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SYNTHESIS OF 6,8-SUBSTITUTED DERIVATIVES OF IMIDAZO[5,1-*c*][1,2,4]TRIAZINES AND 1,4-DIHYDRO-IMIDAZO[5,1-*c*][1,2,4]TRIAZIN-4-ONES

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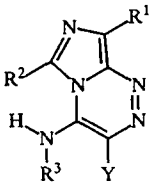
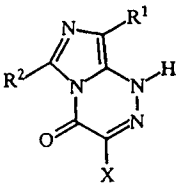
The cyclization of imidazolylhydrazines, synthesized from 5-diazoimidazoles and cyanoacetic acid derivatives, to 4-aminoimidazo[5,1-c][1,2,4]triazines and imidazo[5,1-c][1,2,4]triazin-4-ones has been studied. It was established that electron-withdrawing substituents at position 4 of the imidazole ring had a weak effect on the cyclization process. On the other hand, electron-donating substituents at positions 4 or 2 of this ring inhibited and in some cases completely prevented the formation of bicyclic products.

Hydrazones are formed on azo coupling of diazoazoles with derivatives of cyanoacetic, malonic, and acetoacetic esters, and also acetylacetone, which are then cyclized into azolo[5,1-*c*][1,2,4]triazines. The cyclization reaction of hydrazones has been well studied in the case of derivatives of pyrazole, 1,2,3-, and 1,2,4-triazole, and the results have been correlated in several reviews [1, 2]. Among imidazoles it has been reported for 5-diazoimidazole-4-carboxamide and 2-diazoimidazole [3-6].

The aim of the present work was the synthesis of new derivatives of 4-amino-3-carbethoxyimidazo[5,1-*c*][1,2,4]triazine (I) and 3-cyanoimidazo[5,1-*c*][1,2,4]triazin-4(1H)-one (II), which are of interest as potentially biologically active compounds. It was also assumed that on obtaining these compounds by the cyclization of the corresponding substituted imidazolylhydrazones, data will be obtained on the effect of the character of the substituents in the imidazole ring on the course of this reaction.



Ia-p



IIa-m

Ia-e Y = COOEt, $R^2 = R^3 = H$, a $R^1 = CONH_2$, b R^1 = CONHMe, c $R^1 = CONHC_6H_4Me$-*m*, d $R^1 = NO_2$, e R^1 = COOEt; f, g $R^1 = CONH_2$, $R^2 = R^3 = H$, f Y = CONHMe, g Y = CONH -pyridyl-2; h, i Y = $CONH_2$, $R^2 = R^3 = H$, h $R^1 = CONHC_6H_4Cl$-*p*, i R^1 = CN; j Y = CONHMe, $R^1 = NO_2$, $R^2 = R^3 = H$; k Y = COOEt, $R^1 = CONH_2$, R^2 = SH, R^3 = H; *l*, m Y = CONHMe, R^2 = H, R^3 = COMe, l $R^1 = CONH_2$, m $R^1 = NO_2$; n-p Y = COOEt, $R^2 = R^3 = H$, n R^1 = COOH, o R^1 = NHCOOMe, p R^1 = NHCOOEt.

II a-e X = CN, R^2 = H, a $R^1 = CONH_2$, b R^1 = CONHMe, c $R^1 = CONHC_6H_4Me$-*m*, d R^1 = COOEt, e $R^1 = NO_2$; f X = $CONHC_6H_3(NO_2)_2$-*o,p*, $R^1 = CONH_2$, R^2 = H; g X = CN, $R^1 = CONH_2$, R^2 = SH; h, i X = $CONH_2$, R^2 = H, h R^1 = CONHMe, i $R^1 = CONHC_6H_4Me$-*m*; j X = $R^1 = CONH_2$, R^2 = SH; k-m X = CN, R^2 = H, k R^1 = COOH, *l* R^1 = NHCOOMe, m R = NHCOOEt

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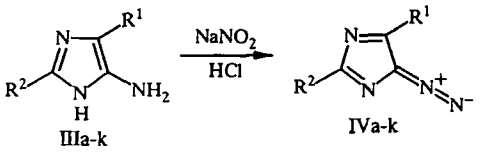
In order to carry out this undertaking the known substituted 5-diazoimidazoles (IVa-m) were synthesized from the aminoimidazoles (IIIa-i) by the procedure described previously [6-12] (Scheme 1). In addition, the new compounds 5-diazo-4-N-(p-chlorophenyl)carboxamide (IVj) and 4-N-(m-tolyl)-carboxamide (IVk) were obtained by the diazotization of the previously unknown corresponding amino derivatives (IIIj, k), which are reduction products of 5-nitroimidazole-4-arylcarboxamides (Va, b) with stannous chloride.

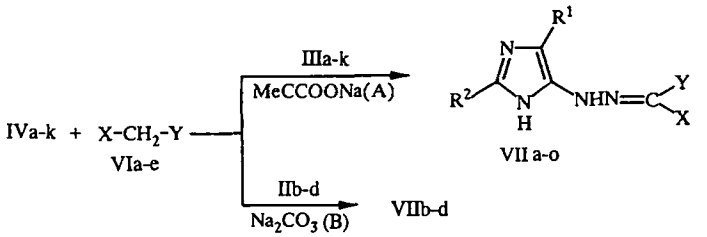
Scheme 1



IIIa-d, IVa-d $R^1 = CONH_2$, a $R^2 = H$, b $R^2 = SH$, c $R^2 = SMe$, d $R^2 = SCH_2COOH$; IIIe-k, IV e-k $R^2 = H$, e $R^1 = CONHMe$, f $R^1 = CN$, g $R^1 = NO_2$, h $R^1 = COOEt$, i $R^1 = CON_3$, j $R^1 = CONHC_6H_4Cl$-*p*, k $R^1 = CONHC_6H_4Me$-*m*

The azo coupling reaction of compounds (IVa-k) with derivatives of cyanoacetic and malonic acid (VIa-e) was carried out by us in the presence of sodium acetate under conditions described previously (method A) [3]. When sulfur-containing substituents were present in position 2 of the initial diazoimidazoles [compounds (IVb-d)], the yields of the corresponding hydrazones (VIIb-d) were significantly less than the analogous products from other diazo derivatives (IV). The yields were successfully increased on using sodium carbonate (method B) in the reaction in place of sodium acetate (Scheme 2).

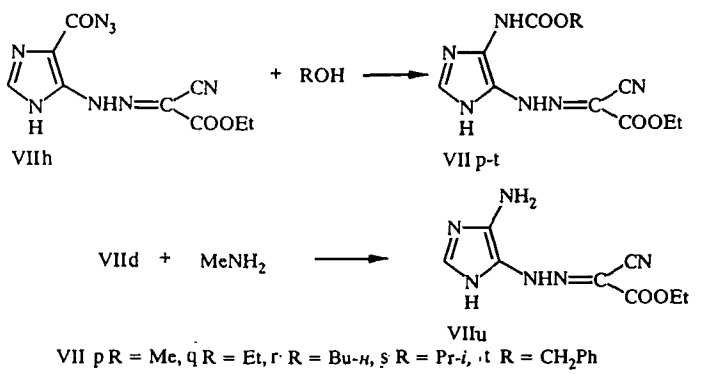
Scheme 2



VIa VII a-j: X = CN, Y = COOEt, a-d $R^1 = CONH_2$, a $R^2 = H$, b $R^2 = SH$, c $R^2 = SMe$, d $R^2 = SCH_2COOH$, e-j $R^2 = H$, e $R^1 = CONHMe$, f $R^1 = NO_2$, g $R^1 = COOEt$, h $R^1 = CON_3$, i $R^1 = CONHC_6H_4Me$-*m*, j $R^1 = CONHC_6H_4Cl$-*p*; VIb, VIIk, *l* X = CN, Y = CONHMe, $R^2 = H$, k $R^1 = CONH_2$, *l* $R^1 = NO_2$; VIc, VIIm X = CN, Y = CONH-pyridyl-2, $R^1 = CONH_2$, $R^2 = H$, VId, VIIn X = $CONHC_6H_3(NO_2)_2$-*o*,*m*, Y = COOEt, $R^1 = CONH_2$, $R^2 = H$; VIe, VIIo X = CN, Y = $CONH_2$, $R^1 = CN$, $R^2 = H$

The synthesis of imidazolylurethanes (VIIo-t) and 4-aminoimidazolylhydrazone (VIIu) was undertaken in order to clarify the effect of electron-donating substituents in the imidazole ring on the cyclization of imidazolylhydrazones (VII) (Scheme 3).

Scheme 3



VII p R = Me, q R = Et, r R = Bu-*n*, s R = Pr-*i*, t R = CH_2Ph

TABLE 1. Spectral Characteristics of the Compounds Synthesized

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm, coupling constant J, Hz
	C=O	NH	CN	
Ia	1660, 1720	3380, 3450		9.00 (1H, s, 6-H); 7.90 (2H, br. s, $CONH_2$); 6.35 (2H, s, NH_2); 4.50 (2H, q, J = 8.02, CH_2); 1.52 (3H, t, J = 8.02 CH_3)
Ib	1650, 1720	3350		8.90 (1H, s, 6-H); 6.80 (2H, s, NH_2); 4.35 (2H, q, J = 8.05, CH_2); 1.52 (3H, t, J = 8.05, CH_3); 3.89 (3H, d, $NHCH_3$)
Ic	1650, 1725	3285, 3320		9.85 (1H, br. s, CONH); 8.75 (1H, s, 6-H); 7.59-8.03 (4H, m, C_6H_4); 6.50 (2H, br. s, NH_2); 4.10 (2H, q, J = 8.16, CH_2); 2.05 (3H, s, CH_3); 1.54 (3H, t, J = 8.16, CH_3)
Id	1725	3270, 3345 †		8.87 (1H, s, 6-H) 6.8 (2H, br. s, NH_2); 4.15 (4H, q, J = 8.07, $2CH_2$); 1.52 (6H, t, J = 8.07, $2CH_3$)
Ie	1720, 1740	3300		9.0 (1H, s, 6-H); 6.35 (2H, s, NH_2); 4.5 (4H, 2q, J = 8.05, CH_2); 1.52 (6H, t, J = 8.05, CH_3)
If	1650, 1660	3250, 3380		8.78 (1H, s, 6-H); 7.90 (2H, br. s, $CONH_2$); 6.35 (2H, s, NH_2); 2.89 (3H, d, $NHCH_3$)
Ig	1650, 1660, 1720	3245, 3450		10.35 (1H, br. s, CONH); 8.87 (1H, s, 6-H); 7.60 (2H, br. s, $CONH_2$); 7.10-8.50 (4H, m, C_5H_4N); 6.45 (2H, s, NH_2)
Ih	1650, 1660	3400		8.85 (1H, s, 6-H); 8.50 (2H, br. s, $CONH_2$); 7.30-8.20 (4H, m, C_6H_4); 6.32 (2H, s, NH_2)
Ii	1650	3260	2210	8.70 (1H, s, 6-H); 8.50 (2H, br. s, $CONH_2$); 6.40 (2H, s, NH_2)
Ij	1660	3250, 3360†		9.85 (1H, br. s, CONH); 9.00 (1H, s, 6-H); 6.70 (2H, s, NH_2); 2.87 (3H, d, $NHCH_3$)
Ik	1650, 1720	3300, 3400		8.50 (2H, br. s, $CONH_2$); 6.40 (2H, s, NH_2); 4.50 (2H, q, J = 8.3, CH_2); 1.59 (3H, t, J = 8.3, CH_3); 1.46 (1H, s, SH)
Il	1650, 1660, 1720	3300, 3430		9.80 (1H, br. s, CONH); 8.75 (1H, s, 6-H); 8.50 (2H, br. s, $CONH_2$); 7.90 (1H, s, NHCO); 2.87 (3H, d, $NHCH_3$); 1.91 (3H, s, $COCH_3$)
Im	1660, 1710	3320 †		9.80 (1H, br. s, CONH); 8.79 (1H, s, 6-H); 7.90 (1H, s, NH); 2.78 (3H, d, $NHCH_3$); 1.97 (3H, s, $COCH_3$)
In	1720, 1730	3370		10.50 (1H, s, COOH); 8.70 (1H, s, 6-H); 8.50 (2H, br. s, NH_2); 4.4 (2H, q, J = 7.8, CH_2); 1.33 (3H, t, J = 7.8, CH_3)
Io	1710, 1720	3340		9.25 (1H, s, NH); 8.79 (1H, s, 6-H); 6.65 (2H, br. s, NH_2); 4.45 (2H, q, J = 8.2, CH_2); 3.30 (3H, s, OCH_3); 1.33 (3H, t, J = 8.2, CH_3)

TABLE 1 (continued)

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm, coupling constant J, Hz
	C=O	NH	CN	
I p	1720, 1730	3285, 3400		9.37 (1H, s, NH); 8.83 (1H, s, 6-H); 6.87 (2H, br. s, NH_2); 4.54 (2H, q, J = 8.2, CH_2); 4.23 (2H, q, J = 8.4, CH_2); 1.57 (3H, t, J = 8.2, CH_3); 1.24 (3H, s, CH_3)
II a	1650	3360	2230	8.80 (1H, s, 6-H); 7.85 (2H, br. s, $CONH_2$)
II b	1640, 1700	3290	2230	9.40 (1H, s, NH); 8.70 (1H, s, 6-H); 2.87 (3H, d, $NHCH_3$)
II c	1650, 1710	3280, 3360	2220	9.80 (1H, br. s, CONH); 8.70 (1H, s, 6-H); 7.74-8.03 (4H, m, C_6H_4); 2.07 (3H, s, CH_3)
II d	1700, 1720	3320	2220	9.50 (1H, s, NH); 8.90 (1H, s, 6-H); 4.35 (2H, q, J = 7.8, CH_2); 1.50 (3H, t, J = 7.8, CH_3)
II e	1700	3340	2215 †	9.78 (1H, s, NH); 8.90 (1H, s, 6-H)
II f	1650, 1710	3280, 3450		9.80 (1H, br. s, CONH); 8.90 (1H, s, 6-H); 8.50 (2H, br. s, $CONH_2$); 7.20-8.00 (3H, m, C_6H_3)
II g	1650, 1710	3400	2220	9.97 (1H, s, NH); 8.90 (1h, s, 6-H); 7.89 (2H, br. s, $CONH_2$)
II h	1650, 1660	3300, 3420		9.25 (1H, s, NH); 9.15 (1H, br. s, CONH); 8.79 (1H, s, 6-H); 6.65 (2H, br. s, $CONH_2$); 2.76 (3H, d, $NHCH_3$)
II i	1640, 1650	3380, 3460		9.80 (1H, br. s, CONH); 8.70 (1H, s, 6-H); 7.74-8.03 (4H, m, C_6H_4); 7.89 (2H, br. s, $CONH_2$); 2.07 (3H, s, CH_3)
II j	1650, 1655	3340		9.60 (1H, s, NH); 7.89 (2H, br. s, $CONH_2$); 7.45 (2H, br. s, $CONH_2$)
II k	1650, 1720, 1725	3400		10.34 (1H, s, COOH); 9.70 (1H, s, NH); 8.70 (1H, s, 6-H); 6.92 (2H, br. s, $CONH_2$)
II *l*	1700, 1720	3450	2220	9.25 (1H, s, NH); 9.00 (1H, s, NH); 8.94 (1H, s, 6-H); 3.30 (3H, s, OCH_3)
II m	1700, 1725	3290	2225	9.37 (1H, s, NH); 8.83 (1H, s, 6-H); 4.29 (2H, q, J = 8.4, CH_2); 1.28 (3H, s, J = 8.4, CH_3)
VII a	1660, 1720	3330, 3400	2220	9.00 (1H, s, 2-H); 8.50 (2H, br. s, $CONH_2$); 7.90 (1H, s, NH); 4.5 (2H, q, J = 8.0, CH_2); 1.52 (3H, t, J = 8.0, CH_3)
VII b	1650, 1720	3300	2220 ‡	8.50 (2H, br. s, $CONH_2$); 7.76 (1H, s, NH); 4.50 (2H, q, J = 8.0, CH_2); 1.52 (3H, t, J = 8.0, CH_3); 1.41 (1H, s, SH)
VII c	1650, 1720	3300, 3450	2220	8.75 (2H, br. s, $CONH_2$); 7.78 (1H, s, NH); 4.5 (2H, q, J = 8.1, CH_2); 1.52 (3H, s, 2-SCH_3); 1.32 (3H, t, J = 8.1, CH_3)
VII d	1650, 1720, 1730	3270, 3370	2230	10.60 (1H, s, COOH); 8.75 (2H, br. s, $CONH_2$); 7.70 (1H, s, NH); 4.50 (2H, q, J = 8.4, CH_2); 3.87 (2H, s, SCH_2); 1.52 (3H, t, J = 8.4, CH_3)
VII e	1650, 1720	3330, 3400	2220	10.75 (1H, br. s, CONH); 8.90 (1H, s, 2-H); 7.80 (1H, s, NH); 4.35 (2H, q, J = 8.0, CH_2); 2.75 (3H, d, $NHCH_3$); 1.52 (3H, t, J = 8.0, CH_3)
VII f	1720	3265, 3320	2220 †	8.75 (1H, s, 2-H); 8.10 (1H, s, NH); 4.25 (2H, q, J = 8.1, CH_2); 1.35 (3H, t, J = 8.0, $2CH_3$)
VII g	1720, 1725	3330, 3400	2220	9.00 (1H, s, 2-H); 7.90 (1H, s, NH); 4.50 (4H, 2q, J = 8.0, $2CH_2$); 1.52 (6H, 2t, J = 8.0, $2CH_3$)
VII h	1670, 1720	3280, 3370	2220 ••	8.70 (1H, s, 2-H); 7.90 (1H, s, NH); 4.30 (2H, q, J = 8.1, CH_2); 1.52 (3H, t, J = 8.1, CH_3)

TABLE 1 (continued)

Compound	IR spectrum, ν, cm^{-1}			PMR spectrum, δ, ppm, coupling constant J, Hz
	C=O	NH	CN	
VII i	1650, 1670, 1730	3270, 3460	2220	9.80 (1H, br. s, CONH); 8.70 (1H, s, 2-H); 7.59-8.03 (4H, m, C_6H_4); 4.10 (2H, q, J = 8.0, CH_2); 2.07 (3H, s, CH_3); 1.35 (3H, t, J = 8.0, CH_3)
VII j	1730	3300	2220, 2230	9.00 (1H, s, 2-H); 7.90 (1H, s, NH); 6.87-7.67 (4H, m, C_6H_4); 4.08 (2H, q, J = 8.1, CH_2); 1.40 (3H, t, J = 8.1, CH_3)
VII k	1650, 1660	3290, 3450	2210	9.80 (1H, br. s, CONH); 8.75 (1H, s, 2-H); 7.60 (2H, br. s, $CONH_2$); 2.70 (3H, d, $NHCH_3$)
VII l	1670	3280, 3350	2215†	9.80 (1H, br. s, CONH); 9.00 (1H, s, 2-H); 7.90 (1H, s, NH); 2.87 (3H, d, $NHCH_3$)
VIIm	1650, 1660	3290, 3350	2215	10.35 (1H, br. s, CONH); 8.80 (1H, s, 2-H); 7.60 (2H, br. s, $CONH_2$); 7.10-8.50 (4H, m, C_5H_4N)
VII n	1660, 1720	3285, 3450*		9.80 (1H, br. s, CONH); 8.90 (1H, s, 2-H); 8.50 (2H, br. s, $CONH_2$); 7.20-8.00 (3H, m, C_6H_3); 4.30 (2H, q, J = 8.1, CH_2); 1.57 (3H, t, J = 8.1, CH_3)
VII o	1650	3260, 3350	2220, 2230	8.70 (1H, s, 2-H); 8.50 (2H, br. s, $CONH_2$)
VII p	1720, 1725	3270, 3450	2215	9.40 (1H, s, NH); 8.79 (1H, s, 2-H); 7.76 (1H, s, NH); 4.30 (2H, q, J = 8.0, CH_2); 3.34 (3H, s, OCH_3); 1.57 (3H, t, J = 8.0, CH_3)
VII q	1720, 1730	3285, 3380	2220	9.75 (1H, s, NH); 8.90 (1H, s, 2-H); 7.60 (1H, s, NH); 4.50 (2H, q, J = 8.15, CH_2); 4.25 (2H, q, J = 8.0, OCH_2); 1.57 (3H, t, J = 8.15, CH_3); 1.28 (3H, t, J = 8.0, CH_3)
VII r	1670, 1725	3330	2215	12.35 (1H, br. s, NH); 9.27 (1H, s, 2-H); 7.33 (1H, s, NH); 4.40 (2H, q, J = 8.2, CH_2); 4.13 (2H, t, OCH_2); 1.47 (3H, t, J = 8.2, CH_3); 1.30-1.90 [4H, m, $(CH_2)_2$]; 0.92 (3H, br. t, CH_3)
VII s	1690, 1720	3270, 3370	2220	10.25 (1H, br. s, NH); 9.05 (1H, s, 2-H); 8.20 (1H, s, NH); 4.91 (1H, sept, CH); 4.40 (2H, q, J = 7.8, CH_2); 1.50 (3H, t, J = 7.8, CH_3); 1.25 (6H, d, CH_3)
VII t	1680, 1720	3270, 3370	2220	9.40 (1H, s, NH); 8.76 (1H, s, 2-H); 7.50-7.80 (5H, m, C_6H_5); 4.27 (2H, q, J = 8.1, CH_2); 3.90 (2H, s, CH_2); 1.67 (3H, t, J = 8.0, CH_3)
VII u	1720	3380, 3450	2220	9,55 (1H, s, NH); 8,70 (1H, s, 2-H); 5,50 (2H, br. s, NH_2); 4,15 (2H, q, J = 8,0, CH_2); 1,56 (3H, t, J = 8,0, CH_3)

*The chemical shifts of the signal for the NH group proton in compounds (Ib, f, h), (IIa-c, f, g, i, m), and (VIIa, g, i, k-u) were not determined due to marked broadening. Compounds (IIg, j) were in the thione form since the SH group signal was absent from the spectrum.

†Vibrational bands for the NO_2 group were observed in the spectra at 1340, 1540 (Ih); 1380, 1580 (Ij); 1380, 1580 (Im); 1360, 1540 (IIe); 1375, 1570 (VIIIh); 1340, 1350, 1570, 1580 (VIIIm) cm^{-1}.

‡There was also a vibrational band for the SH group at 2540 (w) cm^{-1} in the spectrum.

**The spectrum also contained a vibrational band for the N_3 group at 2155 cm^{-1}.

TABLE 2. Characteristics of the Compounds Synthesized

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	R_f, eluent	Yield, %
		C	H	N	S(Cl)			
1	2	3	4	5	6	7	8	9
Ia	$C_9H_{10}N_6O_3$	43.5 43,2	3.9 4,0	33.85 33,6		280	0,46 a	85
Ib	$C_{10}H_{12}N_6O_3$	45.7 45,45	4.65 4,55	32.1 31,8		306	0,45 c	75
Ic	$C_{16}H_{16}N_6O_3$	56.8 56,5	4.85 4,7	24.9 24,7		268	0,56 a	70
Id	$C_8H_8N_6O_4$	38.5 38,1	3.0 3,2	33.6 33,3		240	0,65 a	82
Ie	$C_{11}H_{13}N_5O_4$	47.6 47,3	4.6 4,7	25.4 25,1		276	0,78 a	80
If	$C_8H_9N_7O_2$	43.6 43,5	3.6 3,6	35.7 35,5		261	0,39 a	80
Ig	$C_{12}H_{10}N_8O_2$	55.35 55,2	4.2 4,3	25.9 25,8		295	0,63 a	80...86
Ih	$C_{13}H_{10}ClN_7O_2$	47.35 47,05	3.3 3,0	29.75 29,55	(10.85) (10,7)	283	0,45 a	65
Ii	$C_7H_5N_7O$	41.8 41,4	2.5 2,5	48.4 48,3		290	0,66 b	67
Ij	$C_7H_7N_7O_3$	36.0 35,5	3.05 2,95	41.3 41,35		269	0,44 a	78
Ik	$C_9H_{10}N_6O_3S$	38.7 38,3	3.7 3,55	30.0 29,8		188	0,43 b	36
Il	$C_{10}H_{11}N_7O_3$	43.8 43,4	3.6 4,0	35.5 35,7		273	0,65 a	86
Im	$C_9H_9N_7O_4$	38.9 38,7	3.5 3,2	35.5 35,7		230	0,46 a	85
In	$C_9H_9N_5O_4$	43.0 43,2	3.6 3,4	27.9 28,2		176	0,43 b	45
Io	$C_{10}H_{12}N_6O_4$	43.5 42,9	4.1 4,3	30.5 30,0		187	0,65 a	50
Ip	$C_{11}H_{14}N_6O_4$	45.05 44,9	4.45 4,8	28.9 28,7		174	0,63 a	48
IIa	$C_7H_4N_6O_2$	43.2 43,0	3.4 3,6	28.0 27,9		302	0,34 c	65
IIb	$C_8H_6N_6O_2$	44.5 44,0	2.9 2,7	39.0 38,5		272	0,28 c	60
IIc	$C_{14}H_{10}N_6O_2$	56.8 57,1	3.6 3,4	29.0 28,6		283	0,47 c	54
IId	$C_9H_7N_5O_3$	46.9 46,3	3.0 3,0	30.3 30,0		260	0,35 c	68
IIe	$C_6H_2N_6O_3$	34.7 34,95	0.9 1,0	40.5 40,8		238	0,6 a	70
IIf	$C_{13}H_8N_8O_7$	40.2 40,2	2.2 2,1	30.1 29,8		> 300	0,47 a	53
IIg	$C_7H_4N_6O_2S$	36.0 35,6	1.95 1,7	35.2 35,6	13.55 14,0	189	0,45 b	35
IIh	$C_8H_8N_6O_3$	40.9 40,7	3.45 3,4	35.85 35,6		276	0,48 a	80
IIi	$C_{14}H_{12}N_6O_3$	54.05 53,85	4.1 3,85	27.2 26,9		287	0,35 c	83

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9
II j	$C_7H_6N_6O_3S$	33,5 33,1	2,7 2,4	33,4 33,1	12,65 12,6	290	0,45 b	50
II k	$C_7H_3N_5O_3$	40,65 41,0	1,65 1,5	34,4 34,15		208	0,37 b	45
II *l*	$C_8H_6N_6O_3$	41,2 41,0	2,5 2,6	36,05 35,9		186	0,54 b	45
II m	$C_9H_8N_6O_3$	44,0 43,5	3,2 3,3	34,0 33,9		189	0,52 b	40
VII a	$C_9H_{10}N_6O_3$	43,5 43,2	4,0 4,0	33,85 33,6		245	0,34 a	85...90
VII b	$C_9H_{10}N_6O_3S$	38,7 38,3	3,7 3,55	29,9 29,8	11,4 11,4	179	0,56 c	65
VII c	$C_{10}H_{12}N_6O_3S$	41,0 40,5	4,0 4,05	25,0 24,8	11,45 11,4	172	0,45 c	40
VII d	$C_{11}H_{12}N_6O_5S$	39,3 38,8	3,5 3,5	25,0 24,7	23,6 23,5	159	0,75 c	35
VII e	$C_{10}H_{12}N_6O_3$	45,6 45,45	4,6 4,55	32,0 31,8		278	0,58 c	85...90
VII f	$C_8H_8N_6O_4$	38,1 38,7	3,2 3,45	33,3 33,65		267	0,54 c	83
VII g	$C_{11}H_{13}N_5O_4$	47,5 47,3	4,66 4,7	32,0 31,8		240	0,56 a	85...90
VII h	$C_9H_8N_8O_3$	39,6 39,1	3,1 2,9	42,74 4 2,4		148	0,39 a	65
VII i	$C_{16}H_{16}N_6O_3$	56,85 56,5	4,85 4,7	24,8 24,7		238	0,4 a	63...67
VII j	$C_{15}H_{13}N_6O_3Cl$	50,45 49,9	3,4 3,6	23,8 23,3	(10,1) (9,8)	248	0,45 c	86
VII k	$C_8H_9N_7O_2$	40,95 40,85	4,1 3,9	42,1 41,7		234	0,34 a	80...85
VII *l*	$C_7H_7N_7O_3$	35,7 35,4	3,0 2,9	41,5 41,35		254	0,43 a	84...87
VII m	$C_{12}H_{10}N_8O_2$	55,2 55,2	4,4 4,3	25,9 25,8		217	0,27 c	76
VII n	$C_{15}H_{14}N_8O_8$	41,8 41,5	3,5 3,2	26,0 25,8		213	0,54 a	56
VII o	$C_7H_5N_7O$	41,45 41,4	2,5 2,5	48,35 48,3		192	0,37 c	88
VII p	$C_{10}H_{12}N_6O_4$	42,8 42,8	4,2 4,3	30,55 30,0		256	0,65 a	75
VII q	$C_{11}H_{14}N_6O_4$	45,2 44,9	4,8 4,8	28,7 28,6		240	0,34 a	68
VII r	$C_{13}H_{18}N_6O_4$	48,6 48,4	5,6 5,6	26,5 26,1		174	0,54 c	56
VII s	$C_{12}H_{16}N_6O_4$	46,8 46,75	2,05 1,95	27,5 27,3		168	0,72 c	50
VII t	$C_{16}H_{16}N_6O_4$	54,0 53,8	4,5 4,5	23,9 23,6		189	0,57 c	48
VII u	$C_8H_{10}N_6O_2$	43,7 43,2	4,5 4,5	37,9 37,8		110 (decomp)	0,43 a	30

The first were obtained by boiling compound (VIIh) in methyl, ethyl, butyl, isopropyl, or benzyl alcohols. Heating butylurethane (VIId) with methylamine gave ethyl 4-amino-5-imidazolylhydrazonocyanoacetate (VIIu) and not the corresponding ureido derivative. The imidazolylhydrazones (VIIa-u) were identified with the aid of IR spectra and PMR data (Table 1).

The desired derivatives of 4-aminoimidazo[5,1-*c*][1,2,4]triazine (Ia-c, e-h, k) were obtained on carrying out the cyclization of hydrazones (VIIa, b, e, g, i-k, m) under the conditions for obtaining imidazotriazine (Ia) in [2], and particularly in a mixture (1:1) of acetic acid and ethanol or in butanol. Unlike the initial hydrazones, the band for the stretching vibrations of the nitrile group was absent from the IR spectra of these compounds and bands characteristic of an amino group were observed (Table 1). The acetamidoimidazotriazines (*II*, m) were obtained from imidazolylhydrazones (VIIk, *l*) in acetic anhydride.

Imidazotriazinones (IIa-f) were obtained from compounds (VIIa, b, e-g, i) in 1% alcoholic KOH as in the synthesis of compound (IIa) [3]. In the cyclization of hydrazones (VIIb, e, i) it was found that more prolonged heating under these conditions leads to saponification of the nitrile group and the isolation of 3-carbamoylimidazotriazinones (IIj, h, i) respectively. In the case of hydrazone (VIIn), which contains an ethoxycarbonyl and N-(2,4-dinitrophenyl) amide groupings,

cyclization under base catalyzed conditions gave 3-N-(2,4-dinitrophenyl)carboxamidoimidazotriazin-4-one (IIf) and not the 3-carbethoxyimidazotriazinone (IIa). No cyclization of compound (VIIn) was observed under acid catalyzed conditions. Boiling compound (VIIh) in concentrated acetic acid and in 1% alkaline solution leads to the formation of products (In) and (IIk) respectively, the carboxazide grouping being hydrolyzed to carboxyl in both cases. The structures of the synthesized imidazotriazinones (I) and (II) were confirmed by IR spectra and by PMR (Table 1).

The presence of electron-withdrawing substituents at position 4 of the imidazole ring proved to have no significant effect on the cyclization of hydrazones to imidazotriazines (I) and (II). Some reduction in yield (to 65%) was noted only for arylamides (VIIi, j). In the case of compounds (VIIf, *l*), containing a nitro group in the imidazole ring, no formation of N-acetyl derivatives was observed even under forcing conditions (boiling for 6 h in concentrated acetic acid). Compound (Im) was not obtained on heating hydrazone (VII*l*) in acetic anhydride. On the other hand, hydrazone (VIIo) containing a nitrile group in the imidazole ring was converted into 4-aminoimidazotriazine (Ii) by just stirring in alcohol at room temperature for 20-30 min.

Unlike electron-withdrawing substituents at positions 2 and 4 of the imidazole ring, electron-donating groups proved to have a significant effect on the conversion of hydrazones (VII) into imidazotriazines. The cyclization of compound (VIIb) to triazines (Ik) and (IIf) proceeds in 50% yield under all the conditions studied but we failed to convert hydrazones (VIIc-d) containing a methylthio and a carboxymethylthio group into the corresponding imidazotriazines (I) and (II).

Hydrazones (VIIp, q) were cyclized with the formation of imidazotriazines (Io, p) and (II*l*, m) in acetic acid and alcoholic KOH, respectively, although it was far more difficult than when electron-withdrawing substituents were present in position 4 of the imidazole ring (yields did not exceed 35-40%). It should be noted that the corresponding imidazotriazines (I) and (II) were generally not obtained from butyl-, isopropyl-, and benzylurethanes (VIIr-t) or from the amino derivative (VIIu) under the same conditions. The use of more intense forcing cyclizations [heating imidazolylhydrazones (VIIr-u) in concentrated sulfuric acid or with a concentrated alkaline solution] were not crowned with success due to the profound destruction of the compounds mentioned.

It may be concluded from the results obtained that electron-withdrawing substituents at position 4 of the imidazole ring proved to have no significant effect on the cyclization of imidazolylhydrazones (VIIb, e-o) into imidazotriazines and imidazotriazinones. On the other hand, electron-donating substituents at positions 2 and 4 of the ring hindered, and in certain cases completely prevented, the formation of bicyclic products.

EXPERIMENTAL

The IR spectra were described on a Specord IR 75 instrument in KBr disks. The PMR spectra were obtained on a Bruker WP 80 (80 MHz) instrument, solvent was DMSO-D_6, internal standard was TMS. A check on the progress of reactions and the purity of the substances obtained was effected by TLC on Sorbfil UF 254 plates, eluents were 3:1 chloroform–ethanol a), ethyl acetate (b), and 2:1 chloroform–ethanol (c). Diazoimidazolecarboxamide (IVa) was synthesized by the procedure in [7], the 2-thio derivatives of diazoimidazolecarboxamide (IVb-d) as described in the patent [8], and diazoimidazoles (IIIe-k) according to known procedures [9-13].

Characteristics for the compounds synthesized are given in Table 2; the IR spectra and PMR data are given in Table 1.

5-Nitro-4-imidazole-N-(p-chlorophenyl)carboxamide (Va). Phosphorus pentachloride (3.32 g, 0.016 mole) was added to a solution of 5-nitro-4-imidazolecarboxylic acid (5 g, 3.2 mmole) in dry benzene (50 ml). The obtained mixture was boiled for 1 h in a water bath, cooled to room temperature, and p-chloroaniline (4.47 g, 0.035 mole) was added to it. The mixture was boiled for 2.5 h, cooled, the solid filtered off, dried, and recrystallized twice from 60% alcohol. Yield was 65%, mp 288°C. IR Spectrum: 1650 (C=O), 1360, 1540 cm^{-1} (NO_2). PMR Spectrum: 9.4 (1H, s, NH); 8.75 (1H, s, 2-H); 7.2-7.4 ppm (4H, d.d, C_6H_4). Found, %: C 45.3; H 2.8; N 21.4; Cl 13.6. $C_{10}H_7N_4O_3Cl$. Calculated, %: C 45.0; H 2.6; N 21.0; Cl 13.3.

5-Nitro-4-imidazole-N-(m-tolyl)carboxamide (Vb) was obtained analogously to compound (Va) from 5-nitro-4-imidazolecarboxylic acid and m-toluidine. Yield was 65%, mp 240°C (from alcohol). IR Spectrum: 1660 (C=O), 1360, 1540 (NO_2) cm^{-1}. PMR Spectrum: 9.43 (1H, s, NH); 8.95 (1H, s, 2-H); 7.2-7.4 (4H, m, C_6H_4); 2.05 ppm (3H, s, CH_3). Found, %: C 53.5; H 4.2; N 23.0. $C_{11}H_{10}N_4O_3$. Calculated, %: C 53.7; H 4.1; N 22.8.

5-Amino-4-imidazole-N-(p-chlorophenyl)carboxamide Hydrochloride (IIIj·HCl). Compound (Va) (5 g, 0.018 mole) was added in portions during 5 h to a solution of $SnCl_2 \cdot 2H_2O$ (21.17 g, 0.094 mole) in concentrated hydrochloric acid (100 ml) at 0-5°C. The mixture was stored at room temperature for 12 h. The precipitate was then filtered off, dissolved in water (200 ml), and hydrogen sulfide passed into the solution until complete precipitation of tin sulfide. The solid was filtered off and the filtrate evaporated to dryness in vacuum. The solid product (IIIj·HCl) was crystallized from alcohol. Yield was 50%, mp 296°C. IR Spectrum: 1650 (C=O), 3270, 3330 cm^{-1} (NH, NH_2). PMR Spectrum: 9.4 (1H, s, NH); 8.75 (1H, s, 2-H); 7.26-7.45 (4H, d.d, C_6H_4); 6.5 ppm (2H, br. s, NH_2). Found, %: C 44.2; H 3.8; N 20.75; Cl 25.8. $C_{10}H_9N_4OCl \cdot HCl$. Calculated, %: C 44.0; H 3.7; N 20.5; Cl 26.0.

5-Amino-4-imidazole-N-(m-tolyl)carboxamide hydrochloride (IIIk·HCl) was obtained from compound (Vb) analogously to compound (IIIj·HCl). Yield was 50%, mp 276°C. IR Spectrum: 1660 (C=O), 3270, 3350 cm^{-1} (NH, NH_2). PMR Spectrum: 9.4 (1H, s, NH); 8.95 (1H, s, 2-H); 7.26-7.45 (4H, m, C_6H_4); 6.68 ppm (2H, br. s, NH_2). Found, %: C 52.6; H 5.35; N 22.4. $C_{11}H_{12}N_4O \cdot HCl$. Calculated, %: C 52.3; H 5.15; N 22.2.

5-Diazo-4-imidazole-N-(p-chlorophenyl)carboxamide (IVj). A solution of compound (IIIj·HCl) (2.2 g, 0.011 mole) in 1 N HCl (20 ml) was added in portions during 1.5 h to a cooled (0-2°C) solution of $NaNO_2$ (0.73 g, 0.011 mole) in water (25 ml). The precipitated solid diazoimidazole (IVj) was filtered off, the filtrate was extracted with chloroform (3 × 30 ml), and evaporated in vacuum, to give a further quantity of compound (IVj). Yield was 70%, mp 103°C (decomposing explosively). IR Spectrum: 1650 (C=O), 2160 cm^{-1} (N_2). Found, %: C 48.7; H 2.5; N 28.7; Cl 14.7. $C_{10}H_6N_5OCl$. Calculated, %: C 48.5; H 2.4; N 28.3; Cl 14.3.

5-Diazo-4-imidazole-N-(m-tolyl)carboxamide (IVk). Product (IVk) was obtained from compound (IIIk·HCl) analogously to compound (IVj). Yield was 67%, mp 117°C (decomposing explosively). IR Spectrum: 1660 (C=O), 2170 cm^{-1} (N_2). Found, %: C 58.5; H 4.0; N 30.7. $C_{11}H_9N_5O$. Calculated, %: C 58.15; H 4.0; N 30.8.

Substituted 2-(5-Imidazolylhydrazono)cyanoacetic Acid Ethyl Esters (VIIa-j). Substituted Amides of 2-(5-Imidazolylhydrazono)cyanoacetic Acids (VIIk-m, o). 2-(5-Imidazolylhydrazono)malonic Acid Ethyl Ester (VIIn). A. The cyanoacetic or malonic acid derivative (VIa-e) (7.5 mmole) and sodium acetate (3 mmole) were added with stirring during 30 min to a solution of 5-diazoimidazole (IVa-k) (5 mmole) in acetone (75 ml). The mixture was stirred at room temperature for 1.5 h, the solid product (VIIa-o) was filtered off, washed with alcohol (10 ml), and crystallized from ethanol. The obtained known ethyl ester of 2-(4-carboxamido-5-imidazolylhydrazono)cyanoacetic acid (VIIa) was identical (mp, IR spectrum, PMR data) with a sample synthesized by the procedure of [3, 4].

B. Cyanoacetic ester (VIa) (4.2 mmole) was added to a solution of 5-diazoimidazole (IVb-d) (3.5 mmole) in acetone (35 ml) and sodium carbonate was then added to pH 6.5-7.0. The reaction mixture was stirred for 2 h, the solid product (VIIb-d) was filtered off, and crystallized from 60% aqueous alcohol.

2-(4-Methoxycarbonylamino-5-imidazolylhydrazono)cyanoacetic Acid Ethyl Ester (VIIp). A solution of hydrazone (VIIh) (0.7 g, 2.5 mmole) in methanol (20 ml) was boiled for 1.5 h and cooled. The solid was filtered off and crystallized from 50% aqueous alcohol. Urethanes (VIIq-t) were obtained analogously from hydrazone (VIIh) and ethyl, butyl, isopropyl, and benzyl alcohols respectively.

2-(4-Amino-5-imidazolylhydrazono)cyanoacetic Acid Ethyl Ester (VIIu). A solution of hydrazone (VIIr) (5 g, 0.023 mole) in 30% aqueous methylamine (35 ml) was stirred for 2 h at 30-35°C. The reaction mixture was then cooled to 0-2°C. The precipitated solid was filtered off, dried, crystallized from alcohol, and stored in a cool, dark place.

4-Aminoimidazo[5,1-*c*][1,2,4]triazines (Ia-c, e-h, k). A. Imidazolylhydrazone (VIIa, b, e-g, i-k, m) (1.2 mmole) was added to a 50% solution (10 ml) of acetic acid in ethanol. The mixture was boiled for 40 min, cooled, the solid was filtered off, dried, and crystallized from 70% aqueous alcohol. The obtained known 4-amino-3-carbethoxyimidazo[5,1-*c*][1,2,4]triazine (Ia) was identical (mp, IR spectrum, PMR data) with a sample synthesized by the procedure in [3].

B. Imidazolylhydrazone (VIIa, b, e, g, i-k, m) (1.2 mmole) was added to butanol (25 ml). The reaction mixture was boiled for 0.5 h, half the butanol was distilled off, the remainder was cooled, the precipitated solid was filtered off, washed with alcohol, dried, and recrystallized (see A).

4-Amino-8-nitroimidazo[5,1-*c*][1,2,4]triazines (Id, j). Imidazolylhydrazone (VIIf, *l*) (1.2 mmole) was boiled in concentrated acetic acid (10 ml) for 6 h, the reaction mixture was evaporated to dryness, the solid was triturated with water, filtered off, and recrystallized from alcohol.

4-Amino-3-carbamoyl-8-cyanoimidazo[5,1-*c*][1,2,4]triazine (Ii). Imidazolylhydrazone (VIIo) (0.3 g, 1.6 mmole) in ethanol (10-15 ml) was stirred at room temperature. The solid was filtered off and washed with a small quantity of ether.

4-Acetamido-3-carbethoxyimidazo[5,1-*c*][1,2,4]triazines (*Il*, m). Imidazolylhydrazone (VIIk, *l*) (1.2 mmole) in acetic anhydride (10 ml) was boiled for 1.5 h. The reaction mixture was evaporated to dryness, the solid triturated with water, filtered off, and crystallized from alcohol.

4-Amino-3-carbethoxy-8-carboxyimidazo[5,1-*c*][1,2,4]triazine (In). Imidazolylhydrazone (VIIh) (0.3 g, 1.2 mmole) was added to concentrated acetic acid (15 ml). The mixture was boiled for 1.5 h, then cooled. The precipitated solid was filtered off, washed with ether, and dried.

4-Aminoimidazo[5,1-*c*][1,2,4]triazines (Io, p). A solution of imidazolylhydrazone (VIIIp, q) in concentrated acetic acid (15 ml) was boiled for a week. The solid precipitated after cooling was filtered off, dried, and crystallized from 70% aqueous alcohol.

1,4-Dihydroimidazo[5,1-c][1,2,4]triazin-4-ones (IIa-f). Imidazolylhydrazone (VIIa, b, e, f, h, i) (1.2 mmole) was added to 1% alcoholic KOH solution, the mixture was boiled for 1 h, cooled, 1 N HCl solution was added to pH 6.5, and the mixture boiled for 0.5 h. After cooling the solid was filtered off and crystallized from 60% aqueous ethanol. The synthesized 3-cyano-1,4-dihydroimidazo[5,1-*c*][1,2,4]triazin-4-one (IIa) was identical (mp, IR spectrum, PMR data) with a sample obtained by the procedure of [3].

3-Carboxamido-1,4-dihydroimidazo[5,1-*c*][1,2,4]triazin-4-ones (IIh, i, j). Imidazolylhydrazone (VIIb, i, e) (1.2 mmole) was added to a 1% alcoholic KOH solution and the mixture boiled for 12 h. After cooling the reaction mixture was left for 12 h at room temperature, then treated as above for compounds (IIa-f).

8-Carboxy-3-cyano-1,4-dihydroimidazo[5,1-*c*][1,2,4]triazin-4-one (IIk). Imidazolylhydrazone (VIIh) (0.3 g, 1.2 mmole) was added to a 1% alcoholic NaOH solution, the mixture was boiled for 2 h, and cooled. The reaction mixture was then treated as described for compounds (IIh, i, j). The product was crystallized from 50% aqueous ethanol.

1,4-Dihydroimidazo[5,1-*c*][1,2,4]triazin-4-ones (III*l*, m). Imidazolylhydrazone (VIIp, q) (1.2 mmole) was added to a 1% alcoholic KOH solution, the mixture was boiled for 20 h, cooled, and then treated as described for compounds (IIa-f).

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