NOVEL SYNTHESIS OF DIHYDROTHIAZOLO[2,3-f]XANTHINE DERIVATIVES

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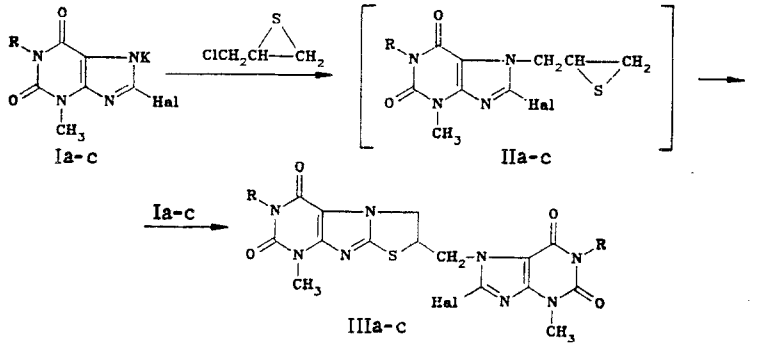
Dihydrothiazolo[2,3-f]xanthines are synthesized from 8-mercaptoxanthines and dibromoethane in an alkaline medium [1] and also by cyclization of 8-(2-chloroethylthio)xanthines in the presence of bases and 7-(2-haloethyl)-8-haloxanthines in the presence of sodium sulfide [2].

In the reaction of potassium salts of 8-haloxanthines Ia-c with epithiochlorohydrin, we unexpectedly obtained dihydrothiazolo[2,3-f]xanthine derivatives IIIa-c instead of the hypothesized 8-halo-7-(2,3-epithiopropyl)xanthines IIa-c.

The formation of compounds IIIa-c probably occurred as a result of the reaction of intermediate thiiranes IIa-c with the starting potassium salts of Ia-c.



I-IIIa R = CH_3 b, c R = H; a,b Hal = Cl, c Hal = Br

Dihydrothiazolo[2,3-f]xanthines IIIa-c were obtained in quantitative yields in the reaction of reagents in equimolar ratios in a DMFA medium at 95-100°C for 1-2 h.

The mass spectrum of compound III contained peaks of the molecular ion ($M^{+\cdot}$) with intensity ratio 3:1, which indicates the presence of one chlorine atom in the molecule. The peak with m/z 251, corresponding to abstraction of 1,3-dimethyl-8-chloroxanthine from the $M^{+\cdot}$ fragment, was maximum.

2,3-Dihydro-6,8-dimethyl-2-[(1,3-dimethyl-8-chloro-7-xanthinyl)methyl]thiazolo[2,3-f]-xanthine (IIIa). The compound had mp 287-289°C (from DMFA). Proton NMR spectrum (CF_3COOH, HMDS): 3.02 (3H, singlet, NCH_3), 3.08 (3H, singlet, NCH_3), 3.26 (6H, singlet, $2NCH_3$), 4.06...4.92 ppm (5H, multiplet, SCH and $2NCH_2$). Mass spectrum, m/z (relative intensity, %): 466 (12) and 464 (30) ($M^{+\cdot}$), 429 (45), 253 (11), 251 (100), 250 (62), 249 (35), 218 (14), 192 (11), 107 (10), 99 (38), 73 (15), 67 (14).

2,3-Dihydro-8-methyl-2-[(3-methyl-8-chloro-7-xanthinyl)methyl]thiazolo[2,3-f]xanthine (IIIb). The compound had mp >330°C (with decomposition, from acetic acid). Proton NMR

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spectrum (CF_3COOH, HDMS): 3.20 (3H, singlet, NCH_3), 3.23 (3H, singlet, NCH_3), 4.02-4.90 ppm (5H, multiplet, SCH and $2NCH_2$).

2-[(8-Bromo-3-methyl-7-xanthinyl)methyl]-2,3-dihydro-8-methylthiazolo[2,3-f]xanthine (IIIc). The compound had mp >330°C (with decomposition, from acetic acid). Mass spectrum: m/z 482 and 480 ($M^{+\cdot}$).

The data of elemental analysis of compounds IIIa-c corresponded to the calculated values.

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REGIOSELECTIVE ADDITION OF DICHLOROCARBENE TO 2-VINYLOXY-3,4-DIHYDROPYRANS

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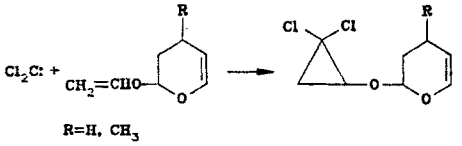
We have found that the reaction (temperature ~10°C, time ~2.5 h) between 2-vinyloxy-3,4-dihydropyrans and dichlorocarbene (generated from chloroform and the two-phase system CH_2Cl_2–50% NaOH) in the presence of triethylbenzylammonium chloride (TEBA) gives 3,4-dihydro-2-(2,2-dichlorocyclopropoxy)pyrans (the products of addition to the vinyloxy group) only:



Increasing the temperature and the reaction time failed to afford the products of addition to the endocyclic double bond. Omission of the methylene chloride from this system results in the partial formation of the diadduct.

To a mixture of 6.3 g of 2-vinyloxy-3,4-dihydropyran, 0.2 g of TEBA, 10 ml of CH_2Cl_2 and 16 ml of 50% NaOH was added at 10°C over 0.5 h with vigorous stirring a solution of 8 ml of chloroform in 10 ml of CH_2Cl_2. The mixture was stirred for 2 h at 10°C, and worked up in the usual way to give 5.95 g (57%) of 3,4-dihydro-2-(2,2-dichlorocyclopropoxy)pyran, bp 89°C (15 mm), n_D^{20} 1.4860, d_4^{20} 1.2370. PMR spectrum ($CDCl_3$), δ: 6.22 (1H, d, 6-H), 5.23 (1H, m, 2-H), 4.79 (1H, m, 5-H), 3.66 (1H, d.d, 1'-H), 1.92 (4H, m, 3- and 4-H), 1.62 ppm (2H, m, 3'-H). According to [1], bp 65°C (1 mm), n_D^{20} 1.4860, d_4^{20} 1.2368.

Obtained similarly was 3,4-dihydro-2-(2,2-dichlorocyclopropoxy)-4-methylpyran, bp 81°C (1 mm), n_D^{20} 1.4883, d_4^{20} 1.2312, yield 49%. PMR spectrum ($CDCl_3$), δ: 6.17 (1H, d, 6-H), 5.37 (1H, m, 2-H), 4.60 (1H, m, 5-H), 3.60 (1H, d.d, 1'-H), 1.87 (3H, m, 3- and 4-H), 1.58 (2H, m, 3'-H), 1.07 ppm (3H, d, 4-CH_3).

Elemental analytical data agreed with that calculated.

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