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A NOVEL REACTION OF α-DIAZO-β-OXO-5-(4-CHLOROPYRIMIDINE)PROPIONATE WITH HYDRAZINE. A FORMATION OF 1,2-DIHYDRO-4-HYDROXYPYRIMIDO-[4,5-c]PYRIDAZINE-3-CARBOXAMIDE.

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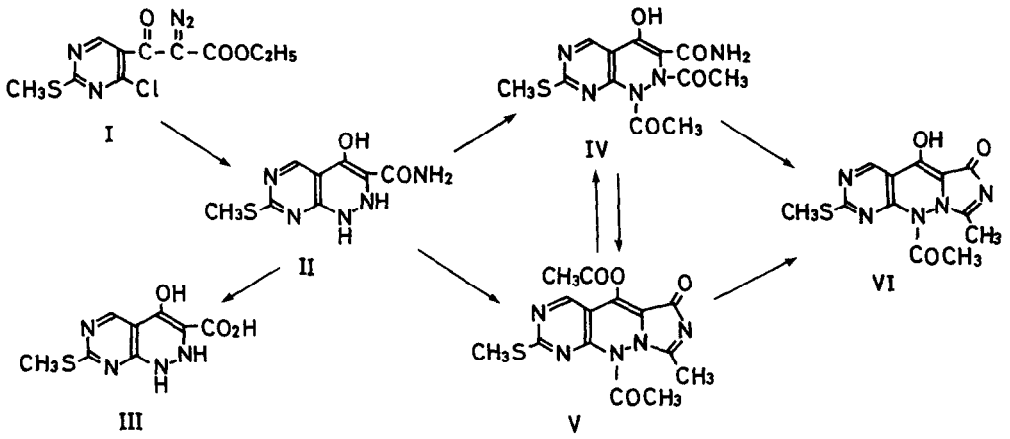
During the course of a study on the reaction of α-diazo-β-oxo-5-(4-chloro-2-methylthiopyrimidine)propionate (I), mp 63-64°, $C_{10}H_9O_3N_4SCl$; ir (KBr): 2150 cm^{-1}; uv (EtOH): 222sh and 279 nm, which was available from the reaction of 4-chloro-2-methylthiopyrimidine-5-carbonyl chloride with ethyl diazoacetate, it was found that treatment of I with a 4-fold molar amount of hydrazine hydrate at 8-20° in EtOH produced a nearly quantitative yield of a compound (II), mp 260-265° dec, $C_8H_9O_2N_5S$, M^+ m/e 239; nmr (d_6-DMSO) δ : 2.61 (s, SCH_3), 5.82 (br, 5H, exchangeable with D_2O), and 8.93 (s, ring H); uv: 219, 275, and 320 nm (H_2O), 234, 295, and 384 nm (0.01N-NaOH), of which structural elucidation is the subject in this paper. On the basis of the evidence described below, II was established to be 1,2-dihydro-4-hydroxy-7-methylthiopyrimido[4,5-c]pyridazine-3-carboxamide resulting from the nucleophilic substitution of hydrazine to the α-carbon of the α-diazo-β-oxo-propionate (I). No precedent, however, for reactions of the α-carbon in this type of compounds with nucleophiles seems to have yet appeared in the literature, although there are some reports concerning with nucleophilic reactions on the β-carbon.[1]

The compound (II) underwent hydrolysis with 5% aq HCl in EtOH to give an acid (III), mp 250-252° dec, $C_8H_8O_3N_4S$, M^+ m/e 240; nmr (d_6-DMSO) δ: 2.61 (s, SCH_3), 6.00 (br, 2H, exchangeable with D_2O), 8.90 (s, ring H), and 10.0

Scheme I

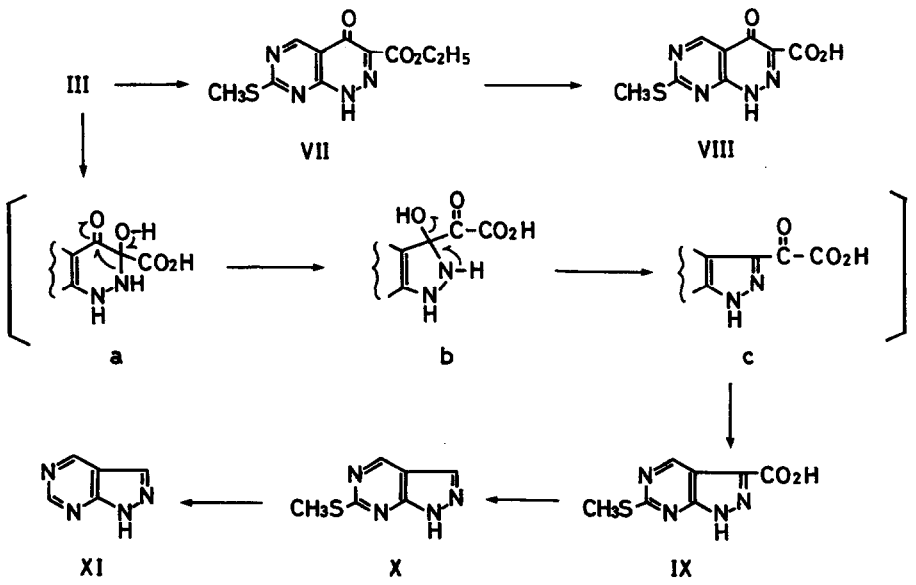


(br, 2H, exchangeable with D_2O); uv: 226, 278, and 336 nm (H_2O), 256, 308, and 460 nm (0.01N-NaOH). The uv spectra of II and III, showing a bathochromic shift by alkali, suggest the conjugation of a keto or enol group with the pyrimidine chromophore. Acetylation of II with Ac_2O at 50° produced a diacetate (IV), mp 291-292°, $C_{12}H_{13}O_4N_5S$, M^+ m/e 323; nmr (d_6-DMSO) δ: 2.11 (s, $COCH_3$), 2.18 (s, $COCH_3$), 2.57 (s, SCH_3), 8.97 (s, ring H), 9.65 (s, NH), 10.79 (s, NH), and 12.30 (br, OH), in a 86 % yield. The lowest field signal at δ 12.3 assignable to a proton of hydroxyl is probably due to a hydrogen bonding with the carboxamide group, indicating ortho location of these groups. Treatment of II with Ac_2O at 120° afforded an anhydrodiacetate (V) in a 96 % yield, mp 224-225°, $C_{14}H_{13}O_4N_5S$, M^+ m/e 347; nmr ($CDCl_3$) δ: 2.38 (s, two $COCH_3$), 2.54 (s, SCH_3), 2.74 (s, CH_3), and 9.03 (s, ring H), which was identical with that obtained by further treatment of IV with Ac_2O at 120°. Treatment of V with aq 1N-NaOH at 80° gave back IV. The nmr spectrum of V shows no longer the signal ascribable to the labile protons as possessed by II but a new signal at δ 2.74 attributable to methyl protons on the imidazole ring arising from intramolecular dehydration between the carboxamide and acetamide groups; hence the two groups were revealed to be adjacent each other in position. The anhydrodiacetate (V) in which the presence of an enol acetate function was suggested by its ir band at 1730 cm^{-1} was easily hydrolyzed with 28 % aq NH_4OH to give, as expected, a 72 % yield of deacetyl derivative (VI),

mp 219-221°, $C_{12}H_{11}O_3N_5S$, M^+ m/e 305; nmr (d_6-DMSO) δ: 2.15 (s, $COCH_3$), 2.58 (s, SCH_3), 2.68 (s, CH_3), 9.15 (s, ring H), and 10.52 (br, OH), which was obtained alternatively from III by heating above 300°.

Treatment of III with an excess of benzoyl peroxide in EtOH in the presence of Et_3N furnished a dehydro ester (VII), mp 269-270°, $C_{10}H_{10}O_3N_4S$, M^+ m/e 266; nmr (d_6-DMSO) δ: 1.33 (t, J=7 Hz, CH_3), 2.62 (s, SCH_3), 4.37 (quar, J=7 Hz, CH_2), 9.20 (s, ring H), and 14.0 (br, NH); ir (KBr): 3030, 1710, 1640sh cm^{-1}, in a 50 % yield. Subsequently VII was hydrolyzed to the corresponding acid (VIII), mp 279-280°, $C_8H_6O_3N_4S$; ir (KBr): 3200-3050, 1720, and 1630 cm^{-1}. Oxidation of III with $KMnO_4$ in an alkaline solution afforded 6-methylthio-1H-pyrazolo[3,4-d]pyrimidine-3-carboxylic acid (IX), mp 291-292°, $C_7H_6O_2N_4S$, M^+ m/e 210; nmr (d_6-DMSO) δ: 2.60 (s, SCH_3), 9.20 (s, ring H), and 14.3 (br, OH), which arised in concequence of bond migration (a→b), followed by dehydration (b→c) and decarboxylation of a resulting α-ketocarboxylic acid (c). In order to confirm the structure, IX was converted by heating at 300° into a decarboxylated product (X), mp 216-217°, $C_6H_6N_4S$, M^+ m/e 166; nmr

Scheme II

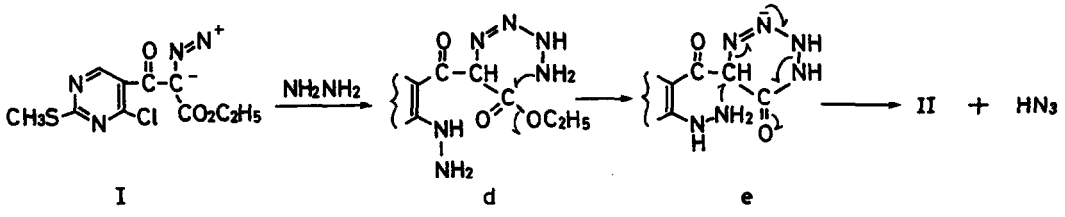


(d_6-DMSO) δ: 2.58 (s, SCH_3), 8.25 (s, C_3-H), and 9.12 (s, C_4-H), followed by desulfurization with Raney Ni into 1H-pyrazolo[3,4-d]pyrimidine (XI), mp 209-210°, which was identical in all respects with the sample prepared according to the literature.[2] This fact demonstrates that a hydrazo group is present at the position 4 on the pyrimidine ring of III and hence of II.

The compound (II) and its derivatives (III-XI) thus are best formulated as the assigned structures in good agreement with their spectral data and the chemical transformations.

The formation of II from the reaction of I with hydrazine is reasonably explained by a probable mechanistic pathway as given in Scheme III; thus, both the C-4 on the pyrimidine ring and the positively charged nitrogen of the diazo group are subjected at first to nucleophilic displacement with hydrazine to form an intermediate (d), which subsequently converts into a tetrazolone (e) by ring closure, and then the hydrazino group attacks the α-carbon with simultaneous ruptures of C-N and N-N bonds, resulting in the formation of II along with HN_3. This mechanism was rationalized by detection of HN_3 in the reaction mixture as silver and ferric azides by Feigl's procedure.[3]

Scheme III



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