Synthesis of New Substituted 5-Methyl-3,5-diphenylimidazolidine-2,4-diones from Substituted 1-(1-Cyanoethyl-1-phenyl)-3-phenylureas

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The reaction of substituted phenyl isocyanates with 2-amino-2-phenylpropanenitrile and 2-amino-2-(4-nitrophenyl)propanenitrile has been used to prepare substituted 1-(1-cyanoethyl-1-phenyl)-3-phenylureas. In anhydrous phosphoric acid the first products to be formed from 1-(1-cyanoethyl-1-phenyl)-3-phenylureas are phosphates of 4-methyl-4-phenyl-2-phenylimino-5-imino-4,5-dihydro-1,3-oxazoles, which on subsequent hydrolysis give the respective ureidocarboxylic acids. On prolongation of the reaction time, the phosphates of 4-methyl-4-phenyl-2-phenylimino-5-imino-4,5-dihydro-1,3-oxazoles rearrange to give phosphates of 5-methyl-4-imino-3,5-diphenylimidazolidin-2-ones, and these are subsequently hydrolysed to the respective substituted 5-methyl-3,5-diphenylimidazolidin-2,4-diones. The ureidocarboxylic acids were also prepared by alkaline hydrolysis of 5-methyl-3,5-diphenylimidazolidin-2,4-diones. The 5-methyl-3,5-diphenylimidazolidin-2,4-diones and ureidocarboxylic acids were characterised by their ^{1}H and ^{13}C NMR spectra. Structure of the 5-methyl-5-(4-nitrophenyl)-3-phenylimidazolidine-2,4-dione was verified by X-ray diffraction. The alkaline hydrolysis of individual imidazolidine-2,4-diones was studies spectrophotometrically in sodium hydroxide solutions at 25 °C. The rate-limiting step of the base catalysed hydrolysis consists in decomposition of the tetrahedral intermediate. The reaction is faster if electron-acceptor substituents are present in the 3-phenyl group of imidazolidine-2,4-dione cycle. The pK_a values of individual 5-methyl-3,5-diphenylimidazolidine-2,4-diones have been determined kinetically.

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Introduction

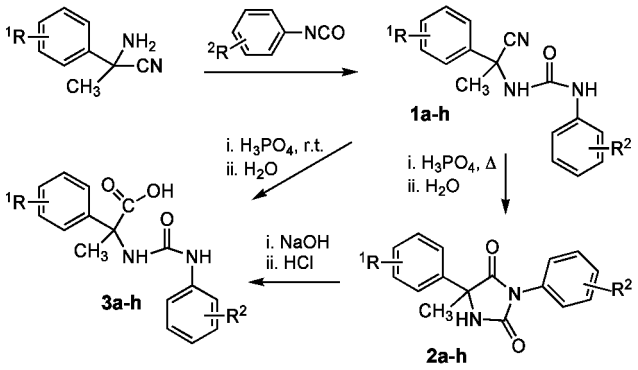
Substituted imidazolidine-2,4-diones (hydantoins), like barbiturates, belong among cyclic ureas with a wide spectrum of applications [1]. The oldest known imidazolidine-2,4-diones represent a significant group of psychopharmaceuticals [2], analgesics [3], cytostatics [4], antihypertensives [5] and herbicides [6]. However, in recent years increasing attention has been paid to the substituted imidazolidine-2,4-diones having bacteriostatic effects particularly against *Mycobacterium tuberculosis*, which is connected with the spread of new resistant strains [7]. The aim of the present paper is to verify the direct synthesis of new substituted 5-methyl-3,5-diphenylimidazolidine-2,4-diones from 1-(1-cyanoethyl-1-phenyl)-3-phenylureas without the necessity of preliminary transformation of the nitrile group into carboxylic or ester group. Another part of this paper covers the characterisation of the new substituted 5-methyl-3,5-diphenylimidazolidine-2,4-diones, inclusive of estimation of their hydrolytic stability and determination of pK_a values of the individual 5-methyl-3,5-diphenylimidazolidine-2,4-diones.

Results and Discussion.

The reaction of racemic 2-amino-2-phenylpropanenitrile [8] and 2-amino-2-(4-nitrophenyl)propanenitrile [8] with substituted phenyl isocyanates was used to prepare the substituted 1-(1-cyanoethyl-1-phenyl)-3-phenylureas **1a**-**h** (Scheme 1). In all the cases, the addition reactions gave high yields (51 to 93%). The ureas prepared (**1a**-**h**) were characterised by their ^{1}H, ^{13}C NMR spectra and elemental analyses.

1, 2, 3	a	b	c	d	e	f	g	h
^{1}R	4-NO_2	4-NO_2	4-NO_2	4-NO_2	4-NO_2	4-NO_2	4-NO_2	H
^{2}R	4-OCH_3	H	3-CF_3	4-$COCH_3$	4-NO_2	3,4-Cl_2	2,4-Cl_2	H

Scheme 1



Next, we treated the substituted 1-(1-cyanoethyl-1-phenyl)-3-phenylureas **1a**-**h** with anhydrous phosphoric acid, presuming a ring closure reaction to take place giving substituted 4-methyl-4-phenyl-2-phenylimino-4,5-dihydro-1,3-oxazol-5-ones. In this way, analogous ring closure reactions proceed in strongly acid anhydrous media transforming substituted 2-cyanophenylureas [9] and *N*-(1-cyano-1,1-

dialkylmethyl)benzamides [10] into benzoxazines and 4,4-dialkyl-2-phenyl-4,5-dihydro-1,3-oxazol-5-ones, respectively. In our case we found out that in anhydrous phosphoric acid the first reaction is ring closure (kinetic control) between the oxygen atom of urea and the protonated nitrile group, giving phosphates of 4-methyl-4-phenyl-2-phenylimino-5-imino-4,5-dihydro-1,3-oxazoles. The subsequent slower step (thermodynamic control) involves a rearrangement of the imonium salt to give phosphates of substituted 5-methyl-4-imino-3,5-diphenylimidazolidin-2-ones (Scheme 2). The rearrangement probably proceeds by a mechanism analogous to that described for transformations of benzoxazines into quinazolindiones in anhydrous phosphoric acid [11]. However, in our attempts at isolation of the individual 4-methyl-4-phenyl-2-phenylimino-5-imino-4,5-dihydro-1,3-oxazoles we only isolated, after the hydrolysis of the salts, either the ureidocarboxylic acids **3a-g** (Method A) or the substituted 5-methyl-3,5-diphenylimidazolidine-2,4-diones **2a-h**, depending on the reaction time in phosphoric acid (Scheme 2). The fact that the hydrolysis produces ureidocarboxylic acids **3a-g** can be considered a piece of indirect evidence in favour of the reaction path *via* the intermediates represented by the phosphates of 4-methyl-4-phenyl-2-phenylimino-5-imino-4,5-dihydro-1,3-oxazoles. 5-Methyl-3,5-diphenylimidazolidine-2,4-diones **2a-h** are not hydrolysed at measurable rate in diluted phosphoric acid, and also the hydrolysis of nitrile group in this medium at room temperature is very slow, hence the only educts for the ureidocarboxylic acids **3a-g** can be derivatives of substituted 4,5-dihydro-1,3-oxazoles (Scheme 2). Another piece of indirect evidence in favour of formation of the phosphates of substituted 5-methyl-4-imino-3,5-diphenylimidazolidin-2-ones by the rearrangement is the fact that during the spectrophotometric monitoring of this reaction in anhydrous phosphoric acid it takes place as a system of two consecutive reactions, *i.e.* the ring closure and rearrangement. This monitoring of the reaction of 1-[1-cyano-1-(4-nitrophenyl)ethyl]-3-phenylurea (**1b**) at first shows an isosbestic point at 244 nm. However, after *ca.* 2 hrs of reaction, the spectra taken at regular intervals gradually cease to cross the isosbestic point, which indicates that a consecutive reaction is taking place (Scheme 2).

Structure of the 5-methyl-5-(4-nitrophenyl)-3-phenylimidazolidine-2,4-dione (**2b**) was verified by means of X-ray diffraction (ORTEP). The geometry of imidazolidine-2,4-dione fragment of **2b** (Figure 1) stands in a good agreement with those of several previously published hydantoins. The structurally closely related imidazolidine-2,4-diones [12] reveal comparable bond lengths and interatomic angles as those observed in **2b**. An important difference in this respect is the system of two intermolecular hydrogen bonds. These two hydrogen bonds in **2b** connect each molecule in the crystal unit cell with a molecule from another crystal unit cell *via* O1···N3 bridges (N3 H3 O1 0.837(19) 2.072(19) 2.8829(15) 163.1(17)). The same arrangement is present also in compounds described elsewhere [12].

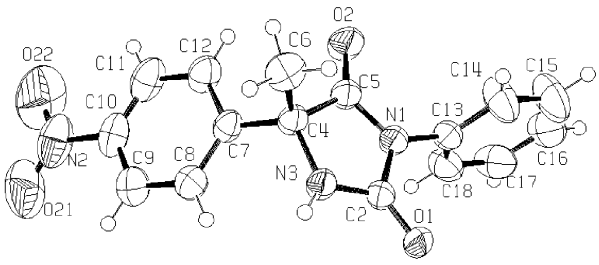
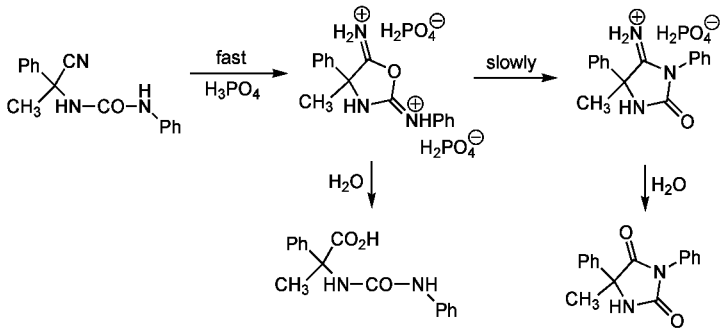


Figure 1. Molecular structure of **2b**, ORTEP 50% probability level. Selected interatomic distances [Å] and angles [°]: N1 C5 1.3668(17), N1 C2 1.4074(16), N1 C13 1.4339(17), C2 O1 1.2161(16), C2 N3 1.3382(17), N3 C4 1.4529(16), N3 H3 0.837(19), C4 C7 1.5275(19), C4 C6 1.532(2), C4 C5 1.5364(18) C5 O2 1.2053(17), N2 O22 1.207(3), N2 O21 1.218(3), C5 N1 C2 111.56(11), C5 N1 C13 124.54(11), O1 C2 N3 128.87(12), O1 C2 N1 124.13(12), N3 C2 N1 106.99(11), C2 N3 C4 113.75(11), N3 C4 C7 113.05(11), N3 C4 C6 111.87(12), C7 C4 C6 110.07(12), N3 C4 C5 100.65(10), C7 C4 C5 111.15(11), O21 N2 C10 118.6(2), hydrogen bond N3 H3 O1 0.837(19) 2.072(19) 2.8829(15) 163.1(17).

Crystallography.

The single crystals were obtained by vapour diffusion of hexane into *ca.* 3% dichloromethane solution of 2b. The X-ray data were collected on the Nonius KappaCCD

Scheme 2



diffractometer, MoKα radiation (λ = 0.71073 Å, graphite monochromator) at 150(2) K. Absorption corrections were carried out for both data sets using a multiscan procedure (SORTAV) [13]. The structure was solved by direct methods (SIR92) [14], full-matrix least-squares refinements on F^2 were carried out using the program SHELXL97 [15].

All non-hydrogen atoms are refined anisotropically, all hydrogen atoms on carbons were calculated into idealised positions (riding model) and assigned displacement factors $H_{iso}(H) = 1.2\ U_{eq}$(pivot atom) or of $1.5U_{eq}$ for the methyl moiety. The positions of remaining hydrogen atoms were found using difference Fourier map and refined as riding on nitrogen with isotropic displacement factors.

Crystallographic parameters for compound **2b**: formula: $C_{16}H_{13}N_3O_4$, *M:* 311.29, crystal system: triclinic, space group: *P-1(No 2.)*, *a*: 7.8840(3)Å, *b*: 9.9340(3)Å, *c*: 10.9630(3)Å, *α*: 69.8400(19)°, *β*: 69.3200(17)°, *γ*: 79.5170(19)°, *Z:* 2, *V*: 752.31(4)Å^3, D_c: 1.374 g.cm^{-3}, dimensions: 0.5 x 0.4 x 0.4 mm, *μ*: 0.101 mm^{-1}, $T_{min} = 0.88$, $T_{max} = 0.979$ reflections measured: 12416, independent (R_{int})[a]: 3295 (0.043), observed [$I > 2\sigma(I)$]: 7413, parameters refined: 400, *S* value[a]: 1.177, *R*(*F* obs. data): 0.065, *wR(F²)*: 0.154, $\Delta\rho_{max}$; $\Delta\rho_{min}$: 1.275; -1.225 eÅ^{-3}.

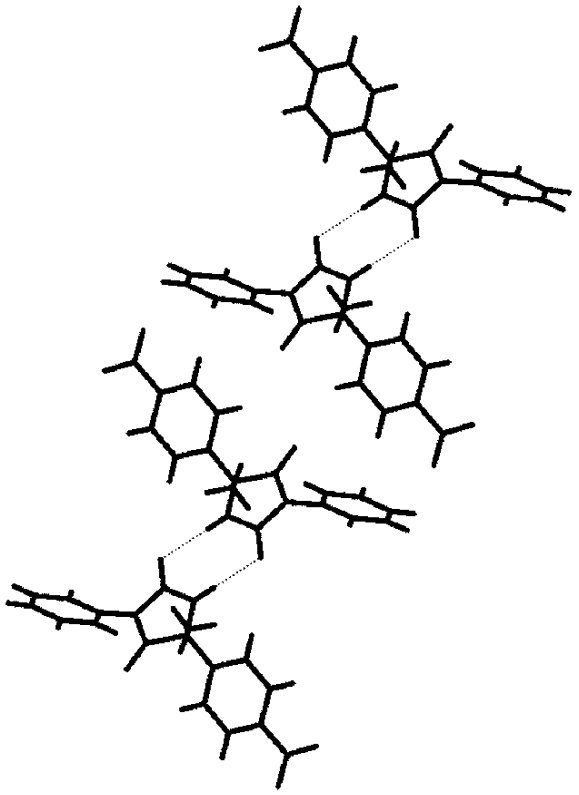


Figure 2. Crystal packing diagram of **2b** with hydrogen bonding system.

In the crystal lattice of **2b** (Figure 2) we found an intermolecular hydrogen bond between amide proton and carbonyl oxygen atom of amide group in the neighbouring molecule, which in our case results in formation of dimers; in similar way, formation of trimers was described in the case of 1,3-nonsubstituted imidazolidine-2,4-diones [16].

The 5-methyl-3,5-diphenylimidazolidine-2,4-diones **2a-h** prepared by us were also characterised by means of ^{1}H, ^{13}C NMR spectra and elemental analyses. The ^{13}C NMR spectra of 5-methyl-3,5-diphenylimidazolidine-2,4-diones show chemical shifts typical of carbonyl carbon atoms C_2=O (δ ~154.0) and C_4=O (δ ~173.0) [17]. Also measured was the ^{15}N NMR spectrum for derivative **2b**, where the nitrogen atoms N1 and N3 exhibit chemical shifts that are comparable with those given in literature [16]. We also prepared and characterised substituted ureidocarboxylic acids **3a-h** as products of alkaline hydrolysis of 5-methyl-3,5-diphenylimidazolidine-2,4-diones **2a-h** (Method B).

Study of Hydrolysis of 5-Methyl-3,5-diarylsubstituted Imidazolidine-2,4-diones **2a-h**.

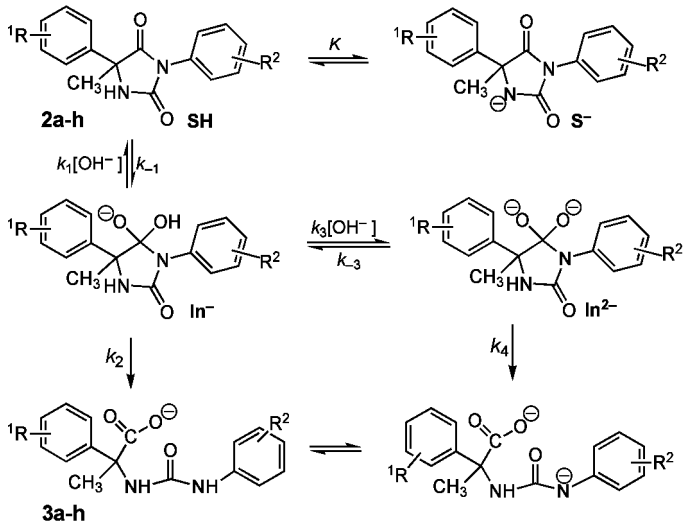
For a wide variety of applications of substituted imidazolidine-2,4-diones it is of considerable significance to estimate their stabilities in aqueous media at various pH values. The hydrolysis of the 5-methyl-3,5-diphenylimidazolidine-2,4-diones **2a-g** prepared by us was studied spectrophotometrically under the conditions of the psudo-first-order reaction. No spectral changes occurred for a period of several months in aqueous solutions of hydrochloric acid at 25 °C. The spectral recordings of 5-methyl-3,5-diphenylimidazolidine-2,4-diones **2a-g** in aqueous solutions of sodium hydroxide (0.01-1.00 mol.l^{-1}) at 25 °C exhibited changes with time and well developed isosbestic points, the only hydrolytic products being sodium ureidocarboxylates **3a-g**. Figure 3 presents the dependences of observed rate constants (k_{obs}, s^{-1}) on sodium hydroxide concentration for individual derivatives carrying various substituents at 3-phenyl group of the imidazolidine-2,4-dione cycle. From the kinetic dependences it can be seen that with derivatives **2a**,**b** and **2h** the observed rate constant at first increases with increasing sodium hydroxide concentration, but at a certain concentration the hydrolysis becomes independent of hydroxide concentration. The following general Scheme 2 can be formulated for the hydroxide-ion-catalysed hydrolysis. By action of sodium hydroxide, the proton is split off from the first nitrogen atom of the imidazolidine-2,4-dione heterocycle in an equilibrium reaction (*K*). However, the reactive species is the starting protonated substrate (SH), which undergoes addition reaction with hydroxide ion (k_1[OH$^-$]) to give the negatively charged intermediate (In$^-$), which is decomposed into the reaction product in the rate-limiting reaction step (k_2). In the cases of the imidazolidine-2,4-diones **2c-g** having electron-acceptor substituents, an increasing sodium hydroxide concentration causes further acceleration of the hydrolysis proportionally to the increasing σ

value of the substituents. In accordance with literature [18], this acceleration of hydrolysis can be explained by operation of another reaction path: the OH^- ion splits off another proton from the intermediate In^- ($k_3[OH^-]$) to give a doubly charged intermediate In^{2-}, which is decomposed into the product (k_4).

EXPERIMENTAL

Unless otherwise stated, all the isocyanates were obtained from Aldrich and used without further purification. Both 2-amino-2-phenylpropanenitrile and 2-amino-2-(4-nitrophenyl)propanenitrile were prepared by a known method [8].

Scheme 3



The experimental points given in Figure 3 are fitted with curves, which correspond to the following rate equation (1). By optimisation of these kinetic dependences we determined the parameters of rate equation; moreover, it was possible to determine the pK_a values from K values (pK_a = 14 – pK) for the individual derivatives, the maximum error being ±0.05 pK_a unit (see Table). The absolute values of constants k_2 and k_3 cannot be determined mathematically, but it is possible to determine the ratios k_3/k_2 (see Table). The k_3/k_2 values express the ratios of operation of the first and the second reaction paths (the decompositions of In^- and In^{2-}, respectively). For instance, with derivative **2a** (4-OCH_3) the second reaction path forms only 4 %, whereas with derivative **2e** (4-NO_2) it forms as much as 40 % of overall transformation.

Table

Values of Ratios k_3/k_2 and Values of pK_a of 5-Methyl-3,5-diphenylimidazolidine-2,4-diones **2a-h**

2	**a**	**b**	**c**	**d**	**e**	**f**	**h**
k_3/k_2	0.040	0.047	0.216	0.314	0.695	0.269	0.023
pK_a	11.69	11.37	11.31	11.35	11.02	11.43	12.08

$$k_{obs} = \frac{k_1 \cdot k_2 \cdot [OH^-] + k_1 \cdot k_3 [OH^-]^2}{1 + K \cdot [OH^-]} \quad (1)$$

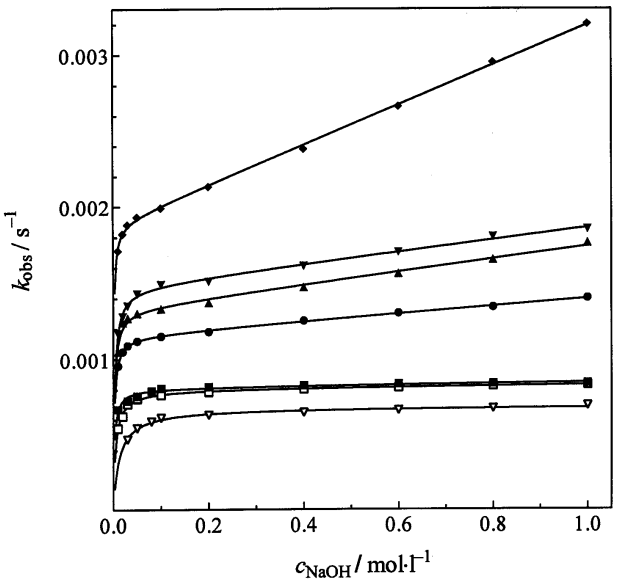


Figure 3. Dependence of k_{obs} (s^{-1}) on NaOH concentration ($mol \cdot l^{-1}$) for hydrolysis of 5-methyl-3,5-difenylimidazolidine-2,4-diones (□ **2a,** ■ **2b**, ● **2c**, ▲ **2d**, ♦ **2e,** ▼**2f**, ▽ **2h**).

The kinetic measurements were carried out on HP UV/VIS Diode Array apparatus in 1 cm closed cells at 25 °C. First, a suitable wavelength was chosen for the kinetics runs on the basis of the spectra scanned from 200 to 1000 nm. Then the cell was always charged with 2 ml aqueous solution of sodium hydroxide.

After attaining the chosen temperature, a methanolic solution of substrate **2a-h** was added. The observed pseudo-first-order rate constants k_{obs} were calculated from the measured time dependence of absorbance with the help of an optimisation program.

The ^{1}H and ^{13}C NMR spectra were measured in hexadeuteriodimethyl sulphoxide (DMSO-d_6), on a Bruker AMX 360 apparatus and a Bruker 500 Avance apparatus, respectively. The full crystallographic data of compound **2b** were deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC-248304. Copies of the data can be obtained free of charge on request; e-mail: deposit@ccdc.ca.ac.uk.

Syntheses of Substances.

Sytheses of Substitututed Ureas **1a-h**.

A saturated solution of 0.01 mol 2-amino-2-(4-nitrophenyl)-propanenitrile (2-amino-2-phenylpropanenitrile) in 4 ml dry acetone was treated with a saturated solution of 0.01 mol substituted phenyl isocyanate in 2-4 ml dry acetone. The reaction proceeded at room temperature with gradual separation of the crystalline ureidonitrile, which was finally collected by suction and washed with 10 ml ether. The raw product was recrystallized from an ethanol/water mixture.

1-[1-Cyano-1-(4-nitrophenyl)ethyl]-3-(4-methoxyphenyl)urea (**1a**).

This compound was obtained in 87 % yield, m.p. 211-213 °C; ^{1}H NMR: 1.86 (s, CH_3); 3.77 (s, OCH_3); 7.00 (d, 2H, H-3´); 7.21 (d, 2H, H-2´); 7.31 (s, 1H, NH); 7.88 (d, 2H, H-2); 8.27 (d, 2H, H-3); 8.78 (s, 1H, NH´); ^{13}C NMR: 25.2; 27.9; 55.6; 62.1; 114.0; 115.1; 123.8; 124.0; 126.8; 127.5; 129.2; 129.8; 147.3; 149.4; 150.0; 155.6; 156.3; 159.4; 158.4; 164.7; 167.2.

Anal. Calcd. for $C_{17}H_{16}N_4O_4$ (340.3): C, 60.00; H, 4.74; N, 16.46. Found: C, 60.07; H, 4.59; N, 16.59.

1-[1-Cyano-1-(4-nitrophenyl)ethyl]-3-phenylurea (**1b**).

This compound was obtained in 93 % yield, m.p. 194-197 °C; ^{1}H NMR: 1.90 (s, CH_3); 6.98 (m, 2H, H-4´); 7.27 (m, 2H, H-3´);7.39 (d, 2H, H-2´); 7.73 (s, 1H, NH); 7.80 (d, 2H, H-2); 8.33 (d, 2H, H-3); 8.85 (s, 1H, NH´); ^{13}C NMR: 25.0; 27.7; 62.0; 62.1; 123.7; 124.0; 127.3; 127.4; 127.8; 128.6; 129.8; 134.1; 147.2; 147.3; 149.1; 149.8; 155.8; 163.4; 166.7.

Anal. Calcd. for $C_{16}H_{14}N_4O_3$ (310.3): C, 61.93; H, 4.55; N, 18.06. Found: C, 62.12; H 4.54; N, 18.24.

1-[1-Cyano-1-(4-nitrophenyl)ethyl]-3-(3-trifluormehtylphenyl)-urea (**1c**).

This compound was obtained in 54 % yield, m.p. 186-188 °C; ^{1}H NMR: 1.90 (s, CH_3); 7.67-7.76 (m, 3H, H-4´,5´,6´); 7.84 (s, 1H, H-2´); 7.88 (d, 2H, H-2); 8.28 (d, 2H, H-3); 8.57 (s, 1H, NH); 8.93 (s, 1H, NH´); ^{13}C NMR: 24.8; 62.1; 123.9; 127.5; 129.8; 131.5; 134.6; 147.3; 148.7; 155.3; 166.2.

Anal. Calcd. for $C_{17}H_{13}F_3N_4O_3$ (378.3): C, 53.97; H, 3.46; N, 14.81. Found: C, 53.88; H, 3.69; N, 14.99.

1-[1-Cyano-1-(4-nitrophenyl)ethyl]-3-(4-acetylphenyl)urea (**1d**).

This compound was obtained in 51 % yield, m.p. 180-182 °C; ^{1}H NMR: 1.95 (s, CH_3); 2.64 (s, 4´-CH_3); 7.65 (d, 2H, H-2´); 7.92 (d, 2H, H-2); 8.05 (d, 2H, H-3´); 8.34 (d, 2H, H-3); 8.69 (s, 1H, NH); 8.99 (s, 1H, NH´); ^{13}C NMR: 24.9; 26.9; 62.1; 123.6; 123.9; 127.2; 127.4; 127.8; 128.5; 129.6; 135.0; 138.1; 147.3; 148.8; 155.3; 166.2; 197.6.

Anal. Calcd. for $C_{18}H_{16}N_4O_4$ (352.4): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.12; H, 4.49; N, 15.76.

1-[1-Cyano-1-(4-nitrophenyl)ethyl]-3-(4-nitrophenyl)urea (**1e**).

This compound was obtained in 81 % yield, m.p. 203-206 °C; ^{1}H NMR: 1.97 (s, CH_3); 7.88 (d, 2H, H-2´); 7.93 (d, 2H, H-2); 8.32 (d, 2H, H-3); 8.34 (d, 2H, H-3´); 8.89 (s, 1H, NH); 9.12 (s, 1H, NH´); ^{13}C NMR: 24.0; 65.7; 123.9; 124.1; 124.9; 127.3; 127.4; 131.0; 131.3; 140.9; 146.8; 147.3; 147.5; 167.4.

Anal. Calcd. for $C_{16}H_{13}N_5O_5$ (355.3): C, 54.09; H, 3.69; N, 19.71. Found: C, 54.18; H, 3.60; N, 19.91.

1-[1-Cyano-1-(4-nitrophenyl)ethyl]-3-(3,4-dichlorphenyl)urea (**1f**).

This compound was obtained in 63 % yield, m.p. 165-167 °C; ^{1}H NMR: 1.89 (s, CH_3); 7.48 (d, 1H, H-5´); 7.69 (d, 1H, H-6´); 7.78 (s, 1H, H-2´); 7.87 (d, 2H, H-2); 8.27 (d, 2H, H-3); 8.62 (s, 1H, NH); 8.94 (s, 1H, NH´); ^{13}C NMR: 24.86; 62.2; 123.6; 123.9; 127.6; 127.7; 128.7; 129.2; 129.5; 130.4; 130.8; 131.5; 132.0; 134.0; 147.3; 148.8; 155.1; 166.0.

Anal. Calcd. for $C_{16}H_{12}Cl_2N_4O_3$ (379.2): C, 50.68; H, 3.19; N, 14.77. Found: C, 50.53; H, 3.13; N, 14.50.

1-[1-Cyano-1-(4-nitrophenyl)ethyl]-3-(2,4-dichlorphenyl)urea (**1g**).

This compound was obtained in 78 % yield, m.p. 187-190 °C; ^{1}H NMR: 1.94 (s, CH_3); 7.32 (dd, 1H, H-5´); 7.62 (d, 1H, H-3´); 7.81 (d, 2H, H-2); 8.06 (dd, 1H, H-6´); 8.34 (d, 2H, H-3); 8.51 (s, 1H, NH); 8.54 (s, 1H, NH´); ^{13}C NMR: 29.2; 53.4; 53.5; 119.9; 121.5; 122.3; 124.1; 125.8; 126.2; 127.6; 128.5; 134.7; 134.8; 147.2; 148.0; 152.8; 152.9.

Anal. Calcd. for $C_{16}H_{12}Cl_2N_4O_3$ (379.2): C, 50.68; H, 3.19; N, 14.77. Found: C, 50.96; H, 2.98; N, 14.82.

1-(1-Cyano-1-phenylethyl)-3-phenylurea (**1h**).

This compound was obtained in 88 % yield, m.p. 148-152 °C; ^{1}H NMR: 1.82 (s, CH_3); 6.93 (m, 1H, NH); 7.22 (t, 2H, H-2); 7.33-7.36 (m, 3H, H-3´, 4´); 7.41-7.45 (m, 3H, H-3, 4); 7.51 (d, 2H, H-2´); 8.66 (s, 1H, NH´); ^{13}C NMR: 29.9; 53.4; 117.9; 120.9; 121.8; 124.3; 125.5; 128.0; 128.7; 139.4; 141.0; 153.4.

Anal. Calcd. for $C_{16}H_{15}N_3O$ (265.3): C, 72.43; H, 5.70; N, 15.84. Found: C, 72.58; H, 5.98; N, 15.73.

Syntheses of Substituted Imidazolidine-2,4-diones **2a-h**.

The respective ureidonitrile **1a-h** (0.01 mol) was added to 10 ml polyphosphoric acid, and the reaction mixture was intensively stirred and heated to a temperature of 100 °C for 5-8 hours. After cooling, the reaction mixture was hydrolysed in a mixture of 100 g ice and water. The separated crystalline imidazolidine-2,4-dione was collected by suction and washed with 20 ml water. The raw product was recrystallized from ethanol.

3-(4-Methoxyphenyl)-5-methyl-5-(4-nitrophenyl)imidazolidine-2,4-dione (**2a**).

This compound was obtained in 92 % yield, m.p. 178-180 °C; ^{1}H NMR: 1.91 (s, 3H, CH_3), 3.82 (s, 1H, OCH_3), 7.05 (d, ^{3}J = 9.0 Hz, 2H, H-3´), 7.33 (d, ^{3}J = 8.9 Hz, 2H, H-2´), 7.93 (d, ^{3}J = 8.9 Hz, 2H, H-2), 8.33 (d, ^{3}J = 8.9 Hz, 2H, H-3), 9.39 (s, 1H, NH); ^{13}C NMR: 25.4, 55.5, 62.9, 114.2, 123.8, 124.5, 127.3, 128.4, 146.9, 147.4, 154.8, 158.9, 173.8.

Anal. Calcd. for $C_{17}H_{15}N_3O_5$ (341.3): C, 59.82; H, 4.43; N, 12.31. Found: C, 60.01; H, 4.36; N, 12.27.

5-Methyl-5-(4-nitrophenyl)-3-phenylimidazolidine-2,4-dione (**2b**).

This compound was obtained in 72 % yield, m.p. 187-189 °C; ^{1}H NMR: 1.92 (s, 3H, CH_3), 7.41-7.50 (m, 4H, H-2´, H-4´), 7.52 (t, ^{3}J = 7.6 Hz, 1H, H-3´), 7.94 (d, ^{3}J = 9.0 Hz, 2H, H-2), 8.35 (d, ^{3}J = 9.0 Hz, 2H, H-3), 9.44 (s, 1H, NH); ^{13}C NMR: 25.3, 62.9, 123.9, 127.0, 127.3, 128.2, 128.9, 131.9, 146.7, 147.4, 154.4, 173.6. ^{15}N NMR: –10 (NO_2), –221 (N-3), –275 (N-1).

Anal. Calcd. for $C_{16}H_{13}N_3O_4$ (311.3): C, 61.73; H, 4.21; N, 13.50. Found: C, 61.94; H 4.25; N, 13.46.

5-Methyl-5-(4-nitrophenyl)-3-(3-trifluoromethylphenyl)imidazolidine-2,4-dione (**2c**).

This compound was obtained in 75 % yield, m.p. 161-163 °C; ^{1}H NMR: 1.94 (s, 3H, CH_3), 7.75-7.82 (m, 3H, H-4´, H-5´, H-6´), 7.92-7.96 (m, 3H, H-2, H-2´), 8.33 (d, ^{3}J = 9.0 Hz, 2H, H-3), 9.56 (s, 1H, NH); ^{13}C NMR: 25.3, 63.1, 123.8, 123.8, 123.9, 124.8, 127.4, 129.7, 130.2, 131.0, 132.8, 146.6, 147.5, 154.0, 173.4.

Anal. Calcd. for $C_{17}H_{12}F_3N_3O_4$ (379.3): C, 53.83; H, 3.19; N, 11.08. Found: C, 53.97; H, 3.19; N, 10.91.

3-(4-Acetyphenyl)-5-methyl-5-(4-nitrophenyl)imidazolidine-2,4-dione (**2d**).

This compound was obtained in 83 % yield, m.p. 163-166 °C; ^{1}H NMR: 1.94 (s, 3H, CH_3), 2.64 (s, 1H, $COCH_3$), 7.63 (d, ^{3}J = 8.5 Hz, 2H, H-2´), 7.94 (d, ^{3}J = 8.8 Hz, 2H, H-2), 8.09 (d, ^{3}J = 8.5 Hz, 2H, H-3´), 8.33 (d, ^{3}J = 8.8 Hz, 2H, H-3), 9.58 (s, 1H, NH); ^{13}C NMR: 25.4, 26.9, 63.1, 123.9, 126.7, 127.4, 128.9, 136.0, 146.4, 146.6, 154.0, 154.0, 173.4, 197.4.

Anal. Calcd. for $C_{18}H_{15}N_3O_5$ (353.3): C, 61.19; H, 4.28; N, 11.89. Found: C, 60.96; H, 4.20; N, 11.65.

5-Methyl-3,5-di(4-nitrophenyl)imidazolidine-2,4-dione (**2e**).

This compound was obtained in 83 % yield, m.p. 217-219 °C; ^{1}H NMR: 1.95 (s, 3H, CH_3), 7.82 (d, ^{3}J = 9.2 Hz, 2H, H-2´), 7.94 (d, ^{3}J = 9.0 Hz, 2H, H-2), 8.33 (d, ^{3}J = 9.0 Hz, 2H, H-3), 8.37 (d, ^{3}J = 9.2 Hz, 2H, H-3´), 9.66 (s, 1H, NH); ^{13}C NMR: 25.3, 63.0, 123.7, 124.0, 127.0, 127.2, 137.7, 146.0, 146.4, 147.4, 153.5, 173.0.

Anal. Calcd. for $C_{16}H_{12}N_4O_6$ (356.3): C, 53.94; H, 3.39; N, 15.72. Found: C, 53.93; H, 3.30; N, 15.56.

3-(3,4-Dichlorophenyl)-5-methyl-5-(4-nitrophenyl)imidazolidine-2,4-dione (**2f**).

This compound was obtained in 80 % yield, m.p. 165-167 °C; ^{1}H NMR: 1.92 (s, 3H, CH_3), 7.51 (dd, ^{3}J = 8.4 Hz, ^{4}J = 1.7 Hz 1H, H-5´), 7.79 (d, ^{3}J = 8.9 Hz, 1H, H-6´), 7.84 (d, ^{4}J = 1.7 Hz, 1H, H-2´), 7.93 (d, ^{3}J = 8.6 Hz, 2H, H-2), 8.33 (d, ^{3}J = 8.7 Hz, 2H, H-3), 9.55 (s, 1H, NH); ^{13}C NMR: 25.3, 63.0, 123.8, 127.1, 127.4, 128.7, 130.7, 131.1, 131.8, 146.5, 147.4, 153.6, 153.8, 173.2.

Anal. Calcd. for $C_{16}H_{11}Cl_2N_3O_4$ (380.2): C, 50.55; H, 2.92; N, 11.05. Found: C, 50.40; H, 3.04; N, 11.15.

3-(2,4-Dichlorophenyl)-5-methyl-5-(4-nitrophenyl)imidazolidine-2,4-dione (**2g**).

This compound was obtained in 74 % yield, m.p. 202-204 °C; ^{1}H NMR: 1.93 and 1.96 (2×s, 1H, CH_3), 7.59-7.63 (m, 1H, H-6´), 7.67 and 7.74 (d and dd, ^{3}J = 8.5 Hz, ^{4}J = 1.7 Hz 1H, H-5´), 7.86-7.93 (2×d, ^{4}J = 2.2 Hz, 1H, H-3´), 7.95 (2×d, ^{3}J = 8.9 Hz, 2H, H-2), 8.36 (m, ^{3}J = 8.6 Hz, 2H, H-3), 9.53 and 9.60 (2×s, 1H, NH); ^{13}C NMR: 24.7, 26.0, 63.7, 124.0, 127.5, 128.6, 129.7, 132.7, 133.4, 135.1, 145.9, 146.5, 147.5, 153.5, 172.9.

Anal. Calcd. for $C_{16}H_{11}Cl_2N_3O_4$ (380.2): C, 50.55; H, 2.92; N, 11.05. Found: C, 50.35; H, 3.14; N, 10.97.

5-Methyl-3,5-diphenylimidazolidine-2,4-dione (**2h**).

This compound was obtained in 78 % yield, m.p. 145-147 °C; ^{1}H NMR: 1.82 (s, 3H, CH_3), 7.35-7.50 (m, 8H), 7.57 (d, ^{3}J = 7.6 Hz, 2H, H-2‘), 9.23 (s, 1H, NH); ^{13}C NMR: 24.9, 62.8, 125.5, 126.8, 128.0, 128.2, 128.7, 128.8, 132.0, 139.6, 154.6, 174.5.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$ (266.3): C, 72.17; H, 5.30; N, 10.52. Found: C, 72.24; H, 5.22; N, 10.41.

Syntheses of Substituted Acids **3a-h**.

Method A.

The respective ureidonitrile **1a-h** (0.01 mol) was added to 10 ml polyphosphoric acid and the reaction mixture was intensively stirred at room temperature for 2-4 hours. Then the reaction mixture was hydrolysed with a 100 g mixture of ice and water. The separated solid was collected by suction and washed with 20 ml water. The raw product was recrystallized from aqueous ethanol.

Method B.

A solution of the respective 5-methyl-3,5-diphenylimidazolidine-2,4-dione **2a-h** (0.01 mol) in 10 ml methanol was added to 200 ml aqueous sodium hydroxide solution (c = 1 mol·l^{-1}). The reaction mixture was stirred at room temperature 24 hours. The resulting solution was cooled and gradually acidified with concentrated hydrochloric acid to pH ~ 1-2. The separated crystals of ureidocarboxylic acid were collected by suction and washed with 10 ml water. The raw product was recrystallized from ethanol.

2-(4-Methoxyphenylcarbamoyl)amino-2-(4-nitrophenyl)-propanoic Acid (**3a**).

This compound was obtained in 92 % (method A) and 90 % (method B) yields, m.p. 168-171 °C (decomp.); ^{1}H NMR: 2.00 (s, 3H, CH_3), 3.71 (s, 1H, OCH_3), 6.83 (d, ^{3}J = 9.0 Hz, 2H, H-2´), 7.26 (d, ^{3}J = 8.9 Hz, 2H, H-3´), 7.20 (s, 1H, NH), 7.76 (d, ^{3}J = 8.9 Hz, 2H, H-2), 8.26 (d, ^{3}J = 8.8 Hz, 2H, H-3), 8.80 (s, 1H, NH´); ^{13}C NMR: 24.2, 55.3, 61.1, 114.0, 119.1, 119.2, 123.3, 127.6, 133.5, 146.6, 150.2, 154.1, 173.6.

Anal. Calcd. for $C_{17}H_{17}N_3O_6$ (359.34): C, 56.82; H, 4.77; N, 11.69. Found: C, 56.75; H, 4.63; N, 11.54.

2-(Phenylcarbamoyl)amino-2-(4-nitrophenyl)propanoic Acid (**3b**).

This compound was obtained in 87 % (method A) and 92 % (method B) yields, m.p. 167-168 °C (decomp.); ^{1}H NMR: 2.02 (s, 3H, CH_3), 7.24 (t, ^{3}J = 7.9 Hz, 1H, H-3´), 7.36-7.38 (m, 3H, H-2´, NH), 7.78 (d, ^{3}J = 8.8 Hz, 2H, H-2), 8.27 (d, ^{3}J = 8.7 Hz, 2H, H-3), 9.05 (s, 1H, NH´); ^{13}C NMR: 23.7, 61.1, 117.5, 121.4, 123.3, 127.6, 128.8, 140.2, 146.6, 150.1, 153.8, 173.6.

Anal. Calcd. for $C_{16}H_{15}N_3O_5$ (329.31): C, 58.36; H, 4.59; N, 12.76. Found: C, 58.18; H, 4.49; N, 12.64.

2-(3-Trifluoromethylphenylcarbamoyl)amino-2-(4-nitrophenyl)-propanoic Acid (**3c**).

This compound was obtained in 85 % (method A) and 70 % (method B) yields, m.p. 174-176 °C; ^{1}H NMR: 2.00 (s, 3H, CH_3), 7.26 (d, ^{3}J = 6.1 Hz, 1H, H-4´), 7.47-7.50 (m, 2H, H-5´,H-

6´), 7.64 (s, 1H, NH), 7.79 (d, ^{3}J = 8.5 Hz, 2H, H-2), 7.96 (s,1H, H2´), 8.27 (d, ^{3}J = 8.6 Hz, 2H, H-3), 9.84 (s, 1H, NH´); ^{13}C NMR: 24.1, 61.3, 113.5, 117.8, 121.3, 123.5, 127.8, 130.1, 141.3, 146.9, 150.0, 154.0, 173.6.

Anal. Calcd. for $C_{17}H_{14}F_3N_3O_5$: (397.31): C, 51.39; H, 3.55; N, 10.58. Found: C, 51.09; H, 3.63; N, 10.76.

2-(4-Acetylphenylcarbamoyl)amino-2-(4-nitrophenyl)propanoic Acid (**3d**).

This compound was obtained in 79 % (method B) yield, m.p. 165-168 °C; ^{1}H NMR: 2.02 (s, 3H, CH_3), 2.52 (s, 1H, $COCH_3$), 7.48 (d, ^{3}J = 8.8 Hz, 2H, H-2´), 7.56 (s, 1H, NH), 7.78 (d, ^{3}J = 8.9 Hz, 2H, H-2), 7.87 (d, ^{3}J = 8.7 Hz, 2H, H-3´), 8.27 (d, ^{3}J = 8.9 Hz, 2H, H-3), 9.59 (s, 1H, NH´); ^{13}C NMR: 23.4, 26.8, 61.1, 122.1, 123.4, 127.5, 132.2, 136.5, 139.4, 146.6, 150.1, 153.0, 173.4, 197.8.

Anal. Calcd. for $C_{18}H_{17}N_3O_6$ (372.35): C, 58.22; H, 4.61; N, 11.32. Found: C, 58.23; H, 4.48; N, 11.46.

2-(4-Nitrophenylcarbamoyl)amino-2-(4-nitrophenyl)propanoic Acid (**3e**).

This compound was obtained in 76 % (method B) yield, m.p. 214-216 °C; ^{1}H NMR: 2.04 (s, 3H, CH_3), 7.58 (d, ^{3}J = 9.2 Hz, 2H, H-2´), 7.64 (s, 1H, NH), 7.78 (d, ^{3}J = 8.8 Hz, 2H, H-2), 8.16 (d, ^{3}J = 9.1 Hz, 2H, H-3´), 8.27 (d, ^{3}J = 8.8 Hz, 2H, H-3), 9.85 (s, 1H, NH´); ^{13}C NMR: 23.2, 61.1, 116.9, 123.3, 125.2, 127.4, 140.6, 146.6, 146.7, 150.1, 152.9, 173.2.

Anal. Calcd. for $C_{16}H_{14}N_4O_7$ (374.3): C, 51.34; H, 3.77; N, 14.97. Found: C, 51.33; H, 3.70; N, 15.04.

2-(3,4-Dichlorophenylcarbamoyl)amino-2-(4-nitrophenyl)-propanoic Acid (**3f**).

This compound was obtained in 86 % (method A) and 98 % (method B) yields, m.p. 166-167 °C; ^{1}H NMR: 2.00 (s, 3H, CH_3), 7.19 (d, ^{3}J = 7.4 Hz, 1H, H-6´), 7.47 (d, ^{3}J = 8.8 Hz, 1H, H-5´), 7.54 (s, 1H, NH), 7.77 (d, ^{3}J = 8.5 Hz, 2H, H-2), 7.81 (s, 1H, H-2´), 8.26 (d, ^{3}J = 8.6 Hz, 2H, H-3), 9.56 (s, 1H, NH´); ^{13}C NMR: 23.6, 61.1, 117.6, 117.7, 122.6, 123.4, 127.6, 130.6, 131.1, 140.4, 146.6, 149.8, 153.5, 173.5.

Anal. Calcd. for $C_{16}H_{13}Cl_2N_3O_5$ (398.2): C, 48.26; H, 3.29; N, 10.55. Found: C, 48.17; H, 3.07; N, 10.31.

2-(2,4-Dichlorophenylcarbamoyl)amino-2-(4-nitrophenyl)-propanoic Acid (**3g**).

This compound was obtained in 84 % (method B) yield, m.p. 165-166 °C; ^{1}H NMR: 1.99 (s, 3H, CH_3), 7.29 (d, ^{3}J = 7.5 Hz, 1H, H-5´), 7.57 (s, 1H, NH), 7.79 (d, ^{3}J = 8.6 Hz, 2H, H-2), 8.08 (d, ^{3}J = 8.9 Hz, 1H, H-6´), 8.24-8.29 (m, 3H, H-3, H-3´), 8.77 (s, 1H, NH´); ^{13}C NMR: 23.9, 61.4, 121.8, 122.1, 123.3, 125.5, 127.4, 127.6, 128.5, 135.7, 146.6, 149.6, 153.5, 173.3.

Anal. Calcd. for $C_{16}H_{13}Cl_2N_3O_5$ (398.2): C, 48.26; H, 3.29; N, 10.55. Found: C, 48.20; H, 3.11; N, 10.44.

2-(Phenylcarbamoyl)amino-2-phenylpropanoic Acid (**3h**).

This compound was obtained in 80 % (method A) and 72 % (method B) yields, m.p. 181-184 °C; ^{1}H NMR: 1.97 (s, 3H, CH_3), 6.93 (t, ^{3}J = 7.3 Hz, 1H, H-4´), 7.11 (s, 1H, NH), 7.25 (t, ^{3}J = 7.6 Hz, 2H, H-3‘), 7.33-7.44 (m, 5H, H-2, H-3, H-4), 7.53 (d, ^{3}J = 7.5 Hz, 2H, H-2´), 8.93 (s, 1H, NH´); ^{13}C NMR: 23.7, 61.2, 117.5, 121.2, 125.9, 127.4, 128.4, 128.8, 140.5, 142.3,154.1, 174.5.

Anal. Calcd. for $C_{16}H_{16}N_2O_3$ (284.31): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.86; H, 5.67; N, 9.68.

Conclusion.

The reaction of 1-(1-cyanoethyl-1-phenyl)-3-phenylureas **1a-h** in the medium of anhydrous phosphoric acid at first gives phosphates of 4-methyl-4-phenyl-2-phenylimino-5-imino-4,5-dihydro-1,3-oxazoles, which subsequently, after a longer reaction time, rearrange to phosphates of substituted 5-methyl-4-imino-3,5-diphenylimidazolidin-2-ones. The hydrolysis of the reaction mixture produces (depending on the reaction time) either ureidocarboxylic acids **3a-g** or substituted 5-methyl-3,5-diphenylimidazolidine-2,4-diones **2a-h.** As compared with the classical method, this new synthetic procedure of preparation of imidazolidine-2,4-diones does not require preliminary hydrolysis of the nitrile group to carboxylic or ester group. The 5-methyl-3,5-diphenylimidazolidine-2,4-diones obtained are practically stable in solutions of strong mineral acids. In aqueous solutions of sodium hydroxide, they undergo hydrolysis to give salts of substituted ureidocarboxylic acids **3a-g**.

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