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SYNTHESIS AND SOME PROPERTIES OF 6-(ω-AROYLBUTYLTHIO)PURINES

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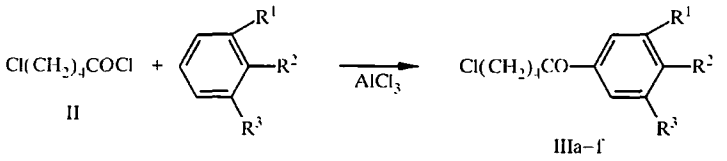
A series of 6-(ω-aroylthio)purines, which have not been described in the literature, has been obtained by the reaction of 6-purinethione with ω-chlorovalerophenone and its substituted derivatives. Some properties of the compounds synthesized have been studied, viz. reaction at the carbonyl group, methylation, and hydrolysis.

We have described previously the reaction of 6-purinethione (I) with α-halo ketones and acetals of bromoacetoacetaldehyde leading to the corresponding 6-β-oxoalkyl(aralkyl)thiopurines [1-3]. Continuing this work with the aim of searching for new biologically active substances the reaction of 6-purinethione I with ω-chlorovalerophenone and its 4-, 3,4-di- and 3,4,5-trisubstituted in the benzene ring derivatives has been studied.

The initial acid chloride of ω-chlorovaleric acid (II) and the ω-chlorovalerophenones (IIIa-f) were obtained by known methods with some modification enabling the isolation to be simplified and the yields of these products to be increased. The chloro ketones IIIe,f were synthesized by us for the first time.



IIIa-f $R^1 = R^3 = H$; a $R^2 = H$, b $R^2 = Me$; c $R^2 = OMe$;
d $R^2 = Cl$, e $R^1 = R^2 = OMe$, $R^3 = H$; f $R^1 = R^3 = Bu\text{-}t$, $R^2 = OH$

The purity of compounds IIIa-f was confirmed by TLC and their structure by IR spectra and ^1H NMR data. In the IR spectra of ketones IIIa-f there was a sharp absorption band for a CO group at 1660-1685 cm^{-1}. In the ^1H NMR spectra of compounds IIIb,c the signals of the aromatic protons had the characteristic form of an AB system at 6.9-7.9 ppm (coupling constant J_{AB} = 9 Hz), which indicates unequivocally their structures as *para* isomers [4].

The reaction of 6-purinethione I with ω-chlorovalerophenones IIIa-f was carried out in aqueous alcohol solution in the presence of an equimolar quantity of KOH. The use of the less reactive ω-chlorovalerophenones III compared with α-halo ketones [1-3] made it necessary to increase both the reaction temperature (to 60-80°C) and its duration (to 15-18 h). As a result the hitherto undescribed 6-(ω-aroylbutylthio)purines IVa-f were synthesized, the characteristics of which are given in Tables 1 and 2.

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TABLE 1. Characteristics of 6-(ω-Aroylbutylthio)purines IVa-f

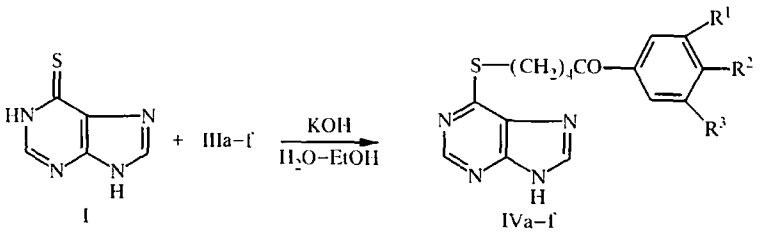
Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	S		
IVa	$C_{16}H_{16}N_4OS$	61.38 / 61.52	5.32 / 5.16	17.83 / 17.93	10.28 / 10.26	165-167	86
IVb	$C_{17}H_{18}N_4OS$	62.48 / 62.55	5.78 / 5.56	17.10 / 17.16	9.76 / 9.82	175-176	87
IVc	$C_{17}H_{18}N_4O_2S$	59.75 / 59.63	5.56 / 5.30	16.10 / 16.36	9.14 / 9.36	180-181	85
IVd	$C_{16}H_{15}ClN_4OS$*	55.67 / 55.41	4.66 / 4.36	15.90 / 16.15	9.40 / 9.24	192-193	79
IVe	$C_{18}H_{20}N_4O_3S$	58.17 / 58.05	5.48 / 5.41	15.12 / 15.04	8.87 / 8.61	196-198	76
IVf	$C_{24}H_{32}N_4O_2S$	65.02 / 65.42	7.87 / 7.32	12.50 / 12.72	7.38 / 7.28	207-208	35

* Found, %: Cl 10.33. Calculated, %: Cl 10.22.

TABLE 2. Spectral Characteristics of Compounds IVa-e

Compound	UV spectrum, λ_{max}, nm (log ε)	^{1}H NMR Spectrum (DMSO-d_6), δ, ppm
IVa*	243.8 (4.22) 290.4 (4.27)	1.71-1.85 (4H, m, $2CH_2$); 3.10 (2H, t, $COCH_2$); 3.43 (2H, t, SCH_2) 7.5-8.03 (5H, m, H_{Ph}); 8.43 (1H, s, 8-H); 8.68 (1H, s, 2-H)
IVb	254.7 (4.83) 290.4 (4.23)	
IVc		1.70-1.87 (4H, m, $2CH_2$); 3.05 (2H, t, $COCH_2$); 3.41 (2H, t, SCH_2) 3.84 (3H, s, CH_3); 6.01-7.93 (4H, two d, J_{AB} = 9 Hz, H_{Ar}) 8.38 (1H, s, 8-H); 8.64 (1H, s, 2-H)
IVd	219.1 (4.06) 283.0 (4.20)	1.68-1.80 (4H, m, $2CH_2$); 3.04 (2H, t, $COCH_2$); 3.42 (2H, t, SCH_2) 7.57-7.59 (4H, two d, H_{Ar}); 8.40 (1H, s, 8-H); 8.64 (1H, s, 2-H)
IVe		1.69-1.87 (4H, m, $2CH_2$); 3.05 (2H, t, $COCH_2$); 3.42 (2H, t, SCH_2) 3.81 (3H, s, OCH_3); 3.84 (3H, s, OCH_3); 6.99-7.70 (3H, m, H_{Ar}) 8.39 (1H, s, 8-H); 8.64 (1H, s, 2-H)

* Mass spectrum: M^+ 312.



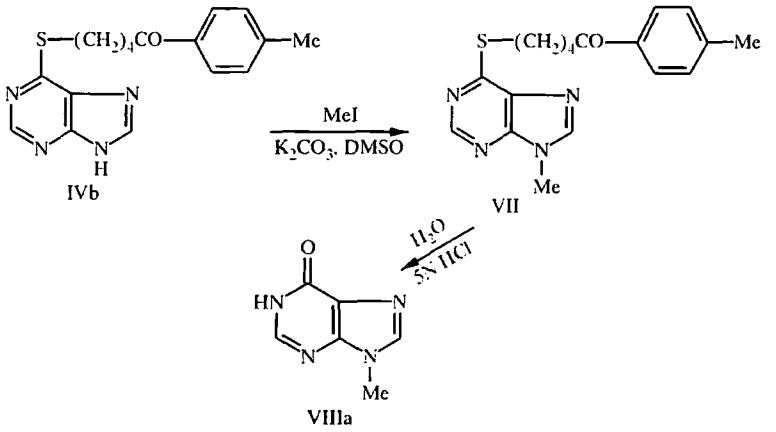
IVa-f $R^1 = R^3 = H$; a $R^2 = H$, b $R^2 = Me$; c $R^2 = OMe$;
d $R^2 = Cl$, e $R^1 = R^2 = OMe$, $R^3 = H$; f $R^1 = R^3 = Bu$-*t*, $R^2 = OH$

The purity and identity of the products IVa-f obtained were confirmed by TLC and by the results of elemental analysis, and their structure by a combination of IR, UV, and ^{1}H NMR spectral data. Sharp bands were seen in their IR spectra for the stretching vibrations of CO and NH groups at 1685-1695 and 3095-3110 cm^{-1} respectively. An absorption maximum was observed in the UV spectra of thioethers IVa-d at 283-290.4 nm. In the ^{1}H NMR spectra of compounds IVa,c-e there were singlet signals for the purine ring protons in the low field part of

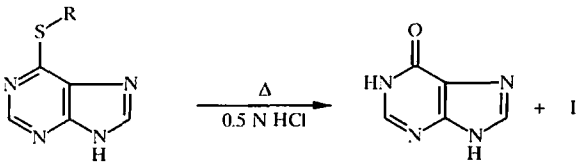
the spectrum (8.38-8.68 ppm). The protons of the aryl fragment were displayed as a multiplet signal at 7.50-8.03 ppm, but in the case of compounds IVc,d, having a substituent in the *para* position of the aromatic ring, as a quartet of an AB system at 6.01-7.98 ppm with coupling constant J_{AB} = 9 Hz.

We also studied certain conversions of the 6-(ω-aroylbutylthio)purines IVa-f obtained, *viz.* reactions at the carbonyl group, methylation, and hydrolytic splitting. Thus the corresponding 2,4-dinitrophenylhydrazone (V) was obtained from ketone IVb and the oxime VI from ketone IVc.

Methylation of 6-(ω-*p*-methylbenzoylbutylthio)purine IVb with methyl iodide in an aprotic solvent (DMSO) in the presence of anhydrous potassium carbonate occurred at position 9 with the formation of 9-methyl-6-(ω-*p*-methyl-benzoylbutylthio)purine (VII). The structure of the latter was confirmed by hydrolytic transformation to 9-methylhypoxanthine (VIIIa) on heating in 5N hydrochloric acid.



It was shown in [1,3] that 6-(acylmethylthio)purines underwent hydrolysis on heating in 5N hydrochloric acid with fission of the $C_{(6)}$–S bond and the formation of methylhypoxanthine (VIIIa). We discovered that if 0.5N HCl is used instead of 5N HCl then partial fission of the S–CH_2 bond of the side chain occurs in addition to the main reaction course. On boiling 6-phenacylthiopurine (IX) [1] and 6-(ω-*p*-methoxybenzoylbutylthio)purine (IVc) in 0.5N HCl then hypoxanthine (VIIIb) and 6-purinethione I were isolated in yields of 52-55 and 4-5% respectively.



IX. IVc VIIIb

IX R = CH_2COPh; IVc R = $(CH_2)_4COC_6H_4OMe$-*p*

It should be mentioned that the formation of hypoxanthine is not the result of hydrolysis of 6-purinethione, since the latter is fairly stable on heating in hydrochloric acid. This property is used in its purification from contaminants of a basic character on recrystallization during manufacture [5].

EXPERIMENTAL

The IR spectra of the synthesized compounds were taken on a Specord IR 75 instrument in vaseline oil, the UV spectra on a Perkin–Elmer 402 instrument, and the ^{1}H NMR spectra on a Tesla BS 587A instrument with an operating frequency of 80 MHz. Internal standard was TMS. The mass spectra were obtained on a MX 1321A

instrument with direct insertion of sample into the ion source. Ionizing voltage was 70 eV, temperature of the ionization chamber was about 170°C. The TLC of compounds was carried out on Silufol UV 254 plates in the system butanol–water–acetic acid, 5:3:2. Visualization was with UV light or iodine vapor.

ω-Chlorovaleric Acid Chloride (II). ω-Chlorovaleric acid (115 ml, 135 g, 0.9 mol) was added with stirring at 50-55°C to a mixture of $SOCl_2$ (85 ml, 140 g, 1.15 mol) and DMF (6.5 ml, 7.2 g, 0.1 mol). The reaction mixture was heated at 75°C for 3 h, then the excess of $SOCl_2$ was distilled off in vacuum. The residue was distilled in vacuum collecting the fraction of bp 80-82°C (10 mm Hg). Yield 122 g (87%), n_D^{20} 1.4642. According to [6] bp 83°C (12 mm), n_D^{20} 1.4653.

ω-Chlorovalerophenone (IIIa). Aluminum chloride (60 g, 0.45 mol) was added in small portions with stirring and cooling to -5 - 0°C to a solution of compound I (64.8 g, 0.42 mol) in anhydrous benzene (130 ml, 112 g, 1.43 mol). The reaction mixture was maintained for 30 min at 0°C, poured onto ice, and extracted with benzene (2 × 50 ml). The extract was washed with 2% sodium carbonate solution, then with water. The solvent was distilled off in vacuum, and the residue recrystallized from hexane. Yield 72 g (89%); mp 60-62°C. Literature [7] mp 61-62°C. IR spectrum: 1680 cm^{-1} (CO).

Chloro ketones IIIb,c were obtained analogously.

4-Methyl-ω-chlorovalerophenone (IIIb). Yield 87%; mp 69-70°C (hexane). Literature [7] mp 70-72°C. IR spectrum: 1680 cm^{-1} (CO). ^1H NMR spectrum ($CDCl_3$): 7.82 and 7.17 (4H, two d, J = 9 Hz, H_{arom}); 3.02 (4H, t, CH_2Cl and $COCH_2$); 2.35 (3H, s, CH_3); 1.83 ppm (4H, m, $2CH_2$).

4-Methoxy-ω-chlorovalerophenone (IIIc). Yield 69%; mp 57-59°C (hexane). Literature [7] mp 56-58°C. IR spectrum: 1685 cm^{-1} (CO). ^1H NMR spectrum ($CDCl_3$): 7.90 and 6.90 (4H, two d, J = 9 Hz, H_{arom}); 3.83 (3H, s, OCH_3); 3.53 (2H, t, CH_2Cl); 3.02 (2H, t, $COCH_2$); 1.83 (4H, m, $2CH_2$).

4-Chloro-ω-chlorovalerophenone (IIId). Aluminum chloride (7.8 g, 0.059 mol) was added in small portions with stirring to a mixture of acid chloride I (6.4 g, 0.041 mol) and nitromethane (10 ml) at 0°C. Chlorobenzene (4 ml, 4.4 g, 0.039 mol) was then added. The reaction mixture was stirred for 6 h at 25°C, poured onto ice, and extracted with ether (3 × 20 ml). The extract was washed with water, dried over $MgSO_4$, and the solvent distilled off in vacuum. The residue was crystallized twice from hexane. Chloro ketone IIId (5.8 g, 62%) was obtained; mp 27-28°C. Literature [7] mp 23-25°C. IR spectrum: 1685 cm^{-1} (CO).

Chloro ketones IIIe,f were obtained analogously with the difference that the reaction mixture was stirred at 0°C for 45 min, and the ether extract washed with sodium carbonate solution, and then with water. The crude product was crystallized from hexane and then from isopropanol.

3,4-Dimethoxy-ω-chlorovalerophenone (IIIe). Yield 69%; mp 42-45°C. IR spectrum: 1690 cm^{-1} (CO). Found, %: C 60.75; H 6.51; Cl 13.74. $C_{13}H_{17}ClO_3$. Calculated, %: C 60.82; H 6.68; Cl 13.82.

3,5-Di(*tert*-butyl)-4-hydroxy-ω-chlorovalerophenone (IIIf). Yield 52%; mp 70-72°C. IR spectrum: 1680 cm^{-1} (CO). Found, %: C 70.56; H 8.73; Cl 10.65. $C_{19}H_{29}ClO_2$. Calculated, %: C 70.24; H 9.00; Cl 10.91.

6-(ω-Aroylbutylthio)purines (IVa-f). A solution of chloro ketone III (0.044 mol) in ethanol (100 ml) was added to a solution of 6-purinethione hydrate (6.8 g, 0.04 mol) in 0.1N KOH solution (40 ml, 0.04 mol). The reaction mixture was stirred at 60-70°C for 15-18 h (check by TLC for the absence of starting thione), then kept at 0-5°C for 12 h. The precipitated solid product IV was filtered off, washed with 50% ethanol, and dried. Compounds IVa,b were recrystallized from ethanol, IVc from acetone, IVd from isopropanol, IVe from an acetone–hexane mixture, and IVf from aqueous ethanol.

2,4-Dinitrophenylhydrazone of 6-(*p*-Methylbenzoylbutyl)thiopurine (V). Derivative V was obtained by heating equimolar quantities of ketone IVb and 2,4-dinitrophenylhydrazine in glacial acetic acid. Yield was 92%; mp 158-160°C (CH_3COOH). Found, %: C 54.38; H 4.34; N 22.41; S 6.36. $C_{23}H_{22}N_8O_5S$. Calculated, %: C 54.53; H 4.38; N 22.12; S 6.33.

Oxime of 6-(*p*-Methoxybenzoylbutylthio)purine (VI). Derivative VI was obtained by boiling a mixture of ketone IVc, hydroxylamine hydrochloride, and sodium acetate in ethanol. Yield was 89%; mp 182-184°C (ethanol). Found, %: N 18.49. $C_{17}H_{19}N_5O_2S$. Calculated, %: N 18.75.

9-Methyl-6-(ω-*p*-methylbenzoylbutylthio)purine (VII). Finely powdered anhydrous K_2CO_3 (2.76 g, 0.02 mol) and methyl iodide (2.84 g, 0.02 mol) were added to a solution of compound IVb (3.26 g, 0.01 mol) in DMSO (15 ml), The mixture was stirred for 15 h at 80°C, and the solvent and excess of methyl iodide were then

distilled off in vacuum. The residue was washed with 1N NaOH solution, then with cold water, dried, and crystallized from acetone. Yield 2.4 g (70%); mp 168-170°C (acetone). IR spectrum: 1690 cm^{-1} (CO). UV spectrum, λ_{max} (log ε): 281.3 nm (4.24). Found, %: C 63.72; H 5.75; N 16.56; S 9.37. $C_{18}H_{20}N_4OS$. Calculated, %: C 63.50; H 5.92; N 16.46; S 9.42.

9-Methylhypoxanthine (VIIIa). A suspension of compound VII (3.4 g, 0.01 mol) in 5N HCl (25 ml) was boiled for 1 h, cooled, and a solution of Na_2CO_3 added to pH 6. The solution obtained was decolorized by heating with carbon, filtered, evaporated in vacuum to small volume, and cooled. The solid was filtered off, washed with water, then with acetone, and dried. Yield 0.8 g (53%); mp >330°C (decomp., from water). Literature [8] mp 390°C (decomp.). IR spectrum: 1730 (CO), 3300 cm^{-1} (NH).

Hypoxanthine (VIIIb) and 6-Purinethione (I). A. A mixture of compound IVc (3.42 g, 0.01 mol) and 5N HCl (25 ml) was boiled and then treated as described above for compound VIIIa. Compound VIIIb (0.95 g, 70%) was obtained; mp >330°C (decomp.). Literature [9] mp >330°C (decomp.). IR spectrum: 1725 (CO), 3080 and 3140 cm^{-1} (NH).

B. A mixture of 6-phenacylthiopurine IX [1] (2.7 g, 0.01 mol) and 0.5N hydrochloric acid (25 ml) was boiled for 30 min. The solution was decolorized with carbon, filtered, and sodium carbonate solution added to pH 6-7. The precipitated solid was filtered off, washed with water, and with acetone, and dried. Compound VIIIb (0.75 g, 55%) was obtained; mp >330°C. IR spectrum: 1725 (CO), 3080, 3140 cm^{-1} (NH).

The mother liquor after separating compound VIIIb was evaporated in vacuum to a quarter of the initial volume, cooled, the solid which precipitated was filtered off, washed with water, and with acetone, and crystallized from alcohol. 6-Purinethione hydrate (0.1 g, 5%) was obtained; mp 310-312°C (decomp.). Literature [10] mp 313-314°C (decomp.). A mixing test with an authentic sample of 6-purinethione gave no depression of melting point. The IR spectra of the samples were identical.

Hypoxanthine and 6-purinethione were obtained under analogous conditions in yields of 55 and 4% respectively by the hydrolysis of thiopurine IVc with 0.5N HCl.

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