CHEMICAL PROPERTIES OF YLIDENE DERIVATIVES OF AZINES.
7.* CONVERSIONS OF 5-METHYL(PHENYL)-SUBSTITUTED 1,2-DIHYDRO-2-PYRIMIDINYLIDENEMALONONITRILES BY NITRIC ACID

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It has been shown that the reaction of 5-methyl(phenyl)pyrimidinylidenemalononitrile with nitric acid leads either to a 2-pyrimidinecarboxylic acid or to a pyrimidinylidene-α-carboxamido(α-carboxamido, α-nitro)-acetonitrile depending on the conditions.

We have investigated the conversion of substituted dihydropyrimidines containing residues of malononitrile using nitric acid in media of various acidity as a continuation of the study of the nitration of tautomeric methylenedihydroazines [1].

Previously we isolated in high yield α-nitro-α-[5-alkyl(aryl)-2-pyrimidinyl]cyanoacetic esters, the product of nitration at the α-carbon atom of the tautomeric side chain, from the reaction of 5-alkyl(aryl)-substituted 1,2-dihydro-2-pyrimidinylidene-cyanoacetic esters with fuming nitric acid in acetic acid at 10-20°C [1]. It was also shown [1] that the α-nitrocyanoacetic esters formed were partially converted during isolation into the corresponding α-hydroxy derivatives which were fairly stable in acid media. In contrast we were unsuccessful in demonstrating the formation of the corresponding α-nitromalononitriles (IIa, b) in the analogous reaction of pyrimidinylidenemalononitriles (Ia, b). The 5-methyl- and 5-phenyl-2-pyrimidinecarboxylic acids (IIIa, b) or their esters (IVa, b) were obtained in high yields on treating the reaction mixture with water or ethanol. It was shown by TLC (see Experimental) that 10-15 min after mixing the reactants only one compound was present which was different from the initial malononitriles (Ia, b) and from the final products (IIIa, b) and (IVa, b).

It was shown in separate experiments that in the absence of nitric acid the pyrimidinylidenemalononitriles (Ia, b) were stable in a medium of high acidity (acetic acid with added 95% H_2SO_4) during the time of the reaction described above and were isolated unchanged on adding water.

Comparison of the results obtained in the present work with the data of [1] suggests that the primary products of the reaction of the substituted malononitriles (Ia, b) with nitric acid in acetic acid are the α-nitromalononitriles (IIa, b). The carboxylic acids (IIIa, b) and the esters (IVa, b) are formed by the subsequent conversion of these derivatives. This conversion is probably brought about in the following manner. Initially, like the reaction described in [1], the unstable α-hydroxy derivatives (Va, b) are formed. The latter, which are cyanohydrins, are converted into the α-ketonitriles (VIa, b) with loss of a molecule of HCN.

A second possible route for the transformation of the malononitriles (Ia, b) into α-ketonitriles (VIa, b) under the conditions indicated may be the initial attack of the electrophilic reagent (NO_2^+) at the heterocyclic nitrogen atom, analogous to the formation of N-nitropyrimidinium salts [2]. The protonated nitroenamines (VIIa, b) obtained in this way are probably capable of reacting with the nucleophile NO_3^- at the α-carbon atom of the side chain and subsequent transition to the α-ketonitrile (VIa, b) analogous to the formation of 4-nitrobenzonitrile in the reaction of 4-nitrophenylmalononitrile with nitric

*For communication 6, see [1].

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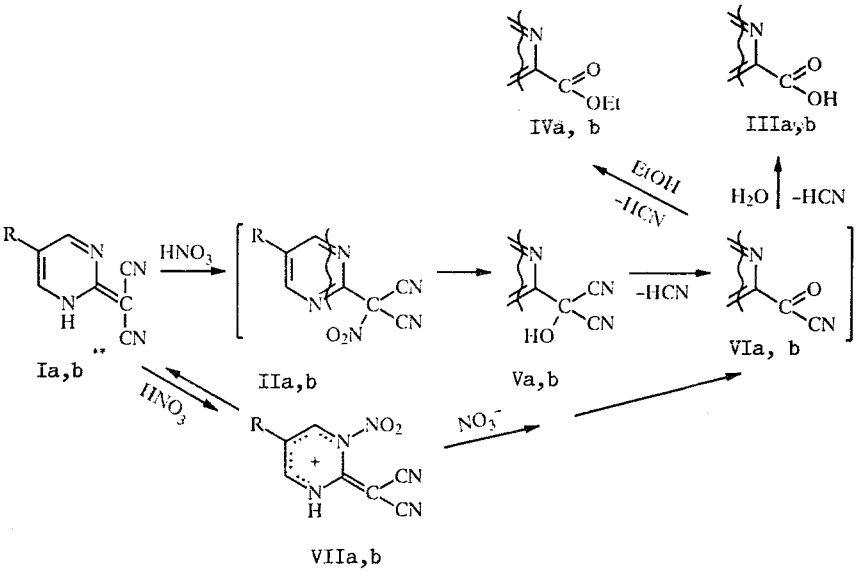


I-VIIa R=Me, b R=Ph

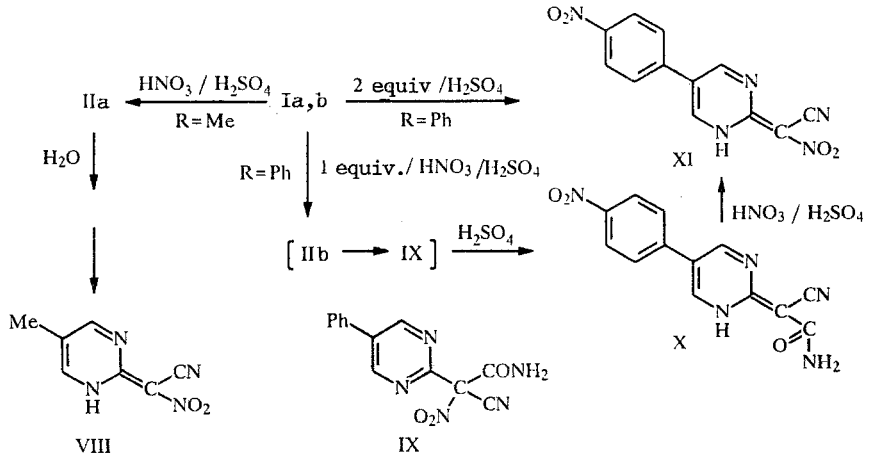
acid in dichloromethane [3]. However, the second route of conversion of malononitriles (Ia, b) into the α-ketonitriles (VIa, b) seems less probable to use from the data given above on the formation of α-nitro- and α-hydroxy-α-[5-alkyl(aryl)pyrimidinyl]-cyanoacetic esters [1] and the isolation of the α-nitronitriles (VIII) and (XI) on nitration of the malononitriles (Ia, b) in sulfuric acid.

The resulting α-ketonitriles (VIa, b), like other α-ketonitriles with a labile CN group [4], readily give the corresponding acids (IIIa, b) or esters (IVa, b) on treating the reaction mixtures with water or alcohol.

This conversion may possibly be used for the preparation of heterocyclic carboxylic acids and esters from the corresponding substituted malononitriles without using harsh oxidation conditions (see [5] for example).

The reaction of the pyrimidinylidenemalononitriles (Ia, b) with fuming HNO_3 in 95% H_2SO_4 at the same temperature as in acetic acid leads to the formation of different compounds. Judging by PMR spectra, the pyrimidinylidenemalononitriles (Ia, b) are stable in concentrated H_2SO_4 solution during the time of carrying out the reaction and are predominantly in the protonated ylidene tautomeric form analogous to 2-pyrimidinylidenecyanoacetic ester [6].

However, on nitration these compounds probably pass into the unprotonated form of (Ia, b), which is more reactive toward electrophiles, as was shown for 1,2-dihydro-2-oxopyrimidine [7].



IaR=Me, bR=Ph

*The structural formula of the preferred tautomeric form of compounds (Ia, b) is shown.

The α-nitroacetonitrile (VIII) was isolated in high yield from the substituted malononitrile (Ia). This compound had been obtained previously by dealkoxycarbonylation of α-nitro-α-(5-methyl-2-pyrimidinyl)cyanoacetic ester on silica gel [1]. The formation of the α-nitroacetonitrile (VIII) from the malononitrile (Ia) probably occurs by nitration of the latter at the α-carbon atom of the tautomeric side chain, subsequent hydrolysis of one of the nitrile groups of the α-nitromalononitrile (IIa), and facile decarboxylation of the resulting substituted α-nitrocyanoacetic acid [8]. The difference in structure of the compounds obtained by reaction of 5-methyl-2-pyrimidinylidenemalononitrile (Ia) with nitric acid in different media is due probably to the change in relative reactivity of the nitro and cyano groups of the α-nitromalononitrile (IIa) formed initially in acetic and sulfuric acids.

α-Carboxamido-α-(5-p-nitrophenyl-1,2-dihydro-2-pyrimidinylidene)acetonitrile (X) was isolated in 95% yield from the reaction of 5-phenyl-1,2-dihydro-2-pyrimidinylidenemalononitrile (Ib) with 1 equivalent of HNO_3 in 95% H_2SO_4. Subsequently, unlike 5-phenyl-1,2-dihydro-2-pyrimidinylidenecyanoacetic ester [1], a compound is formed from the malononitrile (Ib) under analogous conditions which contains a p-nitro group in the phenyl substituent and a carboxamide group in place of one of the nitrile groups. In view of the high ease of hydration in concentrated H_2SO_4 of a nitrile group in aromatic cations of azinylcyanoacetic esters [6], it may be proposed that the conversion of the malononitrile (Ib) into the carboxamidoacetonitrile (X) passes through the stage of forming the α-nitromalononitrile (IIb), hydration of a nitrile group in its protonated form, and rearrangement of compound (IX) into the p-nitrophenyl derivative (X) as was shown in [1] for α-nitro-α-(5-phenyl-2-pyrimidinyl)cyanoacetic ester.

In the presence of 2 equivalents of nitric acid the phenyl derivative (Ib) is converted in 90% yield into α-nitro-α-(5-p-nitrophenyl-1,2-dihydro-2-pyrimidinylidene)acetonitrile (XI). Compound (XI) is also formed from the reaction of the 5-p-nitrophenyl derivative (X) with 1 equivalent of HNO_3 in sulfuric acid. The conversion of the α-carboxamidoacetonitrile (X) into the α-nitroacetonitrile (XI) evidently occurs by the sequential nitration of the derivative (X) at the α-carbon atom, hydrolysis of the amide group, and decarboxylation of the resulting substituted α-nitrocyanoacetic acid.

It follows from the IR and UV spectra of compound (X) that it exists in the solid state and in ethanol solution predominantly in the ylidene tautomeric form. There is an intense absorption band in the IR spectrum of the α-carboxamido-acetonitrile (X) for the amide C=O group at 1640 and a conjugated nitrile group at 2205 cm^{-1}. In the UV spectrum of its alcohol solution there is a long-wave absorption maximum (λ_{max} > 350 nm) characteristic of the ylidene tautomeric methylenedihydroazines [9]. Judging from the PMR spectrum of derivative (X) in DMSO-d_6 this compound exists in the ionized form in this highly basic solvent, like other methylenedihydropyrimidines [9].

It is evident from the data given above that substituted 1,2-dihydro-2-pyrimidinylidenemalononitriles react with nitric acid under mild conditions like the analogous cyanoacetic esters. However, the presence in them of a more accepting second nitrile group in place of the carbethoxy causes the resulting nitration products to be less stable. Products of more extensive conversion, the substituted pyrimidinecarboxylic acids (IIIa, b) and their esters (IVa, b), were isolated from the reaction in acetic acid and the subsequent transformation on treating the reaction mixture with water or ethanol. On carrying out the nitration in concentrated H_2SO_4 the nitro derivatives (VIII), (X), and (XI) containing only one nitrile group were obtained.

EXPERIMENTAL

The IR spectra of samples in KBr disks were recorded on a Specord M-80 instrument and UV spectra (in ethanol) were taken on a Specord UV-Vis instrument. The PMR spectra were taken on a Bruker WP 200 SY (200.13 MHz) spectrometer for solutions in $CDCl_3$ and DMSO-d_6. Molecular weights were determined on an MS 902 instrument. A check on the course of reactions and the homogeneity of the compounds obtained was carried out by TLC on Silufol UV-254 plates in chloroform–ethanol, 5:1, with visualization by UV light.

5-Methyl-1,2-dihydro-2-pyrimidinylidenemalononitrile (Ia, $C_8H_6N_4$). An 80% suspension of NaH in oil (Merck) (1.42 g: 47 mmoles) was sprinkled onto dry dimethylformamide (DMF) (20 ml) at 20°C. A solution of malononitrile (3.16 g: 47 mmoles) in DMF (30 ml) was added dropwise with stirring. Stirring was continued until the end of hydrogen evolution (1 h). 2-Chloro-5-methylpyrimidine (3.48 g: 24 mmoles) was sprinkled in and the reaction mixture heated for 4 h at 110-120°C. After cooling, water (100 ml) was added, and the mixture acidified to pH 5 with acetic acid. The yellow solid was filtered off, washed with water (3 × 10 ml), with ethanol (10 ml), and recrystallized from a mixture of ethanol–DMF, 5:1. The solid was dried in a vacuum desiccator over P_2O_5. Yield was 2.56 g (70%). mp 265°C (with decomposition) (from an ethanol–DMF, 5:1 mixture). IR spectrum: 2195, 2215 cm^{-1} ($C\equiv N_{conj}$). PMR spectrum (DMSO-d_6): 2.12 (3H, s, CH_3); 8.23 ppm (2H, s, 4,6-H pyrim. ring).

5-Phenyl-1,2-dihydro-2-pyrimidinylidenemalononitrile (Ib, $C_{13}H_8N_4$) was obtained analogously from 2-chloro-5-phenylpyrimidine in 95% yield. mp 262°C (with decomposition). IR spectrum: 2195, 2215 cm^{-1} ($C\equiv N_{conj}$). PMR spectrum (DMSO-d_6): 7.34-7.50, 7.58-7.70 (5H, m, CH-arom.); 8.64 ppm (2H, m, 4,6-H pyrim. ring).

Nitration of 5-Methyl-2-pyrimidinylidenemalononitrile (Ia) in Acetic Acid. Fuming nitric acid (the density 1.5) (0.1 ml: 2 mmoles) was added dropwise to a suspension of compound (Ia) (0.32 g: 2 mmoles) in glacial acetic acid (40 ml) at 20°C. Stirring was continued at 20°C for 10-15 min until a solution formed. This coincided with the disappearance of starting material according to TLC (R_f 0.3, yellow in UV light). Only one compound was present in the reaction mixture and this had R_f 0.7 (violet in UV light). The acetic acid was distilled off at 40-50°C at reduced pressure. Subsequent treatment of the residue was carried out in different ways.

A. Water (10 ml) was added to the residue, the solution was kept at 20°C for 15 min, then evaporated in vacuum. The solid residue was dried over NaOH in a vacuum desiccator. 5-Methyl-2-pyrimidinecarboxylic acid (IIIa) (0.24 g: 95%) was obtained (R_f 0.1, violet in UV light) and was identical in mp, mixed mp, and IR spectrum with a sample obtained as described below from 2-carbethoxy-5-methylpyrimidine (Va).

B. The residue was dissolved in ethanol (5 ml), the solution kept for 5 min at 20°C, and the ethanol distilled off on a rotary evaporator. The oily residue was dissolved in chloroform (5 ml), passed through a layer of silica gel (5 × 3 cm, KSK type of particle size 140-315 nm), and eluted with chloroform. The solvent was evaporated off under reduced pressure. **2-Carbethoxy-5-methylpyrimidine (IVa, $C_8H_{10}N_2O_2$)** was obtained, R_f 0.6 (violet in UV light). mp 86-87.5°C (from a benzene–hexane, 2:1 mixture). IR spectrum: 1740 cm^{-1} (C=O). Mass spectrum: 166 (M^+). PMR spectrum ($CDCl_3$): 1.36 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$); 2.33 (3H, s, 5-CH_3); 4.43 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); 8.65 ppm (2H, s, 4,6-H pyrim. ring).

5-Methyl-2-pyrimidinecarboxylic Acid (IIIa). A suspension of 2-carbethoxy-5-methylpyrimidine (VIa) (0.84 g: 0.5 mmole) in 6% aqueous HCl (5 ml) was heated at 45-50°C until disappearance of the starting material according to TLC (6 h). The solution was evaporated at 40-50°C on a rotary evaporator, and the residue dried in vacuum over NaOH. Yield was 0.66 g (95%). mp 145-146°C (according to [10] mp 146-147°C). IR spectrum: 1715 (C=O); 3400 cm^{-1} (OH).

Nitration of 5-Phenyl-1,2-dihydro-2-pyrimidinylidenemalononitrile (Ib) in Acetic Acid. The reaction of compound (Ib) with HNO_3 in acetic acid was carried out under conditions analogous to those for the 5-methyl-substituted compound (Ia). One compound of R_f 0.7 (violet in UV light) was present in the reaction mixture according to TLC 10 min after mixing the reactants and was different from the starting material (Ib) (R_f 0.3 yellow in UV light). The acetic acid was distilled off in vacuum at 40-50°C. After treating the residue according to method A the solid, which was precipitated after adding water, was filtered off, washed with water (3 × 10 ml), and dried in vacuum. **5-Phenyl-2-pyrimidinecarboxylic acid (IIIb, $C_{11}H_8N_2O_2$)** (0.38 g: 95%) was obtained. R_f 0.1 violet in UV light). mp 225-226° (from ethanol). IR spectrum: 1710 (C=O); 3400 cm^{-1} (OH). On treating the residue obtained after distilling off the acetic acid by method B 2-carbethoxy-5-phenylpyrimidine (IVb) (0.36 g: 80%) was obtained. mp 123-125°C (from ethanol), which is in agreement with [11]. IR spectrum: 1740 cm^{-1} (C=O). PMR spectrum ($CDCl_3$): 1.38 (3H, t, J = 7 Hz, $OCH_2C\underline{H}_3$); 4.46 (2H, q, J = 7 Hz, $OC\underline{H}_2CH_3$); 7.35-7.55 (5H, m, H arom.); 9.19 ppm (2H, s, 4,6-H pyrim. ring).

Nitration of Compounds (Ia, b) in 95% Sulfuric Acid. Fuming nitric acid (the density 1.5) (0.1 ml: 2 mmoles) was added dropwise to a cooled (10°C) solution of compounds (Ia) or (Ib) (2 mmoles) in 95% sulfuric acid (6 ml). The mixture was stirred at 10-20°C for 20 min. The solution was poured onto ice (50 g), the precipitated solid was filtered off, washed with water (5 × 10 ml) to pH 6-7, dried in a vacuum desiccator, and recrystallized from ethanol–DMF (1:1). Compound (VIII) (0.32 g: 90%) was obtained from the 5-methyl-substituted compound (Ia) and was identical in melting point and spectral characteristics to a sample obtained by the method in [1]. **α-Carboxamido-α-(5-p-nitrophenyl-1,2-dihydro-2-pyrimidinylidene)acetonitrile (X, $C_{13}H_9N_5O_3$)** (0.54 g: 95%) was obtained from the 5-phenyl derivative (Ib). mp 261-262°C. IR spectrum: 1640 (C=O), 2205 cm^{-1} ($C\equiv N_{conj}$). UV spectrum (in alcohol), λ_{max} (log ε): 204 (3.86), 227 (3.76), 300 (3.73), 374 (4.08). Mass spectrum: 283 (M^+). PMR spectrum (DMSO-d_6): 7.14 (2H, br.s, NH_2); 7.94 (2H, d, J = 8 Hz, o-CH arom.); 8.31 (2H, d, J = 8 Hz, m-CH arom.); 8.75 (1H, br.s, 6-H pyrim. ring); 9.14 ppm (1H, br.s, 4-H pyrim. ring).

5-(p-Nitrophenyl)-1,2-dihydro-2-pyrimidinylidenenitroacetonitrile (XI) (0.52 g: 90%), identical to a sample obtained according to [1], was obtained by the reaction of the 5-phenyl derivative (Ib) (0.44 g: 2 mmoles) with nitric acid (space group 1.5) (0.2 ml: 4 mmoles) in 95% sulfuric acid (6 ml) at 10-20°C and was isolated as described above.

The α-nitroacetonitrile (XI) (0.27 g: 95%), identical to a sample obtained according to [1], was prepared by the reaction of compound (X) (0.28 g: 1 mmole) with nitric acid (the density 1.5) (0.95 ml: 1 mmole) in 95% sulfuric acid at 10-20°C and isolation as described above.

REFERENCES

1. I. V. Oleinik and O. A. Zagulyaeva, Sib. Khim. Zh., No. 4, 117 (1992).
2. G. A. Olah, J. A. Olah, and N. A. Overchuk, J. Org. Chem., No. 10, 3373 (1965).
3. H. Suzuki, H. Koide, and T. Ogawa, Bull. Chem. Soc. Jpn., **61**, 501 (1988).
4. E. N. Zil'berman, Reactions of Nitriles [in Russian], Khimiya, Moscow (1972), pp. 93, 413.
5. A. Pollak, B. Stanovnik, M. Tisler, and J. Venetic-Vortuna, Monatsh. Chem., **106**, 473 (1975).
6. I. V. Oleinik, O. A. Zagulyaeva, A. Yu. Denisov, and V. P. Mamaev, Zh. Geterotsikl. Soedin., No. 7, 960 (1990).
7. C. D. Johnson, A. R. Katritzky, M. Kingsland, and E. F. V. Scriven, J. Chem. Soc. B, No. 1, 1 (1971).
8. S. D. Novikov, G. A. Shvekhgeimer, V. V. Sevost'yanova, and V. A. Shlyapochnikov, Chemistry of Aliphatic and Alicyclic Nitro Compounds [in Russian], Khimiya, Moscow (1974), p. 178.
9. V. V. Lapachev, O. A. Zagulyaeva, O. P. Petrenko, S. F. Bychkov, and V. P. Mamaev, Khim. Geterotsikl. Soedin., No. 6, 827 (1984).
10. A. Holland, British Patent 777465; Chem. Abs., **52**, 12841 (1958).
11. S. G. Baram, O. P. Shkurko, and V. P. Mamaev, Izv. Akad. Nauk SSSR, Ser. Khim., No. 2, 29 (1983).