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Synthesis of Pyridinylketones, and Their Cyclic Derivatives Produced from 6-Methyl-2-thiouracil

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Abstract—A possibility to obtain pyrimidines, containing oxoalkyl moiety in 2 position of the ring from the available 6-methyl-2-thiouracil was shown.

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The known approach to pyrimidines containing keto group in the 2 position are limited to the use of 2-alkyl- and 2-benzylpyrimidines as the starting compounds. Thus, the nitrosation of 2-benzylpyrimidine followed by the hydrolysis of the formed oxime affords 2-benzoylpyrimidines [1, 2]. The formation of 1,4-dimethyl-2-phenacylpyrimidin-6-one via the benzylation of active methyl group of 1,2,4-trimethylpyrimidin-6-one with benzoic acid ester in an alkaline medium as well as the reaction of 1,4-dimethyl-6-oxopyrimidine-2-carbonitrile with acetophenone sodium salt was reported in [3].

A method based on the desulfurization of the alkylation product of 6-methyl-2-thiouracil **I** by the action of α-bromoketones was suggested as promising for the synthesis of the discussed compounds. The reaction of uracil **I** with 2-bromodimedone in alkaline medium was found to give 5,5-dimethyl-2-(6-methyl-4-oxo-3,4-dihydropyrimidin-2(1*H*)-ylidene)cyclohexane-1,3-dione **II**.

As a rule, similar transformations leading to the formation of a carbon-carbon bond owing to the sulfur release from α-azomethine-β-oxoalkyl sulfides require rigid conditions, for example, prolonged heating and the use of trivalent phosphorus compounds that promote desulfurization [4–6].

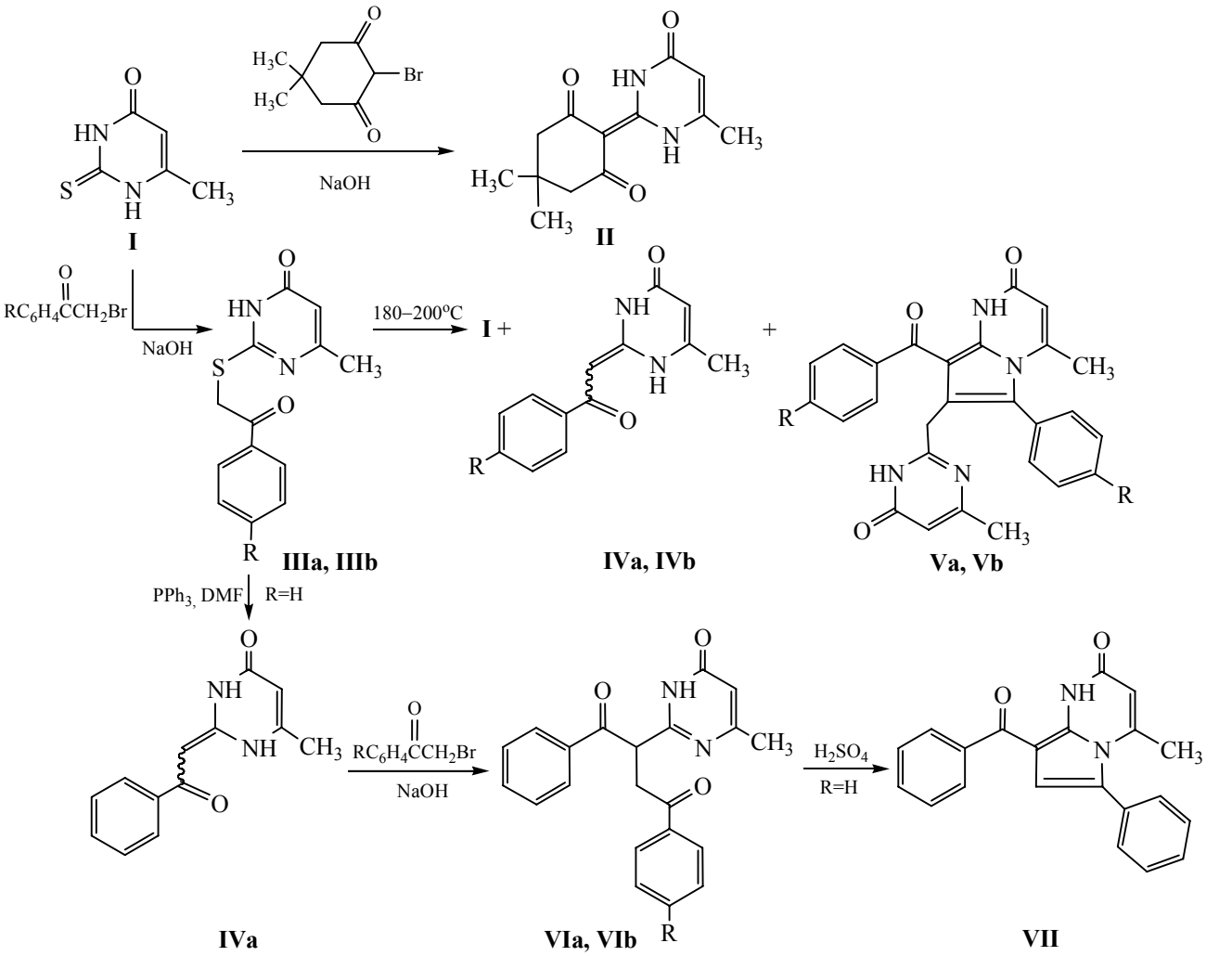
2-Phenacylthiopyrimidines **III**, the products of thiouracil **I** *S*-alkylation with phenacyl bromide [7], were found to be much more stable. Refluxing compounds **III** in dioxane, pyridine, acetic acid, and dimethylformamide did not result in the desulfurization products.

The main component of the product mixture obtained after short-term heating of pyrymidines **III** to 180–200°C is uracil **I.** Also the corresponding 2-phenacylpyrimidines **IVa** (12%) and **IVb** (9%) and pyrrol [1,2-a]pyrymidine derivatives **Va** (21%) and **Vb** (16%) were isolated. Desulfurization of 2-phenacylthiopyrimidine **IIIa** was carried under the continuous reflux of compound **IIIa** in DMF in the presence of triphenylphosphine to give 2-phenacylpyrimidine **IVa** in a high yield.

The absence of the methylene signals in the ^{1}H NMR spectrum of pyrimidines **IVa**, **IVb** and the appearance of the singlet signals of amine and methine protons indicate the enamine structure of these compounds (see the table).

In addition, the doubling of the signals of pyrimidine ring and protons of the substituents indicates the presence of pyrimidines **IV** in a solution as *Z,E*-isomers mixture (1:1).

Compound **IVa** reacts with phenacyl bromides in an alkaline medium involving the exocyclic methine group. In contrast to the initial enaminone **IVa**, the obtained diketones **VIa** and **VIb** are in a keto-imine tautomeric form. According to the ^{1}H NMR data (see the table), they contain a CH–CH_2 fragment with a chiral methine carbon atom and nonequivalent methylene protons.



R = H (**a**), Br (**b**).

Diketone **VIa** is readily dehydrated with sulfuric acid to form pyrrole **VII**.

EXPERIMENTAL

The starting 6-methyl-2-thiouracil **I** and 2-phenacylthiopyrimidines **IIIa**, **IIIb** were obtained according to the procedures [8] and [7] respectively. ω-Bromoacetophenone was obtained according to [9] and 2-bromodimedone, according to [10]. The standard laboratory techniques were used to purify and dry organic solvents and reagents [11]. The preparative separation of compounds **IVa**, **IVb** and **Va**, **Vb** was carried out by chromatography on a silica gel column (100–250 mesh, Merck). TLC analysis was performed on Silufol UV-254-VIS plates eluting with chloroform–acetonitrile (5:1 and 1:1) mixture.

The mass spectra were obtained on a MX 1321 mass spectrometer using a system of direct admission of the sample in an electron ionization mode (70 eV), the ion source temperature 220°C. The ^{1}H NMR spectra were registered on a Varian WXP-300 spectrometer in DMSO-d_6 and $CDCl_3$ at operating frequency 299.95 MHz relative to internal TMS.

5,5-Dimethyl-2-[6-methyl-4-oxo-3,4-dihydropyrimidin-2(1*H*)-ylidene]-cyclohexan-1,3-dione (II). A mixture of 0.7 g of 2-thiouracil **I** and 0.2 g of NaOH was dissolved in 12 ml of 50% aqueous dioxane. The resulting solution was added dropwise to a solution of 1.1 g of 2-bromodimedone in 10 ml of dioxane with vigorous stirring at 50–60°C. The reaction mixture was chromatographed and evaporated at a reduced pressure. The residue was diluted with cold water,

Parameters of the ^{1}H NMR (DMSO-d_6) and mass spectra for compounds **II**, **IV**–**VII**

Comp. no.	Mass-spectrum, m/z (I_{rel}, %)	^{1}H NMR (DMSO-d_6) spectrum, δ, ppm
II	248(100), 233(5), 220(10), 205(6), 192(9), 179(8), 164(27), 151(74)	14.16 s (1H, NH), 13.84 s (1H, NH), 6.03 s (1H, CH), 6.41 s (4H, CH_2), 2.30 s (3H, CH_3), 1.00 s (6H, CH_3)
IVa	228(39), 200(18), 151(37), 105 (100), 84(32), 77(90)	14.40 s (1H, NH), 11.74 s (1H, NH), 7.65–7.47 m (5H, CH_{arom}), 5.80 s (1H, CH), 5.66 s (1H, CH), 2.23–2.15 m (3H, CH_3)
IVb	308(30), 306(33), 280(8), 278(10), 185(98), 183(100), 157(37), 155 (39), 151(90), 84(95)	14.27 s (1H, NH), 11.80 s (1H, NH), 7.70 m (4H, CH_{arom}), 5.76 s (1H, CH), 5.67 s (1H, CH), 2.23 s (3H, CH_3)
Va	450(64), 432(8), 345(38), 341(280), 262(7), 235(29), 105(100), 8(14), 77(52)	11.50 s (2H, 2NH), 7.56–7.20 m (10H, CH_{arom}), 5.85 s (1H, CH), 5.58 s (1H, CH), 3.40 s (2H, CH_2), 2.36 s (3H, CH_3), 1.98 s (3H, CH_3)
Vb[a]	608(26), 590(10), 562(9), 423(16), 183(100), 155(28)	11.56 br.s (1H, NH), 10.98 s (1H, NH), 7.46–7.16 m (8H, CH_{arom}), 5.87 s (1H, CH), 5.67 s (1H, CH), 3.59 s (2H, CH_2), 2.37 s (3H, CH_3), 2.10 s (3H, CH_3)
VIa	346(4), 318(2), 241(50), 224(6), 105 (100), 77(35)	12.60 br.s (1H, NH), 8.03–7.54 m (10H, CH_{arom}), 6.05 s (1H, CH), 5.28 d.d (1H, C<u>H</u>CH_2, *J* 8.1, *J* 5.1 Hz), 3.91 d.d (1H, CHC<u>H</u>$_2$, *J* 19.2, *J* 8.1 Hz), 3.71 d.d (1H, CHC<u>H</u>$_2$, *J* 19.2, *J* 5.1 Hz), 2.02 s (3H, CH_3)
VIb	425(2), 397(1), 320(2), 302(3), 241 (53), 213(16), 185(7), 157(5), 105 (100), 77(33)	12.64 br.s (1H, NH), 8.03–7.53 m (9H, CH_{arom}), 6.06 s (1H, CH), 5.27 d.d (1H, C<u>H</u>CH_2, *J* 8.1, *J* 5.1 Hz), 3.96 d.d (1H, CHC<u>H</u>$_2$, *J* 19.2, *J* 8.1 Hz), 3.72 d.d (1H, CHC<u>H</u>$_2$, *J* 19.2, *J* 5.1 Hz), 2.01 s (3H, CH_3)
VII	328(73), 105(100), 77(22)	12.55 br.s (1H, NH), 7.86–7.41 m (11H, CH_{arom}), 6.20 s (1H, CH), 2.22 s (3H, CH_3)

[a] ^{1}H NMR spectra were taken in $CDCl_3$ solution.

filtered off, dried, and crystallized from ethanol. Yield 0.7 g (57%), mp 186°C. Found, %: C 62.81; H 6.57; N 11.21. $C_{13}H_{16}N_2O_3$. Calculated, %: C 62.89; H 6.50; N 11.28.

Thermolysis of 6-methyl-2-(2-oxo-2-phenylethylthio)pyrimidin-4(3*H*)-one (IIIa). Compound **IIIa** (2.6 g) was heated with stirring at 180–200°C to form a melt, followed by its solidification. The cooled mass was extracted with chloroform, undissolved residue was filtered off, washed with chloroform to discoloration, and dried on air. Yield 0.63 g (44%). Chloroform was evaporated at a reduced pressure. The residue was purified by column chromatography (eluent chloroform) to give **(*E,Z*)-6-methyl-2-(2-oxo-2-phenylethylidene)-2,3-dyhydropyrimidin-4(1*H*)-one (IVa).** Yield 0.26 g (12%), mp 250–252°C. Found, %: C 68.48, H 5.36; N 12.21. $C_{13}H_{12}N_2O_2$. Calculated, %: C 68.41, H 5.30; N 12.27. When chloroform–acetonitrile mixture (1:1) was used as eluent, **8-benzoyl-4-methyl-7-[(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)methyl]-6-phenylpyrrole[1,2-*a*]pyrimidin-2(1*H*)-one (Va)** was obtained. Yield 0.32 g (21%), mp 168–170°C. Found, %: C 72.11; H 5.12; N 12.37. $C_{27}H_{22}N_4O_3$. Calculated, %: 71.99; H 4.92; N 12.44.

Thermolysis of 2-[2-(4-bromophenyl)-2-oxoethylthio]-6-methylpyrimidin-4(3*H*)-one (IIIb) was similarly carried out using 3.38 g of compound **IIIb** to obtain **thiouracil I** (0.67 g, 47%) and **(*E,Z*)-2-[2-(4-bromophenyl)-2-oxoethylidene]-6-methyl-2,3-dihydropyrimidin-4(1*H*)-one (IVb)** [0.28 g (9%), mp 168–170°C. Found, %: C 68.48, H 5.36; N 12.21. $C_{13}H_{11}BrN_2O_2$. Calculated, %: C 50.84, H 3.61; N 9.12.

8-(4-Bromobenzoyl)-6-(4-bromophenyl)-4-methyl-7-[(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)methyl]-pirrole[1,2-*a*]pyrimidin-2(1*H*)-one (Vb). Yield 0.98 g (16%), mp > 220ºC (decomp.) Found, %: C 53.22; H 3.34; N 9.14. $C_{27}H_{20}Br_2N_4O_3$. Calculated, %: C 53.29; H 3.29; N 9.21.

(*E,Z*)-6-Methyl-2-(2-oxo-2-phenylethylidene)-2,3-dihydropyrimidin-4(1*H*)-one (IVa). A mixture of 0.5 g of compound **IIIa** in 25 ml of DMF and 0.5 g of PPh_3 was refluxed for 6 h. After cooling the mixture was poured into 100 ml of water. The resulting precipitate was filtered off, dried, and washed with hot benzene to remove the phosphorus compounds. The residue was crystallized from ethanol. Yield 0.34 g (86%), mp 250–252°C. Found, %: C 68.48; H 5.36; N 12.21. $C_{13}H_{12}N_2O_2$. Calculated, %: C 68.41; H 5.30; N 12.27.

2-(4-Methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-1,4-diphenylbutane-1,4-dione (VIa). A mixture of 2.3 g compound **IVa** and 0.4 g of NaOH was dissolved in a minimal amount of 50% aqueous dioxane. To the

solution was added in small portions 2 g of phenacyl bromide in 7 ml of dioxane while stirring at 60°C, and then the obtained mixture was kept at this temperature for 30 min. The solvents were distilled off at a the reduced pressure, the residue was stirred with cold water until the reaction mass solidifies. The resulting precipitate was filtered off, dried in air, and dissolved in benzene. The unreacted **IVa** was filtered off, and benzene was distilled off at a reduced pressure. The solid residue was crystallized from ethanol. Yield 1.6 g (46%), mp 185–190°C. Found, %: C 72.80; H 5.20; N 7.95. $C_{21}H_{18}N_2O_3$. Calculated, %: C 72.82; H 5.24; N 8.09.

4-[4-Bromophenyl-2-(4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)-1-phenylbutan-1,4-dione (VIb) was obtained similarly from 2.28 g of compound **IVa**. Yield 1.7 g (41%), mp 170–175°C. Found, %: C 59.27; H 4.00; N 6.55. $C_{21}H_{17}BrN_2O_3$. Calculated, %: C 59.31; H 4.03; N 6.59.

8-Benzoyl-4-methyl-6-phenylpyrrole[1,2-*a*]pyrimidin-2(1*H*)-one (VII). A solution of 0.35 g of compound **VIa** in a minimal amount of sulfuric acid was kept for 3 days at 10–15°C. The reaction mixture was diluted with water, the precipitate was filtered off, washed with water, and neutralized with sodium acetate. To the resulting solution was added acetic acid to complete precipitation of the product. The precipitate was filtered off, washed with water, and crystallized from alcohol. Yield 0.25 g (74%), mp > 300°C. Found, %: C 76.80; H 4.90; N 8.50. $C_{21}H_{16}N_2O_2$. Calculated, %: C 76.86; H 4.91; N 8.53.

REFERENCES

1. Kato, T., Yamanaka, H., and Hiranuma, H., *Yakugaku Zasshi,* 1970, vol. 90, p. 877.
2. Sakamoto, T., Konno, S., and Yamanaka, H. *Heterocycles,* 1977, vol. 6, no. 9–10, p. 1616.
3. Yamanaka, H., Abe, H., Hiranuma, H., and Sakamoto, T., *Chem. Pharm. Bull.* 1978, vol. 26, p. 842.
4. Roth, M., Dubs, P., Gotschi, E., and Eschenmoser, A., *Helv. Chim. Acta,* 1971, vol. 54, p. 710.
5. Eschenmoser, A. *Pure Appl. Chem.,* 1973, vol. 33, p. 69.
6. Grishchuk, L.V., Ivanov, E.I., Zubatyuk, R.I., Shishkin, O.V., Ivanova R.Yu., and Rakipov, I.M. *Ukr. Khim. Zh.,* 2004, vol. 70, no. 12, p. 95.
7. *Beilsteins Handbuch der Organischen Chemie*, Berlin: Springer, 1936, Bd 25, S. 463.
8. Busev, A.I., *Sintez novykh organicheskikh reagentov dlya neorganicheskogo analiza* (Synthesis of New Organic Reagents for Inorganic Analysis), Moscow: Mosk. Gos. Univ., 1972, p. 115.
9. Langley, W.D., *Org. Synth.,* 1929, vol. 9, p. 20.
10. Vorländer, D. and Kohlman, M., *Lieb. Ann.,* 1902, vol. 322, p. 248.
11. Gordon, A.J. and Ford, R.A., *The Chemist's Companion. A Handbook of Practical Data, Techniques and References*, New York: Wiley, 1972.