ALKYLATION OF 2-METHYLTHIO-4-HYDROXYPYRIMIDINES BY METHYL BROMOACETATE

P. I. Vainilavichyus and V. Yu. Syadyaryavichyute

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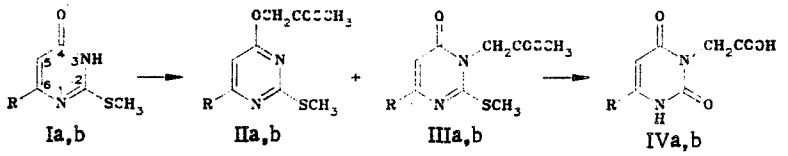
2-Methylthio-4-hydroxypyrimidines react with methylbromoacetate in methanol–sodium methoxide solution to give O- and $N_{(3)}$-alkylated products, namely, 2-methylthio-4-(methoxycarbonyl)methoxypyrimidines and 2-methylthio-3-(methoxycarbonyl)methylpyrimid-4-ones.

O- and N-alkoxycarbonylmethyl substituted 2-methylthio-4-hydroxypyrimidines are useful and promising intermediates in the synthesis of a variety of pyrimidine derivatives.

The simplest method for the preparation of these compounds involves alkylation of alkali metal salts of 2-methylthio-4-hydroxypyrimidines with haloacetic acid esters. Contradictory information has appeared, however, concerning this problem. Thus, the alkylation product of 2-ethylthio-4-hydroxypyrimidine with ethylchloroacetate in a mixture of ethanol–sodium ethoxide has been reported in one paper [1] to be the $N_{(1)}$ derivative, while in a later paper the alkylation products of 6-methyl-2-methylthio-4-hydroxypyrimidine by methyl and ethyl bromoacetate esters, in mixtures of methanol–sodium methoxide or ethanol–sodium ethoxide, have been reported to be the O-derivatives [2].

We have studied the reactions of 2-methylthio-4-hydroxypyrimidines (I) with methyl bromoacetate in methanol–sodium methoxide.



Ia,b IIa,b IIIa,b IVa,b

I–IV a R=H; b R=CH_3

Two products were isolated from the product mixture, although it is known [3], that three products, namely, O-, $N_{(1)}$-, and $N_{(3)}$-alkylated derivatives, can be formed upon treatment of alkali metal salts of 4-hydroxypyrimidines with alkyl halides. The UV spectra of compounds II contain absorption maxima at 253 (IIa) and 258 nm (IIb). The IR spectra of II contain absorption bands at 1736 (IIa) and 1740 cm^{-1} (IIb), which are characteristic of ester C=O stretching vibrations, and do not contain any bands in the 1600-1720 cm^{-1} region, which would be expected for a lactam C=O stretching vibration in 4-pyrimidones [4]; this rules out the N-alkylated structure. These data agree very well with the UV and IR spectra of model 2-alkylthio-4-alkoxypyrimidines [5, 6], and make it possible to assign 2-methylthio-4-(methoxycarbonyl)methoxypyrimidine structures to isomers II. The UV spectra of compounds III contain bands at 290 (IIIa) and 304 nm (IIIb), while their IR spectra contain not only ester C=O stretching bands at 1736 (IIIa) and 1747 cm^{-1} (IIIb), but also a lactam C=O stretch in the 1669 (IIIa) or 1671 cm^{-1} region (IIIb). The similarity in the IR and UV spectra of compounds III with those of 2-alkylthio-3-alkylpyrimidin-4-ones [5, 6] enables us to assign 2-methylthio-3-(methoxycarbonyl)methylpyrimidin-4-one structures to these compounds III. Further evidence for the structures of III was obtained by their conversion to uracil derivatives IV, in analogy with [7]. The presence of a carboxymethyl group in the 3-position of the uracil ring was confirmed by the bathochromic shift in the UV absorption maximum in the transition from neutral to basic media [8]. The PMR spectra of the O- (II) and $N_{(3)}$-isomers (III) differ from one another to the greatest extent in terms of the positions of the SCH_3 and 5-CH group signals. In the spectra of isomers III the SCH_3 group proton signals are found 0.33-0.42 ppm downfield, and the 5-CH proton signal is found 0.23-0.30 ppm upfield,

V. Kapsukas Vilnius State University, Vilnius 232734. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1520-1522, November, 1987. Original article submitted June 27, 1986.

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relative to the corresponding signals in isomers II. The characteristic signals differentiating the ^{13}C-NMR signals of isomers IIb and IIIb are the $C_{(5)}$ signal and the signals of the CH_2 groups located at the oxygen and nitrogen atoms. Thus, the spectrum of isomer IIIb contains the $C_{(5)}$ signal 5.6 ppm downfield, and the NCH_2 signal 18.19 ppm upfield of the $C_{(5)}$ and OCH_2 signals in the spectrum of isomer IIb.

Alkylation of 2-methylthio-4-hydroxypyrimidines with methyl bromoacetate in a methanol–sodium methoxide system has thus been shown to lead to a mixture of O- and $N_{(3)}$-alkylated products, in approximately equal ratios; this result contradicts data reported earlier [1, 2].

EXPERIMENTAL

The course of the reactions as well as purities of the compounds were monitored by TLC on Silufol plates. Column chromatography was carried out on silica gel (L 100/160 Chemapol). Chloroform–ethyl acetate (5:1) was used as eluent. UV spectra were measured on a Specord UV-Vis spectrophotometer using ethanol solutions. IR spectra were recorded on a Specord IR-75 spectrophotometer using suspensions in Vaseline oil. ^1H- and ^{13}C-NMR spectra were obtained on Tesla BS 487C (80 MHz) and 567Z (25.14 MHz) spectrometers versus HMDS as internal standard.

Compounds I were synthesized according to [9, 10].

2-Methylthio-4-(methoxycarbonyl)methoxypyrimidines (II) and 2-Methylthio-3-(methoxycarbonyl)methylpyrimid-4-ones (III). A mixture of 0.1 mole 2-methylthio-4-hydroxypyrimidine I and 5.4 g (0.1 mole) sodium methoxide in 100 ml methanol was stirred at reflux for 15 min. Methyl bromoacetate (18.4 g, 0.12 mole) was added dropwise. The mixture was refluxed for 4 h, the solvent was evaporated under vacuum, and the residue was worked up with 500 ml water, filtered, and dried. Yield 11.1 g (52%) of a mixture of isomers IIa and IIIa, or 16.6 g (73%) of a mixture of IIb and IIIb. The mixture of isomers was dissolved in chloroform–ethyl acetate (5:1) and separated on a column (h = 120 cm, d = 4 cm). The R_f 0.38 fraction contains 5.05 g (25%) of compound IIa, mp 54-55°C (hexane). IR spectrum: 1740 cm^{-1} (C=O, ester). UV spectrum, λ_{max} (log ε): 204 (4.07), 252 nm (4.16). PMR spectrum (CF_3COOH): 2.25 (3H, s, SCH_3); 3.45 (3H, s, OCH_3); 4.83 (2H, s, OCH_2); 6.58 (1H, d, J = 7 Hz, 5-CH); 7.95 ppm (1H, d, J = 7 Hz, 6-CH). Found: C 45.1; H 4.6; N 12.9%. $C_8H_{10}N_2O_3S$. Calculated: C 44.9; H 4.7; N 13.1%; M 214.

The 0.23 R_f fraction contains 4.7 g (22%) of compound IIIa, mp 95-96°C (hexane). IR spectrum: 1747 (C=O, ester), 1669 cm^{-1} (C=O, lactam). UV spectrum, λ_{max} (log ε): 224 (3.73), 292 nm (3.89). PMR spectrum (CF_3COOH): 2.58 (3H, s, SCH_3); 3.47 (3H, s, OCH_3); 4.66 (2H, s, NCH_2); 6.28 (1H, d, J = 8 Hz, 5-CH); 7.51 ppm (1H, d, J = 8 Hz, 6-CH). Found: C 45.2; H 4.6; N 12.9%. $C_8H_{10}N_2O_3S$. Calculated: C 44.9; N 4.7; N 13.1%; M 214.

The 0.57 R_f fraction contains 7.5 g (33%) of compound IIb, mp 80.5-81.5°C (hexane). IR spectrum: 1736 cm^{-1}(C=O, ester). UV spectrum, λ_{max} (log ε): 204 (4.02), 253 nm (4.11). PMR spectrum (CF_3COOH): 2.14 (3H, s, CH_3); 2.21 (3H, s, SCH_3); 3.41 (3H, s, OCH_3); 4.79 (2H, s, OCH_2); 6.38 ppm (1H, s, 5-CH). ^{13}C-NMR spectrum ($CDCl_3$): 13.64 (SCH_3); 23.54 ($C_{(6)}$–$\underline{CH_3}$); 51.88 (OCH_3); 62.27 (OCH_2); 101.71 ($C_{(5)}$); 167.93; 168.30, 168.67, 171.14 ppm (C=O, $C_{(2)}$, $C_{(4)}$, $C_{(6)}$). Found: C 47.6; H 5.2; N 11.8%. $C_9H_{12}N_2O_3S$. Calculated: C 47.4; H 5.3; N 12.3%; M 228.

The 0.45 fraction contains 7.5 g (33%) of compound IIIb, mp 76-77°C (hexane). IR spectrum: 1736 (C=O, ester), 1671 cm^{-1} (C=O, lactam). UV spectrum, λ_{max} (log ε): 226 (3.71), 290 nm (3.88). PMR spectrum (CF_3COOH): 2.12 (3H, s, CH_3); 2.63 (3H, s, SCH_3); 3.51 (3H, s, OCH_3); 4.72 (2H, s, NCH_2); 6.15 ppm (1H, s, 5-CH). ^{13}C-NMR spectrum ($CDCl_3$): 14.84 (SCH_3); 23.58 ($C_{(6)}$–$\underline{CH_3}$); 44.08 (NCH_2); 52.48 (OCH_3); 107.27 ($C_{(5)}$); 161.13; 161.58; 162.74; 166.99 ppm (C=O), $C_{(2)}$, $C_{(4)}$, $C_{(6)}$). Found: C 46.9; H 5.2; N 12.3%. $C_9H_{12}N_2O_3S$. Calculated: C 47.4; H 5.3; N 12.3%; M 228.

2,4-Dioxo-1,2,3,4-Tetrahydro-3-pyrimidinylacetic Acid (IV). A mixture of 0.5 mmole of compound III and 3.4 ml of a 2N HCl solution was refluxed for 6 h and then cooled. The precipitate was removed by filtration and recrystallized from water. Yield of compound IVa 0.55 g (65%), mp 220-222°C (according to [11], mp 222-224°C). UV spectrum, λ_{max} (log ε): 211 (3.61), 261 nm (3.64); $\lambda_{max}^{pH\ 13}$ (log ε): 223 (3.77), 286 nm (3.84). Yield of compound IVb 0.63 g (68%), mp 244-246°C (according to [2], mp 254-255°C). UV spectrum, λ_{max} (log ε): 210 (3.83), 260 nm (3.91); $\lambda_{max}^{pH\ 13}$ (log ε): 222 (3.96), 294 nm (4.07).

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SOLVATION EFFECTS IN THE METHYLATION OF BARBITURIC ACID AND ITS DERIVATIVES BY DIAZOMETHANE

K. A. Krasnov, V. I. Slesarev, A. P. Zakharov, and É. G. Grigor'eva

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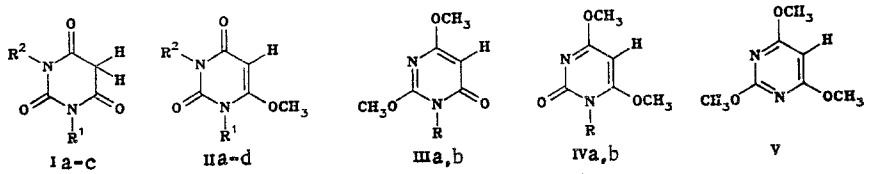
Methylation of barbituric acid and its N-methylderivatives by diazomethane in ethers and methanol occurs only at the oxygen atom of the β-dicarbonyl fragment. The resulting 6-methoxy-2,4-dioxo-1,2,3,4-tetrahydropyrimidine and its derivatives are methylated at both the oxygen and nitrogen atoms; relative to ethers, methanol facilitates a greater degree of methylation at the nitrogen atom.

The mechanism of methylation of acids by diazomethane involves the formation of acid anions [1]. Ionization of barbituric acid (Ia) and its derivatives results in the formation of ambident anions, in which the negative charge is delocalized among the oxygen, nitrogen, and carbon atoms. In ambident anions derived from oxopyrimidines, the oxygen atoms are the "hardest" sites, and the $C_{(5)}$ carbon atom is the "softest" site. Proton donating solvents tend to deactivate to a large extent the hard sites in ambident anions [2, 3], due to hydrogen bonding; thus, methylation of oxopyrimidines in methanol would be expected to lead to an increase in the fraction of alkylation occurring at the soft sites, relative to the corresponding reactions of these compounds in ethers (diethyl ether and 1,2-dimethoxyethane).

In order to determine the qualitative composition of the mixtures formed during the methylation of barbituric acid and its derivatives by diazomethane, we synthesized the following series of model compounds, using known methods:



Ia-c IIa-d IIIa,b IVa,b V

I, II a $R^1=R^2=H$; b $R^1=CH_3$, $R^2=H$; c $R^1=R^2=CH_3$; II d $R^1=H$, $R^2=CH_3$; III, IV a $R=H$, b $R=CH_3$

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