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REACTION OF 1,2,3,4-TETRAHYDRO-2,4,5-TRIMETHYLPYRROLO[1,2-*c*]PYRIMIDINE AND ITS 7-FORMYL-SUBSTITUTED DERIVATIVE WITH NITRIC ACID

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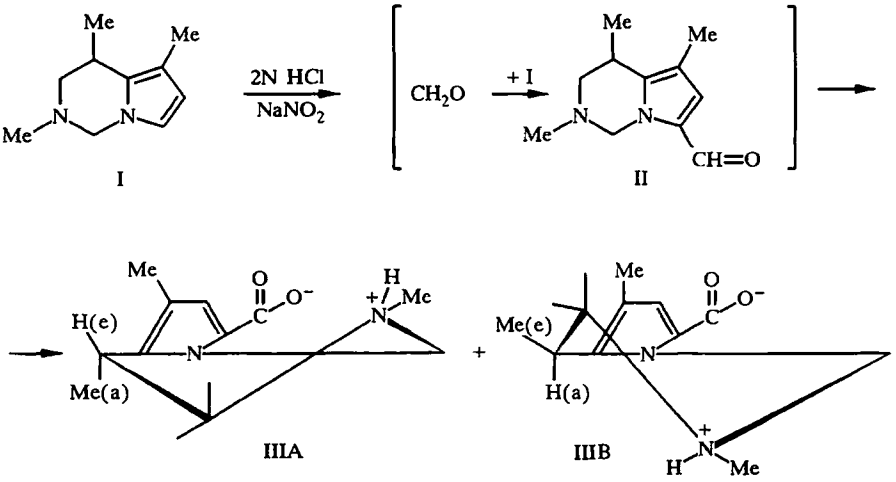
1,2,3,4-Tetrahydro-2,4,5-trimethylpyrrolo[1,2-c]pyrimidine and its 7-formyl derivative when treated with nitric acid are converted to substituted tetrahydropyrrolo-[1,2-c]pyrimidine-7-carboxylic acid. Conversion occurs through opening of the aminal moiety and formylation of the second molecule of tetrahydropyrrolo[1,2-c]pyrimidine by formaldehyde formed to the 7-formyl-substituted derivative.

Continuing the study of chemical conversions of 1,2,3,4-tetrahydro-2,4,5-trimethylpyrrolo[1,2-*c*]-pyrimidine (I) and its 7-formyl-substituted derivative (II) [1], we have studied their reaction with nitric acid in 2N hydrochloric acid.



In contrast to 1,3-diazaadamantanes, in which the aminal moiety is cleaved and bis-nitrosamine derivatives are formed [2], compound I when treated with nitric acid is converted to 7-hydroxycarbonyl-1,2,3,4-tetrahydro-2,4,5-trimethylpyrrolo-[1,2-*c*]pyrimidine (III), the yield of which amounts to 36%. According to PMR spectra, compound III is formed as a mixture of the two conformers A and B, in which the conformer with the axial group (IIIA) predominates (9:1). Earlier we have shown [1] that tetrahydropyrrolopyrimidines I and II exist as an equilibrium mixture of conformers with an axial and equatorial 4-CH_3 group. Probably quaternization of the piperidine nitrogen atom makes interconversion of the conformers impossible.

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TABLE 1 PMR Spectral Characteristics of Tetrahydropyrrolopyrimidine-7-carboxylic acid (III) and Its Iodomethylate (IV), δ, ppm (*J*, Hz)

Compound	1-H_a	1-H_e	3-H_a	3-H_e	4-H
IIIA	3,14 d (10,1)	4,54 dd (10,1; 1,5)	2,51 m	2,72 ddd (11,6; 3,1; 1,5)	2,07 qdd (7,0; 3,1; 3,1)
IIIB	3,54 d (11,6)	4,52 dd (11,6, 1,5)	2,51 m	2,58 m	1,86 qdd (6,7; 11,0; 4,5)
IV* max	4,36 d (11,8)	5,22 d (11,8)	3,72...3.31		2,25 m
IV* min	4,39 d (11,8)	5,24 d (11,8)			

Compound	6-H	2-CH_3	4-CH_3	5-CH_3	OH
IIIA	5,69 q (1,5)	2,42 s	0,78 d (7,0)	1,98 d (1,5)	—
IIIB	5,72 q (1,5)	2,24 s	1,06 d (6,7)	2,12 d (1,5)	—
IV* max	6,08 q (1,5)	2,84 s; 3,18 s	0,93 d (6,4)	2,11 d (1,5)	6,85 s*[2]
IV* min	6,10 q (1,5)	2,98 s; 3,16 s	1,01 d (6,4)	2,02 d (1,5)	6,77 s*[2]

*The spectrum was recorded in DMSO-d_6.

*[2] At 80°C the signals are shifted upfield by 0.15-0.16 ppm and broadened.

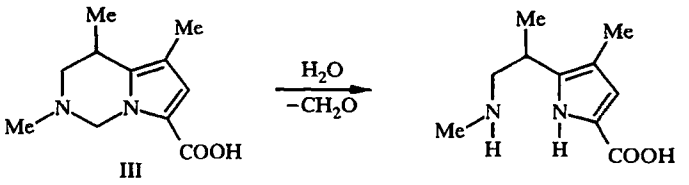
A mixture of conformers IIIA and IIIB in ratio 1.3:1 is also formed in 87% yield from the formyl derivative II under the same conditions.

Probably the first step in conversion of tetrahydropyrrolopyrimidine I to acid III is cleavage of the aminal moiety with formation of formaldehyde. The latter, reacting with molecule of I, is converted to the 7-formyl-substituted derivative, oxidation of which gives acid III. It has been shown experimentally that compound II is formed when formaldehyde reacts with tetrahydropyrrolopyrimidine I. The low yield of acid III may be considered as indirect proof that conversion of I to III is a multistep process.

The mixture of isomers of acid III when treated with methyl iodide is converted to mixture of iodomethylates IV (ratio 2.4:1). In the IR spectra of compounds III and IV, broad bands for bound hydroxyl with maximum at 3250 cm^{-1} and 3440 cm^{-1} respectively are observed, bands at 1700 and 1710 cm^{-1} correspond to stretching vibrations of the CO group. In the PMR spectra of compounds III and IV (see Table 1), two signals from each of the protons in their molecules are observed, indicating the existence of these compounds in the form of a mixture of conformers. The spectra of both compounds are characterized by the presence of signals from 1-CHAHB protons with geminal spin-spin coupling constants ^2J = 10.1-11.8 Hz which are typical of tetrahydropyrrolopyrimidines [1]. The 1-H_e proton in the spectrum of compound III due to the W-arrangement has a long-range spin-spin coupling constant with the 3-H_e proton (^4J = 1.5 Hz). In the predominant conformer IIIA, the 4-H proton has two small vicinal spin-spin coupling constants with the 3-H protons (J_{3a4e} = J_{3e4e} = 3.1 Hz), which indicates an equatorial orientation for it. Thus in this conformer, the 4-CH_3 group is axially located. On the other hand, in conformer IIIB the 4-H proton has a large and a small vicinal spin-spin coupling constant with the 3-H protons (J_{3a4a} = J_{3e4a} = 4.5 Hz), due to the equatorial orientation of the 4-CH_3 group. In the ^{13}C NMR spectrum of the mixture of conformers of compound III, we observe two signals from each carbon atom present in the molecule; in this case, the chemical shifts of the signals from 5-CH_3, $C_{(7)}$ and $C_{(5)}$ in both conformers coincide (see Experimental). In the PMR spectrum of iodomethylate IV, the signals undergo a downfield shift, and the greatest shift occurs for the protons located right next to the quaternized nitrogen atom. Due to strong overlap of the signals, it is not possible to hypothesize about the orientation of the 4-CH_3 group in the predominant conformer. We should note that, probably due to the chemical reaction of iodomethylate with DMSO, "extra" signals appear in its PMR spectrum: a doublet at 0.91 ppm and a singlet at 1.12 ppm.

The fragmentation of compounds III and IV under electron impact is unusual. In the mass spectrum of compound III, the molecular ion peak with *m/z* 208 is missing; an ion with *m/z* 196 (17.9%) is detected, differing by 12 amu from the molecular ion peak. Elimination of OH is typical for the basic decomposition modes of this

ion, as for decomposition of the acids $C_4H_{10}N$ and C_4H_9N, and also loss of hydrogen. These data allow us to assign the ion with *m/z* 196 to the structure of 2-hydroxycarbonyl-4-methyl-5-(α-methyl-β-methylaminoethyl)pyrrole. Probably decomposition of the aminal moiety occurs while the mass spectrum is recorded.



In the mass spectrum of iodomethylate IV, we observe an intense peak for the molecular ion of methyl iodide with *m/z* 142 and an ion peak with *m/z* 196, the decomposition of which is analogous to the decomposition for compound III.

EXPERIMENTAL

The NMR spectra of 2% (1H) and 10% (13C) solutions of the synthesized compounds in CDCl3 or DMSO-d_6 were recorded on a WH-400 (Bruker) at 20°C, internal standard TMS. The chromatography/mass spectra were obtained on a Kratos MS-25-RF. The IR spectra were taken on a UR-20 spectrophotometer in KBr pellets. TLC was performed on silica gel Silufol UV-254 and visualized by iodine vapors.

1,2,3,4-Tetrahydro-2,4,5-trimethylpyrrolo[1,2-*c*]pyrimidine-7-carboxylic acid (III). A. Solution of 1.9 g (2.8 mmol) of $NaNO_2$ in 7 ml of water was added to solution of 0.65 g (4 mmol) of compound I in 25 ml of 2N HCl at 0°C. After 1 h of stirring, the reaction mass was neutralized by aqueous solution of sodium carbonate to pH 6, extracted with chloroform, and dried with magnesium sulfate. The residue was recrystallized from ether. Acid III, 0.3 g (36%) was obtained as white crystals, mp 136-138°C, R_f 0.64 (Silufol, ethyl acetate—ethanol, 1:1), isomer ratio A:B = 9:1. ^{13}C NMR spectra ($CDCl_3$): conformer A: 58.70 (t, $C_{(1)}$; 56.14 (t, $C_{(3)}$); 34.87 (d, $C_{(4)}$); 89.26 (s, $C_{(4a)}$); 163.66 (s, $C_{(5)}$); 121.62 (d, $C_{(6a)}$); 161.03 (s, $C_{(7)}$); 42.24 (q, 2-CH_3); 11.98 (q, 4-CH_3); 14.27 (q, 5-CH_3); 168.20 (s, COOH). Conformer B: 57.63 (t, $C_{(1)}$); 56.42 (t, $C_{(3)}$); 35.40 (d, $C_{(4)}$); 88.70 (s, $C_{(4a)}$); 163.66 (s, $C_{(5)}$); 121.53 (d, $C_{(6)}$); 161.03 (s, $C_{(7)}$); 40.21 (q, 2-CH_3); 13.22 (q, 4-CH_3); 14.27 (q, 5-CH_3); 168.12 (s, COOH).

B. Sodium nitrite (0.24 g, 3.2 mmol) was added in 80 mg portions to solution of 0.16 g (0.8 mmol) of compound II in 20 ml of 2N HCl at 20°C (monitored by TLC). After 1 h, the mixture was neutralized with sodium carbonate solution to pH 6, evaporated under vacuum down to a volume of ~10 ml, extracted with chloroform, and dried with magnesium sulfate. The residue (0.16 g) after driving off the solvent was recrystallized from ethyl acetate—hexane mixture. Compound III, 0.1 g (87%) was obtained as white crystals, mp 86-88°C, R_f 0.6 (Silufol, ethyl acetate—ethanol, 1:1), conformer ratio A:B = 1.3:1. Found, %: C 63.05; H 7.80; N 13.25. $C_{11}H_{16}N_2O_2$. Calculated, %: C 63.46; H 7.69; N 13.46.

Iodomethylate of 1,2,3,4-tetrahydro-2,4,5-trimethylpyrrolo[1,2-*c*]pyrimidine-7-carboxylic acid (IV). Freshly distilled methyl iodide (0.21 g, 1.5 mmol) and 5 ml of ether were added dropwise to solution of 0.1 g (0.5 mmol) of compound III in 5 ml of ethanol. The mixture was allowed to stand overnight in the freezer compartment of a refrigerator. Compound IV, 0.14 g (85%) was obtained as yellowish crystals, mp 170-171°C (from ethanol—acetone mixture). Found, %: C 40.90; H 5.76; N 7.90. $C_{12}H_{19}IN_2O_2$. Calculated, %: C 41.14; H 5.42; N 8.00.

Reaction of tetrahydropyrrolopyrimidine I with formaldehyde. Solution of 0.16 g (1 mmol) of tetrahydropyrrolopyrimidine I and 0.23 g (2.5 mmol) of formalin in 30 ml of ethanol was stirred at 20°C for 1 h, monitored by TLC (Silufol, ethyl acetate—alcohol, 2:1). The solvent was evaporated to dryness under vacuum, the residue was extracted with ether and dried with magnesium sulfate. After driving off the ether, 0.17 g of a viscous dark oil were obtained, containing about 20 compounds according to chromatography/mass spectrometry data; 7-formyl-substituted derivative II content ~ 15-20%.

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