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Cycloacylation of *N*-Phenyl-3-oxobutanethioamide with 3-Aryl-2-propenoyl Chlorides

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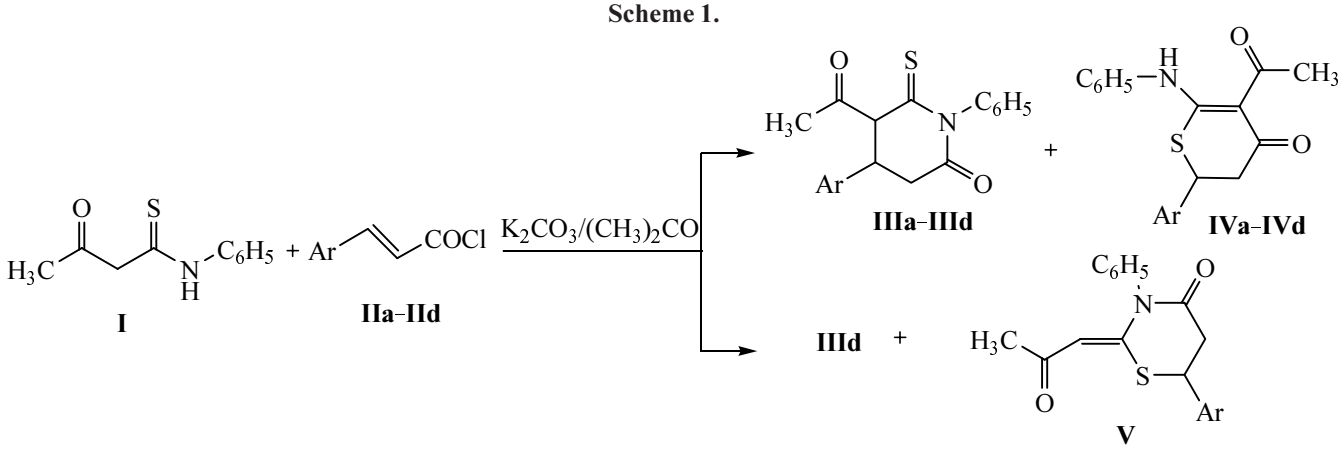
Abstract—Reactions of *N*-phenyl-3-oxobutanethioamide with 3-aryl-2-propenoyl chlorides in acetone in the presence of potassium carbonate give rise to 4-aryl-5-acetyl-1-phenyl-6-thioxopiperidin-2-ones, 2-aryl-5-acetyl-6-phenylamino-2,3-dihydro-4*H*-thiopyran-4-ones, and 6-aryl-2-acetonylidene-3-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-ones whose structure was proved both by spectral methods and chemical transformations.

We formerly have demonstrated that *N*-aryl-3-oxobutanethioamides are highly reactive substances that may serve as initial compounds for preparation of versatile heterocycles: pyrazoles [1], thiazoles [2], and thiophenes [3]. Here we report on investigation of the reaction between *N*-phenyl-3-oxobutanethioamide (**I**) and 3-aryl-2-propenoyl chlorides **IIa–IId**. It should be noted that N-aryl-3-oxobutanethioamides in reactions with electrophilic reagents behave as ambident nucleophiles [4, 5] thus complicating the isolation of products and their identification.

The most suitable medium for the reaction of *N*-phenyl-3-oxobutanethioamide (**I**) with 3-aryl-2-propenoyl-chlorides **IIa–IId** was acetone in the presence of K_2CO_3. This reaction of the type [3+3]-cyclocondensation may presumably take several routes and result in formation of 3,4-dihydro-2*H*-pyran-2-ones, 4*H*-pyran-4-ones, 4*H*-1,3-thiazin-4-ones, 6*H*-1,3-thiazin-6-ones, 4*H*-thiopyran-4-ones, 2*H*-thiopyran-2-ones, 4*H*-piperidin-4-ones and 6-thioxopiperidin-2-ones. However according to TLC data and ^{1}H NMR spectra each reaction gave rise to two products of the same elemental composition. The comparison of elemental analyses and IR, ^{1}H and ^{13}C NMR spectra of compounds we obtained with the corresponding published characteristics [6] of 4*H*-thiopyran-4-ones and 4*H*-piperidin-4-ones revealed that the reaction between *N*-phenylthioamide **I** and 3-aryl-2-propenoylchlorides **IIa–IId** afforded the following products: 4-aryl-5-acetyl-1-phenyl-6-thioxopiperidin-2-ones **IIIa–IIId**, 2-aryl-5-acetyl-6-phenylamino-2,3-dihydro-4*H*-thiopyran-4-ones **IVa–IVc**, and 2-acetonylidene-6-(*m*-nitro-phenyl)-3-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-one (**V**) (Scheme 1).

Scheme 1.



Ar = C_6H_5 (**IIa, IIIa, IVa**), *p*-$CH_3OC_6H_4$ (**IIb, IIIb, IVb**), 2-thienyl (**IIc, IIIc, IVc**), *m*-$NO_2C_6H_4$ (**IId, IIId, V**).

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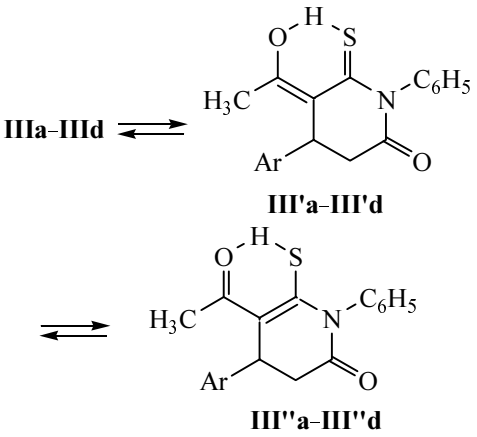
Scheme 2.



Heterocycle type, their relative amount, and yield depend on the character of substituents in the position *3* of the initial 3-aryl-2-propenoyl chlorides **IIa–IId.** At Ar = C_6H_5, *p*-$CH_3OC_6H_4$, and 2-thienyl arose 6-thioxopiperidin-2-ones **IIIa–IIIc** and 4*H*-thiopyran-4-ones **IVa–IVc** in a ratio (1.09–1.56):1. With Ar = *m*-$NO_2C_6H_4$, 6-thioxo-piperidin-2-one **IIId** and 1,3-thiazin-4-one **V** were obtained in a ratio 2.7:1.

Yields, melting points, and elemental analyses of compounds synthesized are presented in Table 1, ^1H, ^{13}C NMR, and IR spectra in Table 2. In the ^1H NMR spectra the following signals are characteristic: from the protons of OH(SH) groups in 6-thioxopiperidin-2-ones **IIIa–IIId** (δ 16.08–16.26 ppm), from protons of NH groups in 4*H*-thiopyran-4-ones **IVa–IVc** (δ 14.36–14.41 ppm), and from protons of the O=C–CH= group in 1,3-thiazin-4-one **V** (δ 5.49 ppm). The following characteristic absorption bands are observed in the IR spectra: stretching vibrations band of the carbonyl group O=C–N in 6-thioxopiperidin-2-ones **IIIa–IIId** (ν 1700–1720 cm^{-1}), bands of group O=C–C in 4*H*-thiopyran-4-ones **IVa–IVc** (ν 1630–1650 cm^{-1}), and bands of groups O=C–CH= (ν 1655 cm^{-1}) and O=C–N (ν 1720 cm^{-1}) in 1,3-thiazin-4-one **V**.

In [6] it was reported on the presence of an intramolecular hydrogen bond NH···O=C in 4*H*-thiopyran-4-one **IVa** revealed by the downfield position (14.4 ppm) of the NH group proton in the ^1H NMR spectrum of the compound. In the ^1H NMR spectra of 6-thioxopiperidin-2-ones **IIIa–IIId** were also observed singlet signals located far downfield (δ 16.08–16.26 ppm). This fact may be understood taking into account that the 6-thioxopiperidin-2-ones **IIIa–IIId** are β-thioxocarbonyl compounds which can exist in keto **IIIa–IIId**, enol **III'a–III'd**, and enthiol **III''a– III''d** forms, and the two latter are apparently stabilized by intramolecular hydrogen bonds (Scheme 2).

Table 1. Characteristics and elemental analyses of compounds **III–X**

Compd. no.	Yield, %	mp, °C	Found, %			Formula	Calculated, %		
			C	H	N		C	H	N
IIIa[a]	44	153–154	70.35	5.28	4.49	$C_{19}H_{17}NO_2S$	70.56	5.30	4.33
IIIb	47	150–152	68.20	5.63	3.75	$C_{20}H_{19}NO_3S$	67.97	5.42	3.96
IIIC	39	136–138	61.75	4.81	4.54	$C_{17}H_{15}NO_2S_2$	61.98	4.59	4.25
IIId	57	184–186	61.68	4.60	7.32	$C_{19}H_{16}N_2O_4S$	61.95	4.38	7.60
IVa[b]	40	140–142[C]	70.68	5.11	4.52	$C_{19}H_{17}NO_2S$	70.56	5.30	4.33
IVb	43	126–127	68.13	5.13	4.20	$C_{20}H_{19}NO_3S$	67.97	5.42	3.96
IVC	25	113–115	62.15	4.44	4.07	$C_{17}H_{15}NO_2S_2$	61.98	4.59	4.25
V	21	175–177	62.13	4.31	7.39	$C_{19}H_{16}N_2O_4S$	61.95	4.38	7.60
VI	76	113–115	70.91	5.39	3.92	$C_{20}H_{19}NO_2S$	71.19	5.68	4.15
VII	73	150–151[d]	64.39	4.88	13.91	$C_{16}H_{15}N_3OS$	64.62	5.08	14.13
VIII	48	131–133[e]	73.10	5.17	–	$C_9H_8O_2$	72.96	5.44	–
IXa	80	210–213	76.49	5.11	3.39	$C_{27}H_{21}NO_2S$	76.57	5.00	3.31
IXb	83	234–237	71.05	4.15	3.31	$C_{27}H_{20}ClNO_2S$	70.81	4.40	3.06
X	87	167–169	74.96	5.76	14.12	$C_{19}H_{17}N_3O$	75.23	5.65	13.85

[a] Found, %: S 9.89. $C_{19}H_{17}NO_2S$. Calculated, %: S 9.91.
[b] Found, %: S 9.94. $C_{19}H_{17}NO_2S$. Calculated, %: S 9.91.
[c] mp 145–146°C [6].
[d] mp 146–147°C [1].
[e] mp 135°C [9].

These tautomer forms apparently exist in solution in a dynamic equilibrium, and the singlet signals in the region 16.19–16.26 ppm are averaged proton signals of chelate OH groups of enol **III'a– III'd** and SH groups of enthiol **III''a– III''d** forms. In the solid states 6-thioxopiperidin-2-ones **IIIa–IIId** presumably exist in enol **III'a–III'd** form since in the IR spectra of these compounds recorded froms samples pelletized with KBr appear absorption bands of OH group (ν 3400 cm^{-1}) and one carbonyl (ν 1700–1720 cm^{-1}). This information is consistent with the data cited in review [7] treating the keto-enol-enthiol tauto-merism of β-thioxocarbonyl compounds.

To gain chemical proofs of the structure of 6-thioxo-piperidin-2-ones **IIIa–IIId** we brought 6-thioxopiperidin-2-one **IIIa** into reactions with methyl iodide, *p*-chloro-benzodiazonium chloride, 1-bromomethyl 1-aryl ketones, and hydrazine hydrate. The products of these processes were respectively 5-acetyl-1,4-diphenyl-6-(methylsulfan-

Table 2. ^{1}H and ^{13}C NMR spectra and IR spectra of compounds **III–X**

Compd. no.[a]	IR spectrum, ν, cm^{-1}	^{1}H NMR spectrum ($CDCl_3$), δ, ppm
IIIa[b]	1330, 1420, 1460, 1500, 1560, 1720, 3000, 3400	2.17 s (3H, CH_3C=O), 3.19 m (2H, H^3), 4.27 m (1H, H^4), 6.87 m (1H, Ar), 7.16 m (1H, Ar), 7.19–7.48 m (8H, Ar), 16.19 s (1H, OH)
IIIb	1310, 1420, 1500, 1510, 1570, 1700, 3000, 3400	2.19 s (3H, CH_3C=O), 3.20 m (2H, H^3), 3.80 s (3H, CH_3O), 4.22 m (1H, H^4), 6.91 m (3H, Ar), 7.16 m (3H, Ar), 7.42 m (3H, Ar), 16.17 s (1H, OH)
IIIc	1320, 1360, 1420, 1470, 1560, 1710, 3000, 3400	2.32 s (3H, CH_3C=O), 3.23 m (2H, H^3), 4.49 m (1H, H^4), 6.77 m (1H, Ar), 6.94 m (2H, Ar), 7.13 m (1H, Ar), 7.24 m (1H, Ar), 7.41 m (3H, Ar), 16.08 s (1H, ONE)
IIId	1420, 1470, 1500, 1540, 1560, 1720, 3000, 3400	2.20 s (3H, CH_3C=O), 3.13 m (1H, H^3), 3.27 m (1H, H^3), 4.40 m (1H, H^4), 6.96 m (1H, Ar), 7.26 m (1H, Ar), 7.46 m (3H, Ar), 7.62 m (2H, Ar), 8.18 m (2H, Ar), 16.26 s (1H, OH)
IVb	1360, 1390, 1420, 1470, 1530, 1590, 1650, 3000	2.65 s (3H, CH_3CO), 2.99 m (1H, H^3), 3.18 m (1H, H^3), 3.78 s (3H, CH_3O), 4.51 m (1H, H^2), 6.87 m (2H, Ar), 7.21–7.46 m (7H, Ar), 14.39 s (1H, OH)
IVc	1350, 1380, 1430, 1550, 1600, 1640, 3100	2.63 s (3H, CH_3CO), 3.15 m (2H, H^3), 4.82 m (1H, H^2), 6.96 m (2H, Ar), 7.20–7.37 m (3H, Ar), 7.41–7.49 (3H, Ar), 14.36 s (1H, OH)
V[c]	1205, 1220, 1360, 1470, 1530, 1655, 1720, 3100	2.04 s (3H, CH_3C=O), 3.40 m (1H, H^5), 3.54 m (1H, H^5), 4.32 (1H, H^6), 5.49 C (1H, CH=), 6.93 br.s (1H, Ar), 7.20 br.s (1H, Ar), 7.53 m (4H, Ar), 7.67 (1H, Ar), 8.18 m (2H, Ar)
VI[d]	1320, 1370, 1430, 1460, 1510, 1610, 1700, 3100	2.02 s (3H, SCH_3), 2.50 s (3H, CH_3C=O), 3.07 m (1H, H^3), 3.06 m (1H, H^3), 4.27 m (1H, H^4), 7.15–7.45 m (10H, $2C_6H_5$)
VII	1340, 1380, 1410, 1430, 1530, 1600, 1650, 3100	2.62 s (3H, CH_3C=O), 7.20–7.71 m (10H, Ar + NH), 13.49 s (=N–NH)
IXa	1280, 1320, 1430, 1470, 1510, 1630, 1705, 3000	2.23 s (3H, CH_3Het), 3.13 m (1H, H^5), 3.37 m (1H, H^5), 4.36 m (1H, H^4), 7.18–7.68 m (15H, $3C_6H_5$)
IXb	1280, 1320, 1430, 1470, 1500, 1630, 1705, 3000	2.25 s (3H, CH_3Het), 3.10 m (1H, H^5), 3.38 m (1H, H^5), 4.34 m (1H, H^4), 7.15–7.64 m (14H, Ar)
X	1295, 1360, 1460, 1510, 1620, 1680, 3100, 3300	1.80 s (3H, CH_3Het), 3.06 m (1H, H^5), 3.14 m (1H, H^5), 4.23 m (1H, H^4), 7.14–7.53 m (11H, Ar + NH)

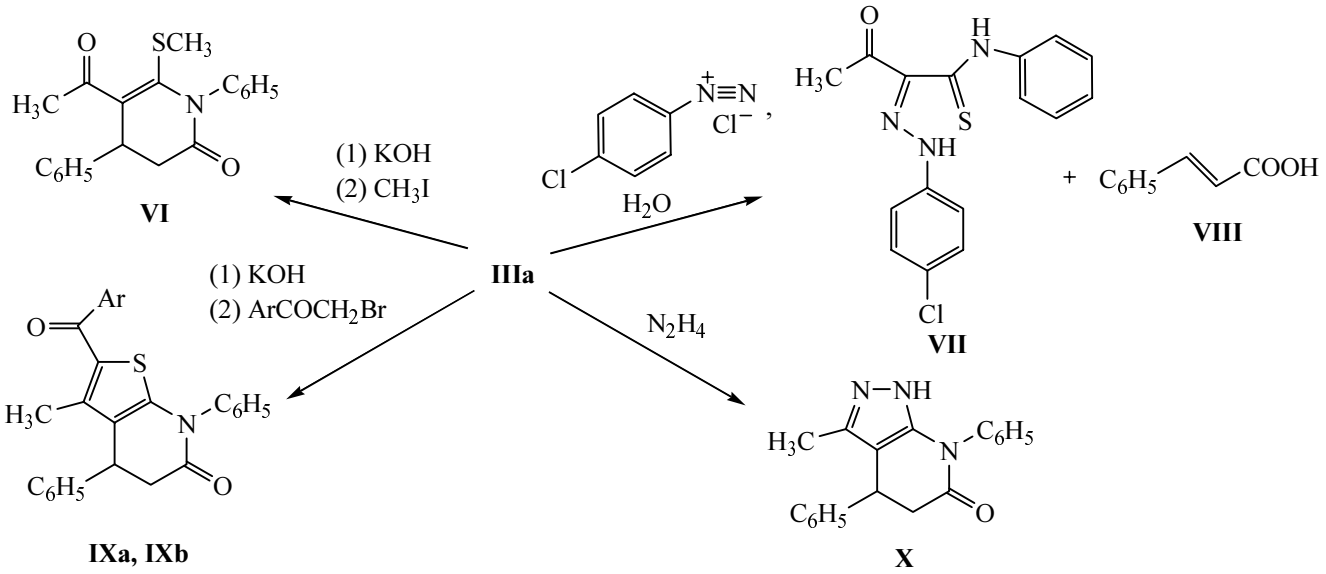
[a] IR, ^{1}H and ^{13}C NMR spectra of compound **IVa** are consistent with those described in [6].

[b] ^{13}C NMR spectrum of compound **IIIa** ($CDCl_3$), δ, ppm: 22.1 (CH_3), 38.1 (C^4), 39.6 (C^5), 109.8 (C^6), 126.6, 127.7, 128.5, 128.8, 129.1, 129.8, 138.5, 139.8 (Ar), 167.8 (C^2), 180.5 (C^3), 194.3 (C=O).

[c] ^{13}C NMR spectrum of compound **V** ($CDCl_3$), δ, ppm: 23.0 (CH_3), 38.2 (C^6), 46.7 (C^5), 101.2 (C^2), 122.5, 124.3, 127.7, 129.5, 129.8, 130.3, 134.7, 136.1, 137.9, 148.3 (Ar), 157.3 (CH=), 173.8 (C^4), 196.1 (C=O).

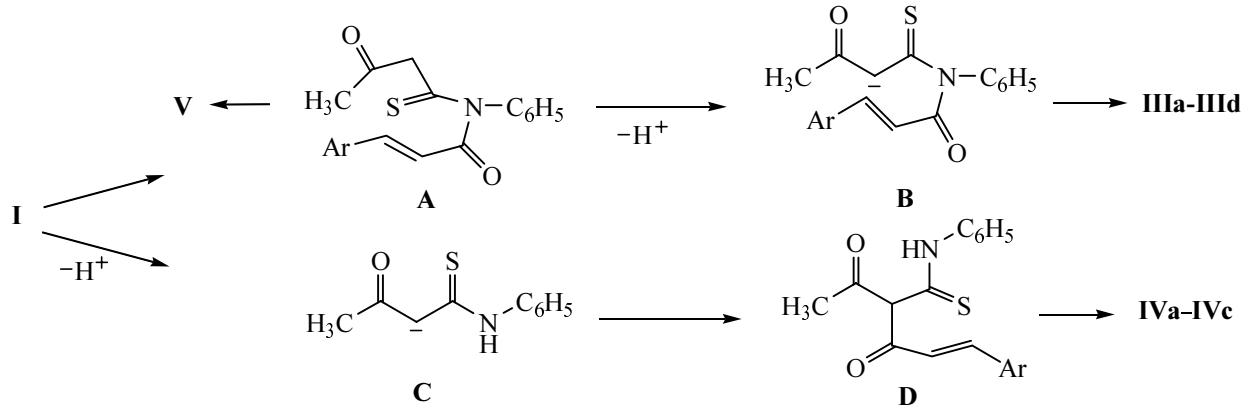
[d] ^{13}C NMR spectrum of compound **VI** ($CDCl_3$), δ, ppm: 18.9 (SCH_3), 31.3 ($\underline{C}H_3C$=O), 38.8 (C^3), 39.0 (C^4), 126.7, 127.3, 127.9, 128.5, 128.8, 128.9, 130.2 (C^6), 137.5, 139.3 (Ar), 144.0 (C^5), 168.8 (C^2), 199.5 ($CH_3\underline{C}$=O).

Scheme 3.



IX, Ar = C_6H_5 (**a**), *n*-ClC_6H_4 (**b**).

Scheme 4.



yl)-3,4-dihydro-2*H*-pyridin-2-one (**VI**), 2-arylhydrazono-*N*-phenylthioamide of 3-oxobutanoic acid (**VII**) and cinnamic acid (**VIII**), 2-aroyl-3-methyl-4,7-diphenyl-4,5-dihydro-6*H*-thieno[2,3-*b*]pyridin-6-ones (**IXa** and **IXb**), and 3-methyl-4,7-diphenyl-4,5-dihydro-1*H*,6*H*-pyrazolo[3,4-*b*]-pyridin-6-one (**X**), and the latter three compounds were obtained in preparative yields (80–87%) (Scheme 3).

The formation of above mentioned compounds unambiguously confirms the structure of 6-thioxopiperidin-2-one **IIIa** and characterizes its chemical properties.

Thiopyran-4-one **IVa** was previously obtained [6] by reaction of 6-phenyl-5-hexene-2,4-dione with phenyl isothiocyanate in dimethyl sulfoxide in the presence of sodium methoxide. The second product of this reaction, 5-acetyl-2,3-dihydro-6-(methylsulfanyl)-1,2-diphenyl-4(1*H*)-pyridone, resembles in the structure 2*H*-pyridin-2-one **VI** we obtained, but the compounds differ both in their melting points (143–144°C [6] and 113–115°C respectively) and in the location of proton and carbon signals in the ^1H and ^{13}C NMR spectra.

Inasmuch as at the double bond of 4*H*-1,3-thiazin-4-one **V** different substituents are present the compound can exist in (*E*)- and (*Z*)-forms. We formerly carried out an X-ray diffraction study of 2-acetonylidene-3,4-diphenyl-2,3-dihydrothiazole similar in structure to compound **V**. It was established that the above compound existed as (*Z*)-isomer due to sterical requirements [8]. It is therefore presumable that 4*H*-1,3-thiazin-4-one **V** is also a (*Z*)-isomer.

The results obtained at acylation of *N*-phenyl-3-oxobutanethioamide (**I**) with 3-aryl-2-propenoyl chlorides **IIa–IId** apparently originate either from direct reaction

of butanethioamide **I** in the presence of K_2CO_3 with 3-aryl-2-propenoylchloride **II** at the NH group giving intermediate **A**, or from preliminary formation of carbanion **C** which should be obviously acylated at the site of the highest nucleophilicity (C^2) transforming into an intermediate product **D** whose intramolecular cyclization affords 4*H*-thiopyran-4-ones **IVa–IVc** (Scheme 4).

In all likelihood in the intermediate **A** containing an electron-withdrawing group (Ar = *m*-$NO_2C_6H_4$) the electron density on the carbon atom C^3 of the 3-aryl-2-propenoyl substituent is reduced to such extent that the attack of the C^3 atom with a thioxo group becomes possible, and it results in the intramolecular cyclization of intermediate **A** into 1,3-thiazin-4-one **V**. When the electrophilicity of the C^3 carbon in intermediate **A** is insufficient for the reaction with the thioxo group (Ar = C_6H_5, *p*-$CH_3OC_6H_4$, 2-thienyl) intermediate **A** transforms into carbanion **B** which then converts into 6-thioxopiperidin-2-ones **IIIa–IIId**.

EXPERIMENTAL

NMR spectra from solutions of compounds in $CDCl_3$ were registerd on a spectrometer Varian-300 at operating frequencies 300 (^1H) and 75 MHz (^{13}C), internal reference TMS. IR spectra were recorded on a spectrophotometer UR-20 from samples pelletized with KBr. The purity and homogeneity of compounds was checked by TLC on Silufol UV-254 plates, eluent petroleum ether (bp 40–80°C)–chloroform–acetone, 5:3:2.

4-Aryl-5-acetyl-1-phenyl-6-thioxopiperidin-2-ones IIIa–IIId, 2-aryl-5-acetyl-6-phenyl-amino-2,3-dihydro-4*H*-thiopyran-4-ones IVa–IVc, and 2-acetonylidene-6-(*m*-nitro-phenyl)-3-phenyl-5,6-dihydro-4*H*-1,3-thiazin-4-one (V). To a solution of 5.79 g (0.03 mol) of 3-oxobutanoic acid *N*-phenylthioamide (**I**) in 15 ml of anhydrous acetone containing 7.59 g (0.055 mol) of dispersed dry K_2CO_3 was added while vigorous stirring at 20°C a solution of 0.03 mol of 3-aryl-2-propenoylchloride **IIa–IId** in 10 ml of acetone. The stirring was continued for 2 h at 20°C, 0.5 h at 50°C, and 0.5 h at 56°C. On cooling the reaction mixture was filtered to separate potassium hydrogen carbonate and chloride. The filtrate was evaporated, the crystalline precipitate was ground with 10 ml of 10% aqueous NaOH. 4*H*-Thiopyran-4-one **IVa–IVc** [1,3-thiazin-4-one (**V**)] insoluble in the alkaline solution was filtered off, dried in air, and recrystallized from a mixture ethanol–water, 2:1. The alkaline filtrate containing 6-thioxopiperidin-2-one **IIIa–IIId** was acidified with 20% water solution of HCl, and the precipitated reaction product **IIIa–IIId** was filtered off, dried in air, and recrystallized from ethanol. Yields and melting points of compounds **IIIa–IIId**, **IVa–IVc,** and **V** are given in Table 1.

5-Acetyl-1,4-diphenyl-6-(methylsulfanyl)-3,4-dihydro-2*H*-pyridin-2-one (VI) and 2-aroyl-3-methyl-4,7-diphenyl-4,5-dihydro-6*H*-thieno[2,3-*b*]-pyridin-6-ones (IXa and IXb). To a solution of 0.323 g (1 mmol) of 1,4-diphenyl-6-thioxopiperidin-2-one **IIIa** and 0.056 g (1 mmol) of KOH in 4 ml of ethanol was added at 20°C a solution of 1.5 mmol of methyl iodide (1 mmol of 1-bromomethyl 1-phenyl ketone), The mixture was kept 30 min at 40°C, 10 min at 78°C, cooled, diluted with cold water (10 ml), the precipitated reaction product **VI** or **IXa** and **IXb** was filtered off, dried in air, and recrystallized from ethanol (compound **VI**) or from acetic acid (compounds **IXa** and **IXb**).

Azo coupling of 6-thioxopiperidin-2-one IIIa with *p*-chlorobenzenediazonium chloride. To a solution of 0.18 g (0.557 mmol) 6-thioxopiperidin-2-one **IIIa** in ml of ethanol was added 0.7 ml of water and 0.36 g of finely powdered anhydrous sodium acetate. At cooling with ice and water was added within 4–5 min while vigorous stirring a water solution of *p*-chlorobenzenediazonium chloride prepared from 0.52 g of *p*-chloroaniline, 0.28 g of sodium nitrite, 1.8 ml of concn..HCl, and 2.7 ml of water. The reaction mixture was stirred for 1 h, then a yellow precipitate was filtered off, washed with cold water (3×5 ml), dried in air, and recrystallized from 2-propanol. The sample of reaction product **VII** thus obtained mixed with compound of analogous structure that we had prepared formerly [1] by azo coupling of 3-oxo-*N*-phenylbutanethioamide with *p*-chlorobenzenediazonium chloride melted without melting point depression. The filtrate was acidified with 3 ml of concn. HCl, kept for 5 h at 10°C, and the precipitated cinnamic acid **VIII** was filtered off, dried, and recrystallized from 2-propanol.

3-Methyl-4,7-diphenyl-4,5-dihydro-1*H*,6*H*-pyrazolo[3,4-*b*]pyridin-6-one (X). To a dispersion of 0.323 g (1 mmol) of 6-thioxopiperidin-2-one **IIIa** in 2 ml of glacial acetic acid was added 0.08 ml of hydrazine hydrate, the mixture was stirred for 24 h at 20°C and 8 h at 50°C till the precipitate of the initial compound completely disappeared and hydrogen sulfide evolution ceased. The solution obtained was neutralized by adding 3 g of potassium hydrogen carbonate, the separated precipitate was filtered off, dried, and recrystallized from a mixture hexane–2-propanol, 3:2.

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