INVESTIGATION OF NITROGEN- AND SULFUR-CONTAINING HETEROCYCLES

XXV.* REACTION OF 5-AMINO-6-MERCAPTOPYRIMIDINES WITH HALO-β-DIKETONES

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5-Acylamino-6-acylmethylmercaptopyrimidines are formed by reaction of 5-amino-6-mercaptopyrimidines with halo-β-diketones in alkaline media, while 7-acylpyrimido[4,5-b]-[1, 4]thiazines are formed in close-to-neutral media.

In a continuation of the research in [1], we have studied the reaction of 4-chloro-5-methylamino-6-mercaptopyrimidine (I) and 4-methoxy-5-amino-6-mercaptopyrimidine (II) with halo-β-diketones. Compound III with an open structure (A) is formed as the primary product in the reaction of I with α-chloro-α-acetylacetone. It followed from the PMR spectra of III that it exists in the enol form, which is stabilized by an intramolecular hydrogen bond (the spectrum contains the signal of two equivalent CH_3 groups at δ 2.22 ppm and a signal of a $N-CH_3$ group at δ 3.06 ppm, and the signal of a methylidyne proton is absent).

Under the influence of acids, III is readily dehydrated to pyrimidothiazine XIII but forms N-methylacetamide IV in alkaline media. Cyclization of III to XIII is also observed when alcohol solutions of III stand at 18-20°. The structure of IV is confirmed by the presence in the IR spectrum of absorption bands of amide (1675 cm^{-1}) and ketone (1720 cm^{-1}) carbonyl groups and by the PMR spectrum (see Fig. 1). The conversion of III to IV apparently proceeds through an intermediate hydroxyamino compound (D), which is dehydrated to XIII in close-to-neutral media but undergoes destructive changes accompanied by cleavage of the C_6-C_7 bond and the formation of IV under the influence of alkali.

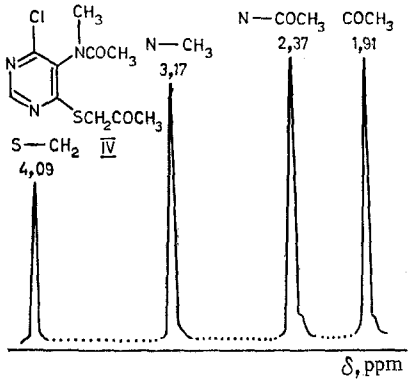
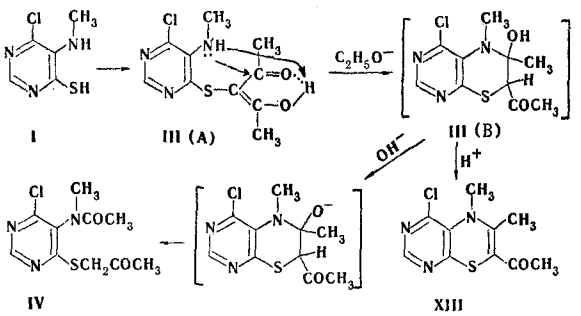


Fig. 1. PMR spectrum of 4-chloro-5-acetylmethylamino-6-acylmethylmercaptopyrimidine (IV).

Similar processes occur in the reaction of II with α-chloro-α-acetylacetone and chlorodibenzoylmethane: pyrimidothiazines XIV and XV are formed in acidic media, while 5-acylamino derivatives V and VI are formed in the presence of alkali. The latter were



*See [4] for communication XXIV.

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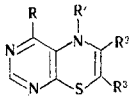
TABLE 1. 5-Acylamino-6-β-ketoalkylmercaptopyrimidines (IV-XII) and 7-Acylpyrimido[4,5-b][1, 4]thiazines (XIII-XVIII)

IV–XII



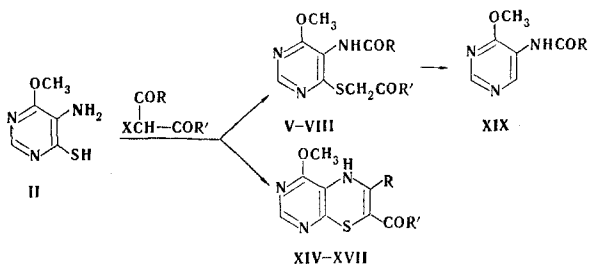
XIII–XVIII

Compound	R	R¹	R²	R³	mp, °C	Empirical formula
IV	Cl	CH_3	CH_3	$COCH_3$	92—94 [a]	$C_{10}H_{12}ClN_3O_2S$ [b]
V	OCH_3	H	CH_3	$COCH_3$	151—152 [c]	$C_{10}H_{13}N_3O_3S$
VI	OCH_3	H	C_6H_5	COC_6H_5	163—164 [d]	$C_{20}H_{17}N_3O_3S$
VII	OCH_3	H	CH_3	COC_2H_5	131—132 [e]	$C_{11}H_{15}N_3O_3S$
VIII	OCH_3	H	CH_3	COC_6H_5	158—160 [e]	$C_{15}H_{15}N_3O_3S$
IX	OCH_3	H	CH_3	C(=N—NHCONH$_2$)—CH_3	218—219 [f]	$C_{11}H_{16}N_6O_3S$
X	OCH_3	H	CH_3	C(=N—NHCONH$_2$)—C_6H_5	240—241 [f]	$C_{16}H_{18}N_6O_3S$
XI	OCH_3	H	CH_3	C(=NOH)—CH_3	172—174 [f]	$C_{10}H_{14}N_4O_3S$
XII	OCH_3	H	CH_3	C(=NOH)—C_6H_5	176—177 [d]	$C_{15}H_{16}N_4O_3S$
XIII	Cl	CH_3	CH_3	$COCH_3$	132—134 [a]	$C_{10}H_{10}ClN_3OS$ [g]
XIV	OCH_3	H	CH_3	$COCH_3$	162—163 [d]	$C_{10}H_{11}N_3O_2S$
XV	OCH_3	H	C_6H_5	COC_6H_5	164—165 [d]	$C_{20}H_{15}N_3O_2S$
XVI	OCH_3	H	CH_3	COC_2H_5	115—117 [d]	$C_{11}H_{13}N_3O_2S$
XVII	OCH_3	H	CH_3	COC_6H_5	193—195 [d]	$C_{15}H_{13}N_3O_2S$
XVIII	OCH_3	H	CH_3	C(=NOH)—CH_3	161—162 [d]	$C_{10}H_{12}N_4O_2S$

TABLE 1 (continued)

Compound	Found, %				Calc., %				Yield, %
	C	H	N	S	C	H	N	S	
IV	44,2	4,6	15,3	11,5	43,9	4,4	15,3	11,7	39
V	47,0	5,4	16,7	12,5	47,0	5,1	16,5	12,6	71
VI	63,6	4,6	10,8	8,4	63,3	4,5	11,1	8,4	58
VII	49,3	5,8	15,2	12,0	49,1	5,6	15,6	11,9	71
VIII	56,5	4,7	13,2	10,3	56,7	4,7	13,2	10,1	55
IX	42,5	5,0	26,9	10,1	42,3	5,1	26,9	10,3	73
X	51,3	4,8	22,8	8,6	51,3	4,8	22,5	8,6	87
XI	44,7	5,3	20,5	11,9	44,4	5,2	20,7	11,7	95
XII	53,9	4,7	16,5	9,6	54,2	4,8	16,8	9,6	83
XIII	46,7	4,1	16,3	12,6	46,9	3,9	16,4	12,5	43
XIV	50,8	4,7	17,9	13,6	50,6	4,7	17,7	13,5	79
XV	66,7	4,4	11,9	8,6	66,5	4,2	11,6	8,9	61
XVI	52,9	5,0	16,7	12,9	52,6	5,2	16,7	12,8	56
XVII	60,4	4,4	14,0	10,6	60,2	4.4	14,0	10,7	65
XVIII	47,6	4,7	21,8	12,7	47,6	4,8	22,2	12,7	61

[a] From ether. [b] Found: Cl 12.6%. Calculated: Cl 12.9%. [c] From alcohol. [d] From benzene. [e] From ethyl acetate. [f] From methanol. [g] Found: Cl 14.0%. Calculated: Cl 13.9%.



II

V–VIII

XIX

XIV–XVII

V, XIV R=R′=CH_3; VI, XV R=R′=C_6H_5; VII, XVI R=CH_3, R′=C_2H_5; VIII, XVII R=CH_3, R′=C_6H_5

characterized by their semicarbazones and oximes. The corresponding oxime (XVIII) was also obtained from pyrimidothiazine XIV.

The structures of V, VI, and pyrimidothiazines XIV-XVII were confirmed by spectral data, and their individuality was confirmed by chromatography in a thin layer of adsorbent. Thus the IR spectra of V and VI contain amide CO and NH absorption bands (1675, 1645 and 3280, 3230 cm^{-1}) and ketone CO bands (1730, 1680 cm^{-1}), while the spectra of XIV-XVII contain bands of NH (3420 cm^{-1}) and CO (1660 cm^{-1}) groups.

In examining the reaction of 5-amino-6-mercaptopyrimidines I and II with halo-β-dicarbonyl compounds, one cannot disregard another possible path for the cyclization of S-β-ketoalkyl derivatives (A) – through the formation of an enol form and subsequent dehydration of the latter. This direction might be realized particularly readily in the case of β-diketones, since enolization of these compounds leads, as is well known, to the formation of an energically favorable chelate form. However, in our investigation of the reaction of II with unsymmetrical halo-β-diketones, we noted that the CO group that primarily reacts with the NH_2 group in the 5 position is that group which is more inclined to undergo enolization. Thus it was shown that 5-acetamido-6-propionyl- or 6-benzoylmethylmercaptopyrimidines (VII, VIII) are formed in high yields in the reaction of II with 1-chloro-1-propionyl- and 1-chloro-1-benzoylacetones in the presence of 1 mole of KOH. The presence in VII and VIII of an acetyl rather than a propionyl (or benzoyl) group attached to the exocyclic nitrogen atom was proved by desulfuration of VII and VIII to the known 4-methoxy-5-acetamidopyrimidine (XIX).

The results are evidence in favor of the preferred reaction of I and II with halo-β-diketones at the unenolized carbonyl group; this is confirmed by the literature data [2, 3].

EXPERIMENTAL

The IR spectra of mineral oil suspensions were recorded with a UR-10 spectrophotometer, and the PMR spectra were recorded with an IN-4H-100 Hz spectrometer with tetramethylsilane as the internal standard.

4-Chloro-5-methylamino-6-diacetylmethylmercaptopyrimidine (III) and 4-Chloro-5-acetylmethylamino-6-acylmethylmercaptopyrimidine (IV). A solution of 0.39 g (2.86 mmole) of α-chloro-α-acetylacetone in 3-5 ml of methanol was added to a solution of 0.5 g (2.86 mmole) of I in 10 ml of methanol containing 0.16 g of KOH, and the mixture was stirred at −10 to −8° for 5 h and allowed to stand at −5° for 20 h. The precipitate was removed by filtration, washed with water, and dried to give 0.2 g (39%) of III with mp 96-97° (from ether). Found: C 43.7; H 4.6; Cl 13.3; N 15.2; S 11.9%. $C_{10}H_{12}ClN_3O_2S$. Calculated: C 43.9; H 4.4 Cl 13.0; N 15.3; S H.9%.

The filtrate was evaporated, 5 ml of water was added to the residual oil, and the mixture was allowed to stand at 0° for 2 days. The precipitate was removed by filtration to give 0.2 g of IV. Compound IV was also obtained by the action of alcoholic alkali on III.

4-Chloro-5-N-methyl-6-methyl-7-acetylpyrimido[4,5-b][1,4]thiazine (XIII). A solution of 0.35 g of III in 30 ml of ether containing one drop of an alcoholic hydrogen chloride solution was allowed to stand at 20° for 24 h. The yellow precipitate was removed by filtration to give 0.14 g of XIII. PMR spectrum in $CDCl_3$, ppm: 2.36 (CH_3), 2.44 ($COCH_3$), 3.41 ($N-CH_3$).

4-Methoxy-5-acetamido-6-acylmethylmercaptopyrimidine (V). A solution of 0.86 g (6.46 mmole) of α-chloro-α-acetylacetone in 5 ml of alcohol was added to a solution of 1 g (6.46 mmole) of II in 30 ml of alcohol containing 0.4 g of KOH at 5°, and the mixture was stirred at 20° for 5 h and allowed to stand overnight. It was then filtered, and the filtrate was vacuum evaporated. Water (20 ml) was added to the residue, and the mixture was allowed to stand at 5° for 24 h. The precipitate was removed by filtration to give 1.15 g of V.

Compounds VI-VIII were similarly obtained.

4-Methoxy-5-acetamido-6-acylmethylmercaptopyrimidine Semicarbazone (IX). A solution of 0.18 g (0.705 mmole) of V, 0.08 g (0.705 mmole) of semicarbazide hydrochloride, and 0.06 g (0.705 mmole) of sodium acetate in a mixture of 15 ml of alcohol and 5 ml of water was stirred at 20° for 1.5 h. The precipitate was removed by filtration and washed with water to give 0.16 g of IX.

Compound X was similarly obtained.

4-Methoxy-5-acetamido-6-acylmethylmercaptopyrimidine Oxime (XI). A solution of 0.6 g (2.35 mmole) of V, 0.17 g (2.35 mmole) of hydroxylamine hydrochloride, and 0.2 g (2.35 mmole) of sodium acetate in a mixture of 30 ml of alcohol and 10 ml of water was stirred for 6 h, after which the solvent was removed by

distillation, 10 ml of water was added to the residue, and the precipitate was removed by filtration to give 0.6 g of XI. Compound XII was similarly obtained.

4-Methoxy-6-methyl-7-acetylpyrimido[4,5-b][1,4]thiazine (XIV). A solution of 0.86 g (6.46 mmole) of α-chloro-α-acetylacetone in 5 ml of alcohol and two drops of concentrated HCl were added to a solution of 1 g (6.46 mmole) of II in 20 ml of alcohol containing 0.4 g of KOH at 0°, and the mixture was stirred for 6 h. The precipitate was removed by filtration and washed with water to give 0.9 g of product. Another 0.29 g of XIV was obtained from the filtrate. Compounds XV-XVII were similarly obtained.

4-Methoxy-6-methyl-7-acetylpyrimido[4,5-b][1,4]thiazine Oxime (XVIII). This compound was obtained in the same way as XI by heating at 70-75° for 12 h.

4-Methoxy-5-acetamidopyrimidine (XIX). A mixture of 0.5 g of VII or VIII, 5 g of Raney nickel, and 20 ml of absolute alcohol was refluxed for 5 h and filtered. The solvent was removed from the filtrate by distillation to give 0.23 g of XIX. No melting-point depression was observed for a mixture of this product with a genuine sample.

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