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HETEROCYCLIC COMPOUNDS BASED ON MALEIC ACID MONOUREIDE

1. STRUCTURE AND TRANSFORMATIONS OF THE PRODUCT OF BROMINATION OF MALEIC ACID MONOUREIDE

I. K. Yurgevits, É. L. Kupche, and U. Ya. Mikstais

UDC 547.781'787'854.9'867.2:541.61

The products of the bromination in water of maleic acid monoureide and its methyl ester have the 2-imino-5-bromocarboxy(carbomethoxy)methyl-4-oxazolidone structure. 2-Imino-5-bromocarboxymethyl-4-oxazolidone undergoes dehydrobromination in aprotic polar solvents to give 2-imino-5-carboxymethylidene-4-oxazolidone. In the presence of dry hydrogen chloride in dimethylacetamide the oxazole ring undergoes dehydrobromination and isomerization to an imidazole ring with the formation of 5-carboxymethylidenehydantoin. Methyl α-bromofumarate monoureide is formed when the oxazole ring of 2-imino-5-bromocarbomethoxymethyl-4-oxazolidone is opened with alkali.

Promising methods for the synthesis of orotic acid (II) and its salts have been developed on the basis of the halogenation of maleic acid monoureide (I) [1-4].

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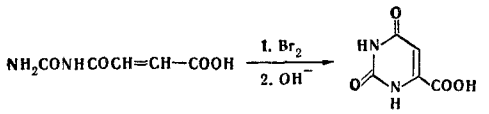
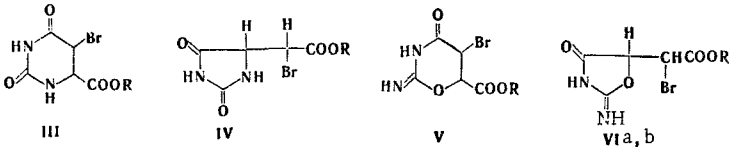


I II

The literature contains contradictory data relative to the structure of the product of bromination of maleic acid monoureide in water. Cavallito and Smith [5] proposed a β-bromomaleic acid monoureide structure for the bromination product. Later [4], a cyclic structure was adopted for bromination product III on the basis of the presence in the PMR spectrum of the products of bromination of maleic acid monoureide and its methyl ester of signals of CH−CH protons, which contradict the β-bromomaleic acid monoureide structure.

However, the formation of four isomeric cyclic structures (III-VI) is possible in the case of intramolecular cyclization of the hypothetical intermediates in the bromination:



III IV V VIa,b

VI a R=H; b R=CH_3

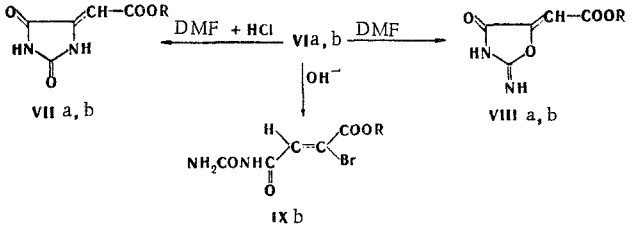
In the present research a study of the dehydrobromination and ring opening made it possible to establish a 2-imino-5-bromocarboxy(carbomethoxy)methyl-4-oxazolidone structure (VIa,b) for the products of bromination of maleic acid monoureide and its methyl ester.

The bromination product is converted to a carboxymethylidenehydantoin (VII) in solution in dimethylformamide (DMF) in the presence of dry hydrogen chloride. 2-Imino-5-carboxymethylidene-4-oxazolidone (VIII) [6] was isolated in the dehydrobromination of VI under conditions that do not lead to isomerization of the oxazole ring to an imidazole such as, for example, by the action of aprotic polar solvents [dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and dimethylacetamide (DMA)].

The formation of oxazolidone VIII and VII in the dehydrobromination of the bromo product excludes the 5-bromo-5,6-dihydroorotic acid structure (III).

Treatment of ester VIb with an equimolar amount of potassium hydroxide in water gives a product of opening of the oxazole ring, viz., methyl α-bromofumarate monoureide (IXb). Under these conditions free acid VIa forms VIIIa.

The IXa,b structure was determined by a comparison of the experimentally found chemical shifts of the olefin protons attached to the C_β atom with the calculated value with allowance for the chemical shift of the proton attached to the C_β atom of a model (fumaric acid monoureide) and the shielding constant of bromine (σ_{trans}) for olefin protons [7].



VII a,b VIa,b VIII a,b IX b

VII–IX a R=H; b R=CH_3

The calculated value of the chemical shift of the olefin proton attached to the C_β atom for IXb (δ_3-H_{calc} 7.76 ppm) is in good agreement with the experimentally found value (δ_3-H_{exp} 7.83 ppm). The difference in the experimentally found chemical shifts of the protons attached to the C_β atom of methyl ester IXb (δ 7.83 ppm)

TABLE 1. Characteristics of the Synthesized Compounds

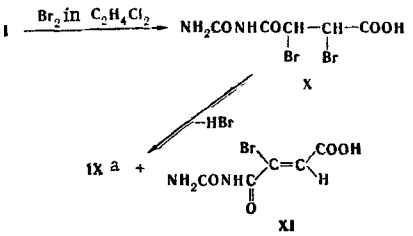
Compound	mp, °C	PMR spectrum, δ, ppm (d_6-DMSO)	IR spectrum, cm^{-1}	UV spectrum in H_2SO_4, λ_{max}, nm, (log ε)	Yield, %
VIa	149—150 (dec.)	4,98 d (J=2,6 Hz), 1H (CH); 5,26 d (J=2,6 Hz), 1H (CH); 8,75 s[a], 3H (NH and COOH)	1712 (sh), 1690 (sh), 1650, 3360, 3300, 3215—2500 (several bands)	217 (4,33)	83,5
VIb	144—145	3,80 s, 3H (CH_3); 5,16 d, (J=2,9 Hz), 1H (CH); 5,31 d (J=2,9 Hz), 1H (CH); 8,70 s[a] 1H (NH); 8,81 s[a], 1H (NH)	1735 (sh), 1725, 1678 (sh), 1650, 1550, 1540 (sh), 3310, 3100—2500 (several bands)[b], 1766, 1744, 1725, 1700 (sh), 1656, 1572[c]	219 (4,28); 248 (3,77) (sh)	82
VIIIa	280 (dec.) >360 (sh)	5,74 s 1H (C=CH); 8,38 s[a], 2H (NH)[d]	1745 (sh), 1715, 1690 (sh), 1680 (sh), 1580, 1560, 3260, 3100, 3000—2500 (several bands)	250 (4,36)	77,5
VIIIb	217—219 (dec.)	3,77 s, 3H (CH_3); 5,81 s, 1H (C=CH); 9,50 s[a], 2H (NH)	1748 (sh), 1715 (sh), 1700, 1680, 1588, 1568, 3280, 3000—2500 (several bands)	250 (4,25)	75
IXb	198—200	3,88 s, 3H (CH_3); 7,47 s[a], 2H (NH_2); 7,83 s 1H (CH=C); 10,61 s[a], 1H (NH)	1752, 1722, 1704, 1676, 1586, 1576 (sh); 3405, 3300, 3260, 3200, 3140	250 (3,71)	100
IXa	188	7,52 s, 2H (NH_2); 7,77 s, 1H (CH=C); 10,63 s[a], 1H (NH)	1725, 1708, 1696, 1644, 1592; 3400, 3300, 3210, 3175, 3070	220 (3,88)	25
X	161—162	4,74 m, 2H (CH—CH); 7,45 s[a], 2H (NH_2); 10,72 s[a], 1H (NH)	1712, 1694 (sh), 1672, 1648 (sh), 1632 (sh), 1576, 3420, 3390, 3320, 3230, 3150	214 (3,84)	100
XI	177—178	7,30 s, 1H (CH=C); 7,58 s[a], 2H (NH_2); 10,72 s[a], 1H (NH)	1725 (sh), 1712, 1688, 1660, 1594, 3375, 3325, 3175, 3050	216 (3,90); 250 (3,79)	25

a) Broad singlet. b) In mineral oil. c) In dioxane. d) The δ_{COOH} peaks here and for IXa (R = H), X, and XI are found at 9.5-13.5 ppm.

and free acid IXa (δ 7.77 ppm) corresponds to the divergence of the shielding constants for the olefin protons of the ester and carboxy groups [7]. The chemical shifts of the olefin protons attached, respectively, to the C_α and C_β atoms calculated for β-bromofumaric acid β-monoureide (XI) and α- and β-bromomaleic acid β-monoureides differ considerably from the values for IXa,b.

The location of the bromine atom at C_α in IXa,b was confirmed by a comparison of the chemical shifts of the C_β and C_α atoms in the ^{13}C NMR spectra of IXa,b and XI, respectively, and also by methylation of IXa. The difference in the ^{13}C chemical shifts of the C_β atoms for IXa,b (δ 134.16 ppm for IXa and δ 135.26 ppm for IXb) and C_α atoms for XI (δ 130.32 ppm) is in agreement with the concept of the distribution of the electron density in the IX and XI molecules.

Free acids IXa and XI were obtained by dehydrobromination of α,β-dibromosuccinic acid monoureide (X), which is formed in the bromination of I in 1,2-dichloroethane. The location of bromine at C_α in IXa,b excludes the possibility of the 2-imino-5-bromo-5,6-dihydro-6-carboxy(carbomethoxy)-1,3-oxazin-4-one structure (V) for the cyclic bromo product.



The 5-bromocarboxymethylhydantoin structure (IV) was rejected in [4] because of the absence of the $\nu_{C=O}$ absorption band at ~1780 cm^{-1} that is expected in the IR spectra for a hydantoin structure. A study of the IR spectra confirms structure VI. As a consequence of rotational isomerism, two $\nu_{C=O}$ bands at 1766 and 1744 cm^{-1} are observed in the IR spectrum of a solution of VIb in dioxane. Only one band at ~1735 cm^{-1}

(shoulder) is observed in the IR spectrum of the solid. The data obtained are in agreement with the results of a study of the $\nu_{C=O}$ absorption of α-halo ketones and esters [8].

Thus in the bromination of maleic acid ureide in water Br^+ adds to C_α of maleic acid with the subsequent formation of an oxazole ring as a consequence of intramolecular nucleophilic addition of the oxygen atom of the carbiminol form of the ureido group at the C_β atom.

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EXPERIMENTAL

The ^1H and ^{13}C NMR spectra of solutions of the compounds in DMSO were recorded with a Brucker Physik Fourier WH-90 spectrometer (90 and 22.63 MHz, respectively) with tetramethylsilane as the internal standard. The IR spectra of KBr pellets, suspensions in mineral oil, and solutions in dioxane were recorded with a Perkin–Elmer 325 spectrometer. The UV spectra of aqueous solutions were recorded with a Unicam SP-8000 spectrophotometer. The compositions of the synthesized compounds were confirmed by the results of elementary analysis. The yields and characteristics of the synthesized compounds are presented in Table 1.

The synthesis of 2-imino-5-bromocarboxy(carbomethoxy)metho-4-oxazolidone (VIa,b) was carried out by the methods in [3, 4].

Dehydrobromination of VIa in the Presence of Hydrogen Chloride. A 2.37-g (0.01 mole) sample of VIa was dissolved in 15 ml of absolute DMF saturated with dry hydrogen chloride, and the mixture was maintained at 25°C for 24 h and heated at 90°C for 2 h. It was then treated with ether, and the precipitate, which was suspended in the water, was removed by filtration, washed with water, and crystallized from water to give 0.8 g (51.2%) of 5-carboxymethylidenehydantoin (VIIa) with mp 360°C (dec.). The product was identical to the standard sample obtained in [4]. IR spectrum (KBr): 3260, 3200 (NH); 3070 (CH); 1787, 1742, 1729, 1696 (C=O); 1682, 1655 cm^{-1} (C=C, NH). PMR spectrum (d_6-DMSO), δ: 5.50 (1H, s, C=CH), 10.4 s, 11.5 s, and 9.5-13.5 ppm (a total of 3H, 1-H, 3-H, and COCH).

Dehydrobromination of VIa in Dimethylacetamide (DMA). A 2.37-g (0.01 mole) sample of VIa was dissolved in 15 ml of absolute DMA, and the solution was maintained at 25°C for 24 h. The mixture was worked up as in the preparation of VIIa and dried in vacuo [1 mm (mercury column)] at 97°C to give 1.35 g (77.5%) of 2-imino-5-carboxymethylidene-4-oxazolidone (VIIIa). 2-Imino-5-carbomethoxymethylidene-4-oxazolidone (VIIIb) (in 75% yield) was similarly obtained and isolated, except that the reaction mixture was heated at 70°C for 1 h.

The rearrangement of 2-imino-5-carboxymethylidene-4-oxazolidone (VIIIa) to 5-carboxymethylidenehydantoin (VIIa) was carried out as in the case of dehydrobromination in the presence of hydrogen chloride. The yield was 70%. The product was identical to the standard sample obtained in [4].

Methyl α-Bromofumarate Monoureide (IXb). A 2.37-g (0.01 mole) sample of VIb was suspended in water, and the suspension was cooled to 0-5°C and treated with 0.01 mole of cold aqueous potassium hydroxide solution. The mixture was maintained at 10-15°C for 15 min, and the resulting precipitate was removed by filtration, washed with water, and dried in vacuo. The yield was quantitative.

α,β-Dibromosuccinic Acid Monoureide (X). A 15.8-g (0.1 mole) sample of I was suspended in 100 ml of 1,2-dichloroethane, and 16 g (0.1 mole) of bromine was added with stirring at 20-25°C in the course of 1-2 h. After clarification, the mixture was filtered, and the solid material was washed with 1,2-dichloroethane and dried. The yield was quantitative.

α-Bromofumaric Acid β-Monoureide (IXa) and β-Bromofumaric Acid β-Monoureide (XI). A 6.36-g (0.02 mole) sample of X was suspended in 10 ml of water, and the suspension was heated at 90-100°C for 15 min. The mixture was cooled, and the precipitate was removed by filtration and dried to give 2.37 g (50%) of IXa and XI, which were separated by extraction with ethanol.

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SYNTHESIS AND STRUCTURE OF 6-SUBSTITUTED 9-(2-ETHOXY-1,3-DIOXAN-5-YL)PURINES

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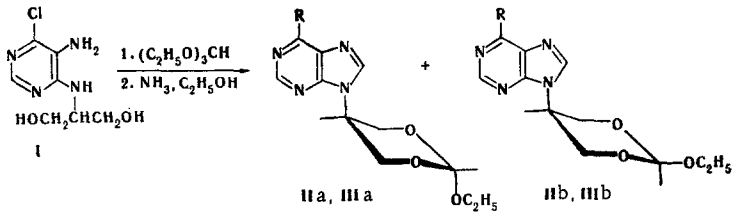
The reaction of 4-chloro-5-amino-6-(1,3-dihydroxy-2-propyl)aminopyrimidine with excess ethyl orthoformate gave a cyclic acetal, viz., 6-chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine, amination of which yielded 6-amino-9-(2-ethoxy-1,3-dioxan-5-yl)purine. The presence of two configurational isomers with a diaxial orientation of the purine ring and the ethoxy group in the trans isomer and an equatorial orientation of the ethoxy group in the cis isomer was established for these compounds by ^1H and ^{13}C NMR and IR spectroscopy. The three-dimensional structure of trans-6-chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine was determined by an x-ray difraction study, and the trans-diaxial orientation of the purine ring and the ethoxy group was confirmed; it is shown that the dioxane ring is in an anti conformation relative to the purine ring.

It has been previously shown [1, 2] that an imidazole ring is formed in the reaction of 4-chloro-5-amino-6-(1,3-dihydroxy-2-propylamino)pyrimidine (I) with ethyl orthoformate under acid catalysis conditions. However, under the same conditions, I, which contains a 1,3-dihydroxypropyl residue, undergoes transesterification with excess orthoester to give a cyclic derivative, viz., 6-chloro-9-(2-ethoxy-1,3-dioxan-5-yl)purine (II), the reaction of which with an alcohol solution of ammonia gave 6-amino-9-(2-ethoxy-1,3-dioxan-5-yl)purine (III).



II R=Cl; III R=NH_2

The interest in II and III, which contain a saturated six-membered heteroring in the 9 position of the purine ring, is due to the fact that, with respect to their biochemical properties, they may be classified as analogs of nucleosides, since some derivatives of this type are capable of forming complexes with enzymes that use natural nucleosides as substrates [3, 4] and display high physiological activity, including antitumorigenic activity [5]. In addition II and III also proved to be of interest in a stereochemical respect.

It is known that a chair conformation with an axial orientation of the alkoxy group (the anomeric effect) is preferred for 2-alkoxy-1,3-dioxane molecules [6]. At the same time, depending on the nature of the

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