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IODOCYCLIZATION OF 2-ALLYLTHIO-4(3H)-PYRIMIDINONES

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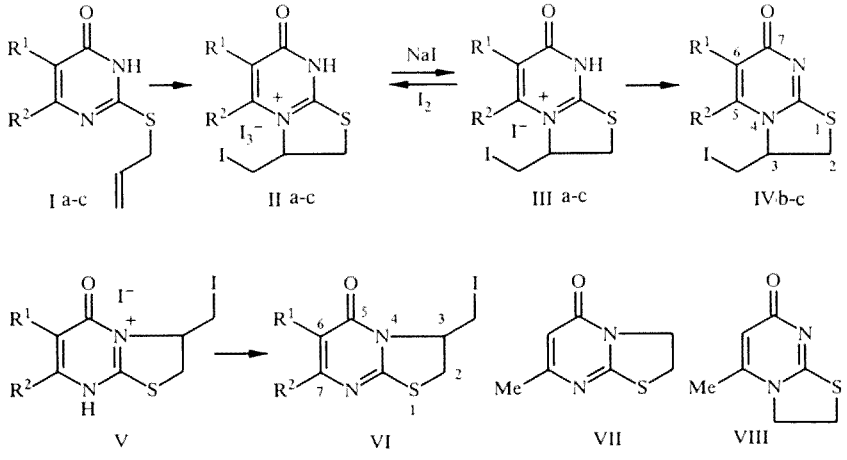
It has been established that the iodocyclization of 2-allylthio-4(3H)-pyrimidinones occurs at the $N_{(1)}$ nitrogen atom with the formation of 3-iodomethyl-7-oxo-2,3-dihydro-8H-thiazolo[3,2-d]pyrimidinium iodides and triiodides.

Thiazolopyrimidinium systems possess a broad spectrum of biological activity [1]. The aim of the present work was the synthesis of new compounds of the thiazolopyrimidine series by the iodocyclization of 2-allylthio-4(3H)-pyrimidinone (Ia), 2-allylthio-6-methyl-4(3H)-pyrimidinone (Ib), and 2-allylthio-5-ethyl-6-methyl-4(3H)-pyrimidinone (Ic).

The allyl sulfides (Ia-c) were obtained by the reaction of the corresponding 2-thiouracils with allyl bromide or chloride in ethanol in the presence of sodium ethylate and by reaction of the sodium salts of 2-thiouracils with allyl bromide in 2-propanol.

It was maintained in [2] that the reaction of 2-thiouracil with allyl bromide in the presence of hexamethyldisilazane gives 1-allyl-2-thiouracil but its melting point (136.7°C) and PMR spectrum conform to the allyl sulfuric (Ia). 1-Allyl-2-thiouracil obtained by the hetero-Claisen rearrangement of the allyl sulfide (Ia) has melting point 189.8°C [3].



I—III a $R^1 = R^2 = H$; b $R^1 = H$, $R^2 = Me$; I—IV c $R^1 = Et$, $R^2 = Me$

Theoretically the iodocyclization of the allyl sulfides (Ia-c) may proceed with the participation of the $N_{(1)}$ or $N_{(3)}$ atoms. A mixture of compounds may therefore be formed as on heterocyclization of 2-thiouracils with 1,2-dibromoethane [4, 5]. We have established that the iodocyclization of the allyl sulfides in various solvents (ethanol, acetone, dichloromethane, chloroform, ether) proceeds in only one of the possible directions. On reacting allyl sulfides (Ia-c) with iodine at an equimolar reactant ratio a mixture of two substances is formed, one of which [iodide (III)] contains one mole of iodine per mole of sulfide and the other [triiodide (II)] two moles of iodine. The triiodide (II) is formed with an excess of iodine and is transformed into the iodine (III) on treatment with sodium iodide in acetone. The iodide (III) reacts with iodine with the formation of the corresponding

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triiodine. The PMR spectra of iodide (II) and triiodide (III) are practically identical to one another, which confirms the iodocyclization but does not show to which nitrogen the ring closure occurs.

We have carried out the dehydrohalogenation of the iodides (IIIb, c) by the action of pyridine or sodium carbonate to establish the structure of the iodocyclization products. If the iodocyclization occurs with the participation of the $N_{(1)}$ nitrogen atom, then compounds (IVb, c) must be formed, but if $N_{(3)}$ participates then compound (VI) is formed. Essentially compounds (IVb, c) have a para-quinonoid structure and compound (VI) an ortho-quinonoid structure.

It is known from the literature [4-7] that the vibrations of the carbonyl group for ortho-quinonoid structures lie in the 1665-1700 cm^{-1} region [at 1690 cm^{-1} for compound (VIII)], and for para-quinonoid structures at 1630-1670 cm^{-1} [at 1640 cm^{-1} for compound (VII)].

The absorption of the carbonyl group in the IR spectra of compounds (IVb, c), the structures of which are close to that of compound (VIII), is located in the 1615-1640 cm^{-1} region. This may indicate the occurrence of iodocyclization at the $N_{(1)}$ nitrogen atom. Unlike compounds (IVb, c), the IR spectra of iodides (IIIa-c) contain an absorption for carbonyl group vibrations at 1680-1710 cm^{-1}, which probably indicates an ortho-quinonoid structure for these compounds.

The iodocyclization of allyl sulfides (Ia-c) therefore occurs with the formation of 3-iodomethyl-7-oxo-2,3-dihydro-8H-thiazolo[3,2-a]pyrimidinium triiodide (IIa) and iodide (IIIa), 3-iodomethyl-5-methyl-7-oxo-2,3-dihydrothiazolo[3,2-a]pyrimidinium triiodide (IIb) and iodide (IIIb), and 6-ethyl-3-iodomethyl-5-methyl-7-oxo-2,3-dihydrothiazolo[3,2-a]pyr imidinium triiodide (IIc) and iodide (IIIc).

EXPERIMENTAL

The IR spectra were obtained on a Specord IR-75 spectrometer in Nujol mulls and in CH_2Cl_2, the PMR spectra of compounds (Ia-c), (IIa-b), and (IIIb) on a Tesla (100 MHz) spectrometer and of compounds (IVb, c) on a Bruker (250 MHz) spectrometer with TMS as internal standard. A check on the course of reactions was carried out by TLC on Silufol UV 254 plates.

The data for the elemental analysis of compounds (IIIa-c) and (IVb, c) for sulfur and iodine corresponded to the calculated values.

2-Allylthio-6-methyl-4(3H)-pyrimidinone (Ib). A. 6-Methyl-2-thiouracil (5.72 g, 0.04 mole) and allyl bromide (5.2 ml, 0.06 mole) were added to a solution of metallic sodium (0.92 g, 0.04 mole) in ethanol (30 ml). The mixture was boiled for 1 h, the ethanol distilled off, and the residue crystallized from octane. The allyl sulfide (Ib) (3.5 g, 48%) was obtained with mp 133°C (literature [3] mp 134.2°C).

B. The sodium salt of 6-methyl-2-thiouracil (13.4 g, 0.1 mole) was suspended in 2-propanol (400 ml). Allyl bromide (10.4 ml) 0.12 mole was added and the mixture stirred for 16 h (~ 20°C). The alcohol was distilled off and the residue crystallized from a benzene–acetone mixture. The allyl sulfide (Ib) (12.7 g, 70%) was obtained with mp 133°C. IR spectrum: 3350 (NH), 1670 (C=O), 975 cm^{-1} (=CH_2). PMR spectrum [$(CD_3)_2SO$]: 2.18 (3H, s, CH_3); 3.80 (2H, d, SCH_2, J = 7 Hz); 5.22 (2H, m, =CH_2); 5.87 (1H, m, CH=); 5.99 (1H, s, 5-H); 12.40 ppm (1H, s, N–H).

2-Allylthio-4(3H)-pyrimidinone (Ia) was obtained by method A from 2-thiouracil and allyl bromide in ethanol in the presence of sodium ethylate. Yield was 73% of mp 134°C (from octane) (literature [3] mp 136°C). IR spectrum: 3280 (N–H), 1670 (C=O), 970 cm^{-1} (=CH_2). PMR spectrum: [$(CD_3)_2SO$]: 3.86 (2H, d, SCH_2, J = 6.6 Hz); 5.23 (2H, m, =CH_2); 5.91 (1H, m, =CH); 6.10 (1H, d, 5-H, J = 6.6 Hz); 7.86 ppm (1H, d, 6-H, J = 6.6 Hz).

2-Allylthio-5-ethyl-6-methyl-4(3H)-pyrimidinone (Ic). A. The compound was obtained from 5-ethyl-6-methyl-2-thiouracil and allyl bromide. Yield was 33% of mp 125°C (from octane).

B. The compound was obtained from the sodium salt of 5-ethyl-6-methyl-2-thiouracil in 2-propanol. Yield was 68% of mp 128°C (from benzene–acetone). IR spectrum: 3350 (NH), 1635 (C=O), 975 cm^{-1} (=CH_2). PMR spectrum ($CDCl_3$); 1.08 (3H, m, CH_3, J = 7.3 Hz); 2.27 (3H, s, 6-CH_3); 2.49 (2H, q, CH_2); 3.81 (2H, d, SCH_2, J = 5.9 Hz); 5.20 (2H, m, =CH_2); 5.90 ppm (1H, m, CH=).

General Procedure for Obtaining Triiodide (IIa-c). Iodine (7.62 g: 0.003 mole) in ether (150 ml) was added to a solution of allyl sulfide (Ia-c) (0.001 mole) in ether (50 ml). After 48 h the precipitated triiodide was filtered off, dissolved in acetone, and reprecipitated with ether.

3-Iodomethyl-7-oxo-2,3-dihydro-8H-thiazolo[3,2-a]pyrimidinium Triiodide (IIa). Yield 74% of mp 152-154°C (with decomposition). PMR spectrum [$(CD_3)_2SO$]: 3.2-4.2 (4H, m, CH_2I, SCH_2); 4.85 (1H, m, 3-H); 6.15 (1H, d, 6-H, J = 7.5 Hz); 8.03 ppm (1H, d, 5-H, J = 7.5 Hz).

3-Iodomethyl-5-methyl-7-oxo-8H-thiazolo[3,2-d]pyrimidinium Triiodide (IIb). Yield 78% of mp 172.8°C (with decomposition). PMR spectrum [$(CD_3)_2SO$]: 2.47 (3H, s, CH_3); 3.5-4.0 (4H, m, CH_2I, SCH_2); 5.34 (1H, m, 3-H); 6.31 ppm (1H, s, 6-H).

6-Ethyl-3-iodomethyl-5-methyl-7-oxo-2,3-dihydro-8H-thiazolo[3,2-a]pyrimidinium Triiodide (IIc). Yield of 75% of an oil. IR spectrum: 1710 cm^1 (C=O).

General Procedure for Obtaining Iodides (IIIa-c). A solution of sodium iodide dihydrate (1 mmole) in acetone (10 ml) was added with stirring to a solution of triiodide (IIa-c) (0.5 mmole) in acetone (5 ml). After 1 h the solid was filtered off and washed with acetone.

3-Iodomethyl-7-oxo-2,3-dihydro-8H-thiazolo[3,2-a]pyrimidinium Iodide (IIIa). Yield 52% of mp 183-185°C. IR spectrum: 1690 cm^{-1} (C=O).

3-Iodomethyl-5-methyl-7-oxo-2,3-dihydro-8H-thiazolo[3,2-a]pyrimidinium Iodide (IIIb). Yield 62% of mp 182°C (with decomposition). IR spectrum: 1700 cm^{-1} (C=O). PMR spectrum [$(CD_3)_2SO$]: 2.45 (3H, s, CH_3); 3.4-4.1 (4H, m, SCH_2, CH_2I); 5.30 (1H, m, 3-H); 6.10 ppm (1H, s, 6-H).

6-Ethyl-3-iodomethyl-5-methyl-7-oxo-2,3-dihydro-8H-thiazolo[3,2-a]pyrimidinium Iodide (IIIc). Yield 62% of mp 172°C (with decomposition). IR spectrum: 1680 cm^{-1} (C=O).

3-Iodomethyl-5-methyl-7-oxo-2,3-dihydrothiazolo[3,2-a]pyrimidine (IVb). A. The iodide (IIIb) (1.38 g, 2 mmole) was added with stirring to a solution of sodium carbonate (0.25 g, 2.4 mmole) in water (50 ml). After the end of CO_2 evolution the solution was extracted with dichloromethane (2 × 50 ml). The extract was dried with anhydrous sodium sulfate, the solvent distilled off, and the residue crystallized from an acetone–chloroform mixture. Compound (IVb) (0.59 g, 95%) was obtained of mp 149-150°C. IR spectrum: 1640 cm^{-1} (C=O).

B. Pyridine (0.16 ml: 2 mmole) was added to iodide (IIIb) (1.38 g, 2 mmole). After 1 h the mixture was extracted with chloroform. The chloroform was distilled off and the residue crystallized from an acetone–chloroform mixture. Yield was 0.55 g (89%). PMR spectrum ($CDCl_3$): 2.30 (3H, s, CH_3); 3.75 (2H, m, SCH_2); 3.55 (2H, m, CH_2I); 4.86 (1H, m, 3-H); 5.89 ppm (1H, s, 6-H).

6-Ethyl-3-iodomethyl-5-methyl-7-oxo-2,3-dihydrothiazolo[3,2-a]pyrimidine (IVc). Yield was 94% by method A and 86% by B, mp 134°C (with decomposition). IR spectrum: 1615 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 0.98 (3H, m, $\underline{CH_3}CH_2$); 2.28 (3H, s, 5-CH_3); 2.40 (2H, q, $CH_3\underline{CH_2}$); 3.17-3.75 (2H, m, SCH_2); 3.51 (2H, m, CH_2I); 4.94 ppm (1H, m, 3-H).

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