HETEROCYCLIC ANALOGS OF XANTHONES

III.* THIOCHROMONO[3,2-d]PYRAZOLES

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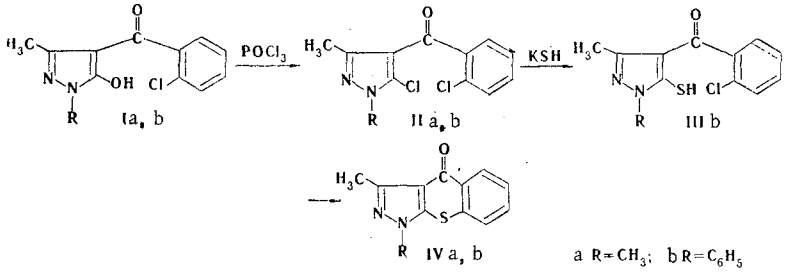
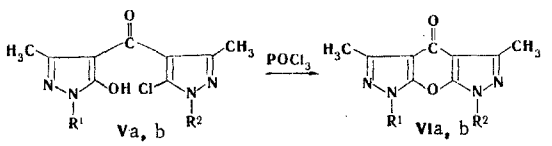
Thiochromono[3,2-d]pyrazoles are formed by the action of potassium hydrosulfide on 5-chloro-4-(o-chlorobenzoyl)pyrazoles. The action of Grignard reagents on them gave 4-dimethylaminopropylidenethiochromonopyrazoles, which are structural analogs of known medicinal substances.

In developing our previous investigations [1, 2], we have studied routes to the synthesis of thiochromonopyrazoles. They were obtained by treatment of o-chlorobenzoyl derivatives of 5-chloropyrazole (IIa,b) with potassium hydrosulfide with subsequent intramolecular cyclization of the products to form the thiopyrone ring.



The 4-(o-chlorobenzoyl)-5-chloropyrazoles (IIa, b) were obtained by treatment of the corresponding 4-(o-chlorobenzoyl) derivatives with phosphorus oxychloride and were also prepared by the reaction of 5-chloropyrazoles with o-chlorobenzoyl chloride in the presence of aluminum chloride [3]. However, the latter method is little suitable for obtaining IIa, since the yields in this case are extremely low [4]. In the reaction of potassium hydrosulfide with dichloro derivatives II, the chlorine atom in the pyrazole portion of the molecule initially undergoes nucleophilic substitution to form an intermediate (III) that is then readily cyclized to the final product (IV).

An attempt was made to synthesize a thiopyrone containing two condensed rings. However, bispyrazolopyrones (VIa, b) were obtained instead of the expected dichloro derivatives of the II type when the corresponding acyl derivatives were treated with phosphorus oxychloride or phosphorus pentachloride.



*See [1] for communication II.

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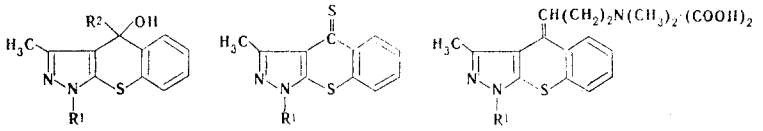
The thiochromonopyrazoles have properties that are similar to those of the oxygen analogs [2]. They are reduced by sodium amalgam in alcohol to the corresponding hydrols (VII) and react with organomagnesium compounds to give substituted hydrols (IX and XI), which are readily converted to colored salts on reaction with strong acids. When $R^2 = (CH_2)_3N(CH_3)_2$, IXa, b were dehydrated by 2 N hydrochloric acid to give substances with presumable psychotropic activity (Xa, b) [5, 6].

Thiochromonopyrazoles do not react with reagents that characterize the carbonyl group such as hydroxylamine, thiosemicarbazide, etc., but they do react with phosphorus pentasulfide to give thiones (VIII). In contrast to the thione of xanthone [7], the latter do not react with hydroxylamine.



VIIb, IXa,b,XIa, b VIIIa, b Xa,b

a $R^1 = CH_3$; b $R^1 = C_6H_5$; VII R^2 = H; IX $R^2 = (CH_2)_3N(CH_3)_2$; XI $R^2 = C_2H_5$

It should be noted that chromono[3,2-d]pyrazoles [1,2] and thiochromono[3,2-d]pyrazoles react with somewhat greater difficulty than xanthone and thioxanthone, apparently as a consequence of the greater electron-acceptor effect of the condensed pyrazole ring as compared with the benzene ring. The latter is confirmed by the IR spectra, in which ν_{CO} of the thiochromonopyrazoles in chloroform (1635 and 1640 cm^{-1} for IVa and IVb) is shifted by 10-15 cm^{-1} relative to thioxanthone (1625 cm^{-1}) ($\Delta\nu_{CO}$ is 5 cm^{-1} for the oxygen analogs [1, 2]), which attests to the lower polarization of the carbonyl group in chromono- and thiochromono[3,2-d]pyrazoles. Replacement of the oxygen atom by sulfur leads to a decrease of 30-35 cm^{-1} in ν_{CO} ($\Delta\nu_{CO}$ of xanthone and thioxanthone is 40 cm^{-1}), and, consequently, to an increase in the polarization of the carbonyl group. Reinforcement of the polarization of the carbonyl group in thiochromonopyrazoles is also confirmed by the electronic spectra – λ_{max} is shifted bathochromically by 60 nm (Fig. 1). Substituents attached to the nitrogen of the pyrazole ring (CH_3 and C_6H_5) have little effect on the spectral characteristics of IVa, b or on their reactivities.

EXPERIMENTAL

The synthesis of I, II, V, and VI was described in [1].

1,3-Dimethylthiochromono[3,2-d]pyrazole (IVa). A 12.55-g (0.05 mole) sample of 1,3-dimethyl-4-(o-chlorobenzoyl)-5-pyrazolone (Ia) was heated for 7 h with 46.0 g (0.3 mole) of phosphorus oxychloride at 100°. The excess phosphorus oxychloride was decomposed with ice water, and the resulting oil (IIa) was extracted with butyl alcohol. The solvent was removed by distillation, 70 ml of dimethylformamide was added to the residue, and the mixture was heated at 100° for 8 h with 6 g of 50% aqueous potassium hydrosulfide solution. The mass was cooled, diluted with 150 ml of water, and the IVa was removed by filtration and crystallized twice from alcohol to give 43.1% of a product with mp 162-163°. Found: N 11.9; S 13.8%. $C_{12}H_{10}N_2OS$. Calculated: N 12.22; S 13.9%.

1-Phenyl-3-methylthiochromono[3,2-d]pyrazole (IVb). This compound was similarly obtained in 71.0% yield from 1-phenyl-3-methyl-4-(o-chlorobenzoyl)-5-chloropyrazole (IIb) and had mp 158-159° (from alcohol). Found: N 9.4; S 10.7%. $C_{17}H_{12}N_2OS$. Calculated: N 9.6; S 10.9%.

1-Phenyl-3-methyl-4-(o-chlorobenzoyl)-5-thiopyrazolone (IIIb). This compound was isolated as an intermediate by acidification with dilute hydrochloric acid in the preparation of IVb from IIb and had mp 112-114° (from alcohol). Found: Cl 10.2; N 10.3%. $C_{17}H_{13}ClN_2OS$. Calculated: Cl 10.8; N 9.8%.

1-Phenyl-3-methyl-4-hydroxythiochromono[3,2-d]pyrazole (VIIb). A 4.9-g (0.016 mole) sample of IVb and 30 ml of ethanol were added to sodium amalgam, prepared from 1.15 g (0.05 g-atom) of sodium and 96 g of mercury, and the mixture was refluxed for 2 h. The mercury was separated, and the hot alcohol solution was filtered. The filtrate was poured into 300 ml of cold water, and the precipitate was removed by filtration to give 3.45 g (70.5%) of VIIb with mp 116-119° (from alcohol). Found: C 69.5; H 4.9; N 9.8; S 10.9%. $C_{17}H_{14}N_2OS$. Calculated: C 69.4; H 4.8; N 9.5; S 10.9%.

1,3-Dimethylthiochromono[3,2-d]pyrazole-4-thione (VIIIa). A mixture of 1.0 g (0.004 mole) of IVa and 1.0 g (0.0045 mole) of phosphorus pentasulfide in 20 ml of xylene was heated at 140° for 5 h. The hot solution was filtered and cooled to give 0.86 g (85%) of VIIIa with mp 178-180° (from alcohol). Found: N 9.6; S 20.7%. $C_{17}H_{12}N_2S_2$. Calculated: N 9.1; S 20.8%.

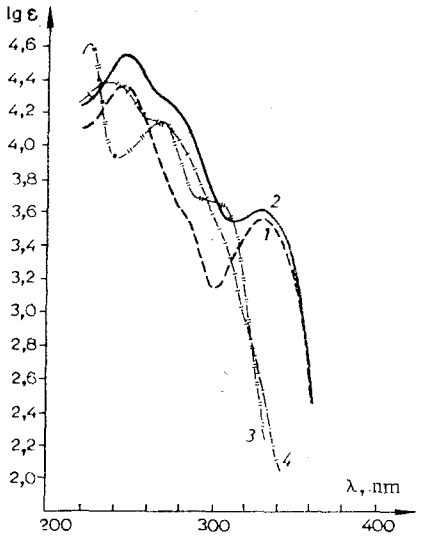


Fig. 1. Absorption spectra of xanthone analogs: 1) 1,3-dimethylthiochromono[3,2-d]pyrazole (IVa); 2) 1-phenyl-3-methylthiochromono[3,2-d]pyrazole (IVb); 3) 1,3-dimethylchromono[3,2-d]pyrazole; 4) 1-phenyl-3-methylchromono[3,2-d]pyrazole.

1-Phenyl-3-methylthiochromono[3,2-d]pyrazole-4-thione (VIIIb). This compound was similarly obtained in 72% yield and had mp 208-210° (from alcohol). Found: N 11.1; S 26.0%. $C_{12}H_{10}N_2S_2$. Calculated: N 11.4; S 26.0%.

Oxalate of 1,3-Dimethyl-4-hydroxy-4-dimethylaminopropylthiochromono[3,2-d]pyrazole (oxalate of IXa). A solution of 2.0 g (0.018 mole) of 3-dimethylaminopropyl chloride in 15 ml of tetrahydrofuran was added dropwise to 0.6 g (0.025 g-atom) of magnesium turnings (activated with iodine) in 50 ml of tetrahydrofuran, and the reaction mixture was refluxed for 1.5 h. A solution of 2.1 g (0.009 mole) of IVa in 20 ml of tetrahydrofuran was added to the solution of the Grignard reagent, and the mixture was refluxed for 1.5 h and cooled. The mixture was then poured into a solution of 9.0 g of ammonium chloride in 27 ml of water in the presence of 20 ml of ether. The ether extracts were washed with water and dried with sodium sulfate, and IXa was precipitated from the ether as the oxalate to give 2.6 g (70%) of a product with mp 141-144° (from absolute alcohol). Found: N 10.3; S 8.0%. $C_{17}H_{23}N_3OS \cdot H_2C_2O_4$. Calculated: N 10.3; S 7.9%.

1-Phenyl-3-methyl-4-hydroxy-4-dimethylaminopropylthiochromono[3,2-d]pyrazole (IXb). This compound was similarly obtained in 78% yield and had mp 83-85° (from acetone). Found: N 11.2; S 8.5%. $C_{22}H_{25}N_3OS$. Calculated: N 11.1; S 8.4%.

Oxalate of 1,3-Dimethyl-4-dimethylaminopropylidenethiochromono[3,2-d]pyrazole (oxalate of Xa). A 1-g sample of the oxalate of IXa was heated at 60° for 1 h in 10 ml of 2N. HCl, and the mixture was made alkaline with 20% sodium hydroxide solution and extracted with ether. The dried ether solution precipitated 0.7 g (70%) of the oxalate of Xa with mp 44-48°. Found: N 11.1; S 8.1%. $C_{17}H_{21}N_3S \cdot H_2C_2O_4$. Calculated: N 10.8; S 8.3%.

Oxalate of 1-Phenyl-3-methyl-4-dimethylaminopropylidenethiochromono[3,2-d]pyrazole (Xb). This compound was similarly obtained in 75% yield and had mp 98-100° (from absolute alcohol). Found: N 9.2; S 6.9%. $C_{22}H_{23}N_3S \cdot H_2C_2O_4$. Calculated: N 9.3; S 7.1%.

1,3-Dimethyl-4-hydroxy-4-ethylthiochromono[3,2-d]pyrazole (XIa). A solution of 0.8 g (0.0035 mole) of IVa in 15 ml of tetrahydrofuran was added to a Grignard reagent prepared from 0.34 g (0.014 g-atom) of magnesium turnings and 1.0 ml (0.014 mole) of ethyl bromide in 10 ml of tetrahydrofuran, and the mixture was refluxed for 1.5 h and worked up as in the preparation of IXb to give 0.91 g (90%) of XIa with mp 118-119° (from acetone). Found: N 10.6; S 12.2%. $C_{14}H_{16}N_2OS$. Calculated: N 10.8; S 12.3%.

1-Phenyl-3-methyl-4-hydroxy-4-ethylthiochromono[3,2-d]pyrazole. (XIb). This compound was similarly obtained in 86% yield and had mp 95-97° (from acetone). Found: N 8.9; S 9.9%. $C_{19}H_{18}N_2OS$. Calculated: N 8.7; S 9.9%.

The UV spectra of ethanol solutions (c $4 \cdot 10^{-5}$ M) were recorded with an SF-8 spectrophotometer.

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