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SYNTHESIS AND DETERMINATION OF THE STRUCTURE OF PYRROLO[1,2-c]PYRIMIDINES

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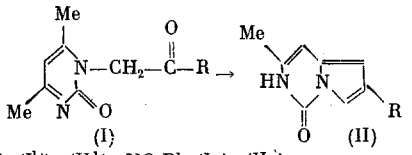
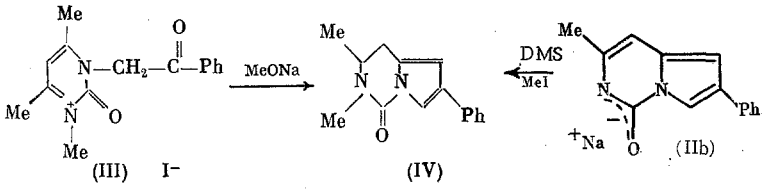
The reaction of 4,6-dimethyl-1-oxoalkyl-2-oxo-1,2-dihydropyrimidines (I) with such agents as hydrazine, phenylhydrazine, hydroxylamine, semicarbazide, triethylamine, alkali metal alcoholates, and aqueous alkali and distillation of (I) all yield the same products, namely, 6-substituted-1-oxopyrrolo[1,2-c]pyrimidines (IIa-c).



R = Me (Ia), (IIa); Ph (Ib), (IIb); NO_2Ph (Ic), (IIc).

The reaction of 1,2-dihydro-1,4,6-trimethyl-3-phenacyl-2-oxopyrimidinium iodide (III) with MeONa yields 1,2-dihydro-2,3-dimethyl-6-phenyl-1-oxopyrrolopyrimidine (IV)



The same product is obtained in the reaction of sodium salt of (IIb) with dimethyl sulfate or MeI.

The IR spectra of (I) and (IV) have a broad medium-intensity band at 1650 cm^{-1} related to the C=C and C=N aromatic bond system, a band at 1700 cm^{-1} (νC=O), and bands at 3010-3200 and 3250 cm^{-1} (νNH). A narrow peak at 3480 cm^{-1} is found in the spectrum taken in CCl_4 solution with concentration $C \sim 10^{-3}$ mole/liter. The position of this band varies with dilution and change in temperature. The PMR spectra of these compounds have a series of signals whose chemical shifts correspond to methyl protons and three aromatic protons.

The mass spectra of (IIb) and (IV) were studied. The fragmentation of these compounds is given in Schemes 1 and 2. The major mass spectral peaks for (IIb) are found at 225 (23), 224 (15), 181 (10), 180 (7.7), 155 (35), 154 (50), 153 (14), 112 (5.5), 77 (12), 42 (40).

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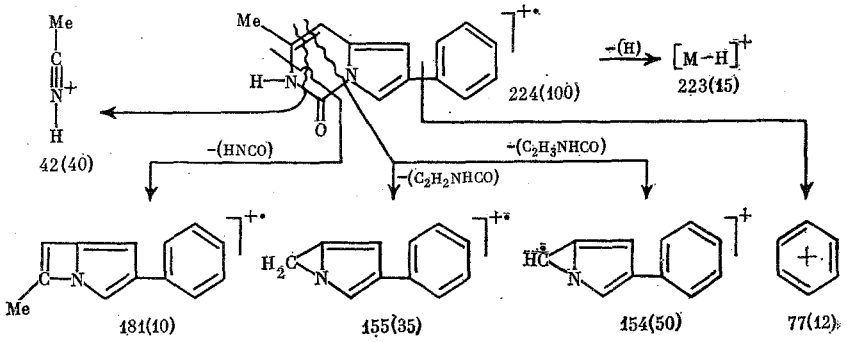
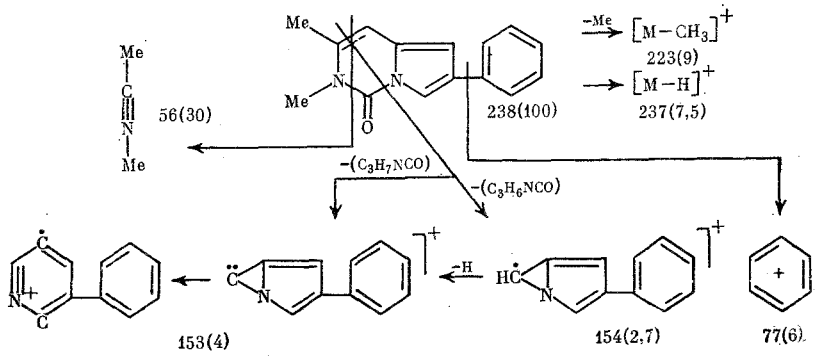
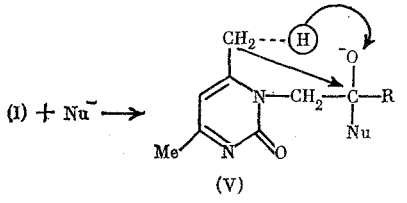
Scheme 1

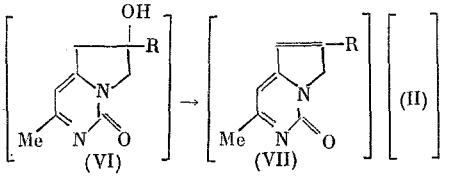


Scheme 2



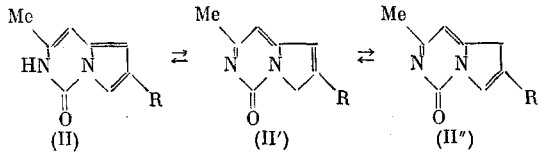
The formation of (II) probably occurs by the following scheme





In all likelihood, the nucleophile attacks the carbonyl carbon atom in (V) in the first step and then a proton is lost from the methyl group at C-4 of the pyrimidine ring. The methylenic anion formed attacks the carbonyl carbon atom in (V). However, such reactions rarely stop at the "aldol condensation" step but rather proceed further with the loss of a water molecule [1]. The formation of (II) may be explained by the tautomerism of (VII) and (II). The pyrrole ring in (VII) is in the dihydro form. The transition from the dihydro form to the fully aromatic form in the pyrrole ring requires 23 kcal/mole while the difference in energy between (II) and (VII) is 3 kcal/mole. Since the last step of the reaction is a tautomeric transition, we became interested in whether there is a tautomeric transition in oxopyrrolopyrimidines (II) and (IV) themselves.

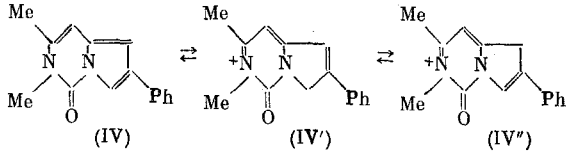
The PMR spectra of these compounds have three signals for the aromatic protons, methyl groups, and substituents. Signals of other tautomeric forms were not observed in the PMR spectra at from 30° to 150°C and only broadening of the peaks due to rapid proton exchange was noted. We then studied the isotope exchange of these compounds with D_2O by mass spectrometry. Upon mixing (II) with D_2O at 40°C with subsequent pumping in vacuum, the molecular ion peak of (II) was shifted by three units towards higher mass, indicating the exchange of three hydrogen atoms by deuterium atoms. This result unequivocally demonstrates that in there is an equilibrium (II) $\rightleftharpoons$ (II') $\rightleftharpoons$ (II") in aqueous medium. If there were either only the (II) $\rightleftharpoons$ (II") or (II') $\rightleftharpoons$(II") equilibrium, only two protons would be exchanged. The exchange of three protons by deuterium may be explained only by the (II) $\rightleftharpoons$ (II') $\rightleftharpoons$ (II") equilibrium



The dissociation energy of the deuterated compounds also indicates the existence of a triple tautomerism of these compounds. Since HNC=O and Me−CH=N−C=O fragments are lost upon dissociative ionization (see Tables 1 and 2), the remaining part of the molecule has two deuterium atoms, which indicates the exchange of two hydrogen atoms by deuterium atoms in the pyrrole fragment.

We might have assumed that there should be no tautomerism or much slower proton exchange in the case of methylated pyrrolopyrimidines which lack a labile NH group hydrogen atom. However, a study of the isotope exchange of N-methylated pyrrolopyrimidines showed that the exchange of hydrogen by deuterium occurs at approximately the same rate as in the nonmethylated analogs.

Mixing with D_2O gave a shift in the mass spectral [M^+] peak for (IV) by two units towards greater mass. This finding is probably explained by the fact that in the medium $D_2O(H_2O)$ in the first stage of this process an attack of a water molecule occurs at C-5 or C-7 of the ring. The next step is rearrangement of the aromatic system with charge transfer to the nitrogen atom

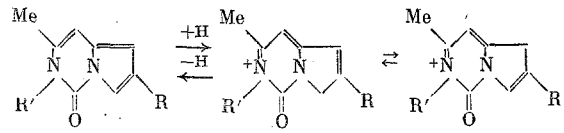


We also studied the protonation of (IIa-c) and (IV). Systems similar to our compounds such as pyrrolo [1,2-a]pyrimidines are protonated not at the nitrogen atom but at the α-carbon atom of the pyrrole ring [2-5]. The protonation of oxopyrrolopyrimidines has not been studied.

The PMR spectra of pyrrolopyrimidines were found to have three aromatic proton peaks. Methylenic proton peaks appear in the PMR spectra of (IIa-c) and (IV) taken in CF_3CO_2H. The ratio of the integral intensities of the methylenic proton peak and the peak for the protons of the methyl group at C-4 is 2:3, indicating that pyrrolopyrimidines exist in a form with the α-carbon atom completely protonated.

Since attack at both C-5 and C-7 in the ring is possible in our case, it is very difficult to make an unequivocal determination of the site of protonation. We may only assume that the observed methylenic proton peak is an averaged peak of both methylenic groups due to rapid proton exchange between the two sites.

The protonation of (IIa-c) and (IV) may be given by the following scheme



R = Me, Ph, NO_2Ph; R′ = H, Me.

EXPERIMENTAL

The IR spectra were taken on a UR-20 spectrometer. The solids were prepared as vaseline oil mulls. The spectra of the solutions were taken in CCl_4 with solvent compensation. The UV spectra were taken on a Specord UV-VIS spectrophotometer. The PMR spectra were taken on a Varian T-60 spectrometer. The column chromatography was carried out on alumina with grade II activity. The columns were consecutively eluted with 70-100 ml petroleum ether, ether, benzene, and chloroform. Physical indices of the compounds prepared are given in Table 1. The spectral data are given in Table 2.

1,2-Dihydro-1-oxo-3,6-dimethylpyrrolo[1,2-c]pyrimidine (IIa). A sample of 5.26 g (Ia) was added with stirring to MeONa obtained from 0.67 g sodium and 30 ml abs. methanol, heated at reflux for 10-15 min, and then, 1.67 ml acetic acid was added. The precipitate formed was filtered off. A sample of 100 ml distilled water was added to the filtrate and the precipitate was again filtered off. Both precipitates were combined and recrystallized from benzene to yield 4.9 g (93%) (IIa) with mp 104-105°C (from benzene).

TABLE 1. Some Physical Indices of Synthesized Pyrrolo[1,2-c]pyrimidines

Compound	Yield, %	mp, °C	Chemical formula	Found/calculated, %		
				C	H	N
(IIa)	93	104–105	$C_9H_{10}N_2O$	66,17 66,66	5,80 6,16	17,38 17,28
(IIb)	90	266 (с разл.)	$C_{14}H_{13}N_2O$	74,73 75,00	5,46 5,35	12,63 12,50
(IIc)	73	275 (с разл.)	$C_{14}H_{11}N_3O_3$	58,36 58,54	4,68 4,53	14,49 14,63
(IV)	93	210–211	$C_{15}H_{13}NO_2$	75,02 75,63	6,12 5,80	11,58 11,76

TABLE 2. Spectral Data for Some Pyrrolo[1,2-c]pyrimidines

Compound	PMR spectrum (δ, ppm)					
	CF_3COOH			$CDCl_3$		
	CH_3	CH_2	H–C_{pyr}	CH_3	H^4, H^5	H^7
(IIa)	2,43, 2,20	5,03	6,26, 6,70	2,23	5,93	5,93
(IIb)	2,26	5,5	6,95, 7,14	–	–	–
(IIc)	2,83	5,86	7,5, 7,13	–	–	–
(IV)	2,76, 3,83	5,56	6,93, 7,13	2,23, 3,46	6,1, 6,36	–

1,2-Dihydro-1-oxo-3-methyl-6-phenylpyrrolo[1,2-c]pyrimidine (IIb). A sample of 2.44 g (Ib) was added with stirring to MeONa obtained from 0.23 g sodium and 30 ml abs. methanol, heated at reflux for 3-5 min with stirring, cooled to 22°C, and neutralized with acetic acid. The precipitate was filtered off. The filtrate was diluted with distilled water to 100 ml and the precipitate formed was again filtered off. Both precipitates were combined, washed with water, dried, and recrystallized from 1:1 benzene–methanol to yield 2.1 g (90%) (IIb) with mp 266°C (dec.).

B. A solution of 2.44 g (Ib) in 50 ml methanol was added with stirring to a solution of 0.032 g hydrazine in 30 ml methanol. The mixture was heated at reflux for 30 min. The precipitate formed was separated and recrystallized from 1:1 methanol–benzene to yield 1.61 g (73%) (IIb) with mp 266°C (dec.).

C. A sample of 0.5 g (Ib) was heated in a sublimation apparatus in vacuum at 180-200°C to yield 0.45 g (90%) (IIb) with mp 266°C (dec.).

1,2-Dihydro-1-oxo-2,3-dimethyl-6-phenylpyrrolo[1,2-c]pyrimidine (IV). A sample of 3 g (III) was added to a solution of 0.17 g sodium in 30 ml abs. methanol. The mixture was stirred for 30 min at 20°C and then 100 ml distilled water was added. The precipitate formed was filtered off, washed with 30 ml water, and dried to yield 1.75 g (93%) (IV) with mp 210°C.

1,2-Dihydro-1-oxo-2,3-dimethyl-6-phenylpyrrolo[1,2-c]pyrimidine (IV). A sample of 2.24 g (IIb) was added to a solution of 0.23 g sodium in 50 ml methanol. The mixture was stirred at reflux for 1 h and then 1.26 g dimethyl sulfate was added dropwise. The mixture was stirred for an additional 30 min. Then, the reaction mixture was poured into 150 ml water. The precipitate formed was filtered off and washed with water to yield 2.15 g (91%) (IV) with mp 210°C.

The reaction of (IIa-c) with hydroxylamine, phenylhydrazine, semicarbazide, triethylamine, and thiosemicarbazide was carried out by a method analogous to that used for the reaction of (IIb) with hydrazine.

CONCLUSIONS

1. 1,2-Dihydro-1-oxo-3-methyl-6-substituted pyrrolo[1,2-c]pyrimidines were obtained for the first time.

2. Deuterium exchange of the hydrogen atoms in D_2O was studied by mass spectroscopy. A triple prototropic tautomerism was shown for 1,2-dihydro-1-oxo-6-substituted pyrrolo[1,2-c]pyrimidines.

3. 1,2-Dihydro-3-methyl-6-substituted pyrrolo[1,2-c]pyrimidines are completely protonated at the α-carbon atom.

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