporate off the solvent, and the required amino-pyrimidine-carboxylic ester separated out in various crystal-form on cooling. They were recrystallized from various suitable solvents, and proved to contain nitrogen but not sulphur by sodium fussion method. The experimental condition for preparing these amino-pyrimidine-carboxylic esters is summarized in Table 1. The empirical formula, the melting point, and the data of analyses are recorded in Table 2.

Table 2

4-Methyl-5-carbethoxy-pyrimidine	Empirical Formula	m. p.	Analyses N%	
			Calcd	Found
2-n-Butylamino-	$C_{12}H_{19}O_2N_3$	71–73°	17.72	17.82, 17.89
2-Methylamino-	$C_9H_{13}O_2N_3$	95–96°	21.54	21.52, 21.07
2-Ethylamino-	$C_{10}H_{15}O_2N_3$	102–104°	20.09	20.16, 20.08
2-Benzylamino-*	$C_{15}H_{17}O_2N_3$	105–106°	15.50	15.50, 15.16
2-Cyclohexylamino-	$C_{14}H_{21}O_2N_3$	111–112°	15.97	16.07, 15.92

*Kenzo Shirokawa, Shoichi Ban, and Masahiko Yoneda[13] reported the melting of the compound (crystallized from ligroin) to be 105—106°.

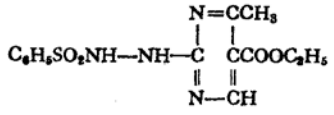
Ethyl 2-Hydrazino-4-methyl-pyrimidine-5-carboxylate



Ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate (1g) was dissolved in anhydrous ethanol (5 ml), into which was introduced 70% hydrazine hydrate (0.5 ml). It was heated on a water bath at 70—80° for 7 minutes, when a strong odour of mercaptan was smelled. On cooling, there separated a voluminous mass of crystalline solid, which was filtered and washed with ether. From the ethereal solution, there was isolated mercapto-pyrimidine-carboxylic ester (80 mg), crystallizing in colourless needles and melting at 52—53°. The dried ether-insoluble solid melted at 170—173°. The yield was 700 mg, or 82% of the theoretical. For purification, it was recrystallized twice from absolute alcohol in colourless needles and melted at 137—174°. It was proved to contain nitrogen, but not sulphur by sodium fusion method.

Analysis: Calcd. for $C_8H_{12}O_2N_4$: N, 28.57%.
Found: N, 28.82, 29.00%.

Ethyl 2-Benzene-sulphonyl-hydrazido-4-methyl-pyrimidine-5-carboxylate,

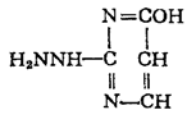


Ethyl 2-hydrazino-4-methyl-pyrimidine-5-carboxylate (2g) was dissolved in dioxan (10 ml) and pyridine (20 ml). To the above solution was introduced drop by drop benzene-sulphonyl chloride (1.3 ml) at room temperature. It was then stirred for 2 hours at ordinary temperature. The solution was treated with hydrochloric acid and ice, when there separated yellowish crystalline solid, which was filtered and dried, m. p. 185—189°. This yield was 1.5 g. It was purified by fractional crystallization from absolute alcohol, and separated out in colourless needles. It melted at 193—194° and was proved to contain nitrogen and sulphur by sodium fusion method.

Analysis: Calcd. for $C_{14}H_{16}O_4N_4S$: N, 16.67%.
Found: N, 16.60, 16.59%.

The easy replacement of methylmercapto-grouping by hydrazino-grouping in ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carbooxylate without formation of 5-carbohydrazide was substantiated by the following experiment: 2-Methylmercapto-4-hydroxy-pyrimidine reacted easily with hydrazine hydrate to form 2-hydrazino-4-hydroxy-pyrimidine.

2-Hydrazino-4-hydroxy-pyrimidine,



2-Methyl-mercapto-4-hydroxy-pyrimidine[1] (1 g) was dissolved in absolute alcohol (10 ml), into which was added 70% hydrazine hydrate (0.5 ml). It was refluxed on a water bath for 3.5 hours. On cooling, there separated crystalline solid from the clear colourless solution, m.p. 192° (with decomposition). The yield was 0.56 g. It was recrystallized from absolute alcohol in white microscopic crystals, melting at 194—195° (with decomposition) and proved to contain nitrogen, but not sulphur by sodium fusion method.

Analysis: Calcd. for $C_4H_6ON_4$; N, 44.45%.
Found: N, 44.14, 44.54%.

Summary

(1) Ethyl ethoxymethylene-acetoacetate condensed with S-methylpseudothiourea sulphate in the presence of sodium ethylate in ethanol to form ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate, which was hydrolyzed by alcoholic potash into its corresponding pyrimidine-5-carboxylic acid.

1) This mereaptopyrimidine was prepared according to Wheeler and Merriam's method. See *Am. Chem. J.* Vol. 29, p. 483 (1902). However, *S*-methylpseudothiourea sulphate instead of S-methylpseudothiourea hydroiodide was condensed with the sodium salt of ethyl formyl-acetate. The authors obtained the compound in white leaflets; m. p. 200°; yield, 50%.

The latter was converted into its silver salt, which was esterified by its action with ethyl iodide, and the proceeding pyrimidine ester was reformed.

(2) Ethyl 2-methylmercapto-4-methyl-pyrimidine-5-carboxylate reacted with hydrazine, ammonia, methylamine, ethylamine, n-butylamine, benzylamine and cyclohexylamine in ethanol, and the corresponding hydrazino-, amino-, alkylamino-, aralkylamino-, and cycloalkyl-amino-derivatives were formed.

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