REACTIONS OF 3,3,4,4-TETRACYANOPYRROLIDINES WITH ALCOHOLS

O. E. Nasakin, A. N. Lyshchikov, P. M. Lukin, and V. A. Tafeenko

It was established that on treatment with alkali, 2,5-disubstituted 3,3,4,4-tetracyanopyrrolidines react with primary alcohols to form 5-alkoxy-2-(N-arylidenamino)-3,4-dicyanopyrroles. Depending on the ratio of the initial reagents, another reaction route is possible, leading to 6-alkoxy-4-amino-2-R-3-CH_2R-5-cyano-3H-pyrrolo[2,3-d]pyrimidines. The effect of substituents on the reaction pathways is examined.

It was previously shown that reactions between 3,3,4,4-tetracyanopyrrolidines and certain lower primary alcohols in the presence of a twofold excess of alkali give 5-alkoxy-2-(N-arylidenamino)-3,4-dicyanopyrroles [2]. However, further studies of this reaction with the use of 1-propanol and 1-butanol as reagents led to an unexpected result. In a number of cases 6-alkoxy-4-amino-5-cyano-3H-pyrrolo[2,3-d]pyrimidines XI were isolated instead of the expected 5-alkoxypyrroles V. Their structure was established by x-ray diffraction analysis (XDA) of 4-amino-6-propoxy-2-(2-furyl)-3-furfuryl-5-cyano-3H-pyrrolo[2,3-d]pyrimidine (XIc) (Fig. 1).

On the basis of this structure we have proposed the following reaction scheme (shown in Scheme 1). It is likely that the reaction occurs in a similar manner as with lower alcohols, yielding the anion IV after addition of alcohol and rearrangement [2]. It can probably be stabilized not only by cleavage of the substituent with elimination of an aldimine molecule but also by loss of a proton in the presence of excess base in a similar manner to the benzoin condensation [3]. The resulting anion VI, for which tautomeric form VIII is probably more stable because of conjugation with the pyrrole ring, after the addition of a proton undergoes intramolecular cyclization via the secondary nitrogen atom of the side chain on to the adjacent nitrile group, forming a pyrimidine ring. During the reaction anion X is isolated as its potassium derivative, which on acidification either in the reaction

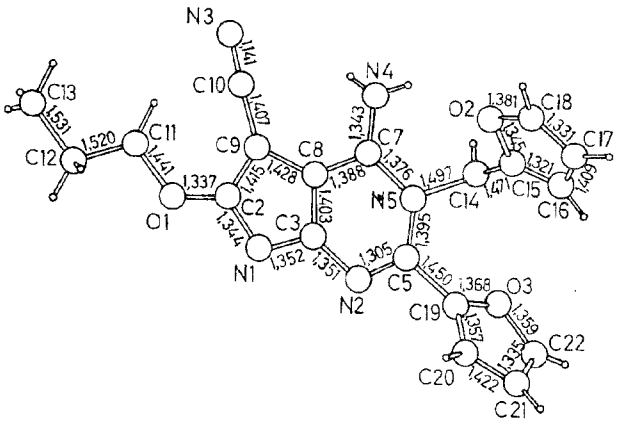
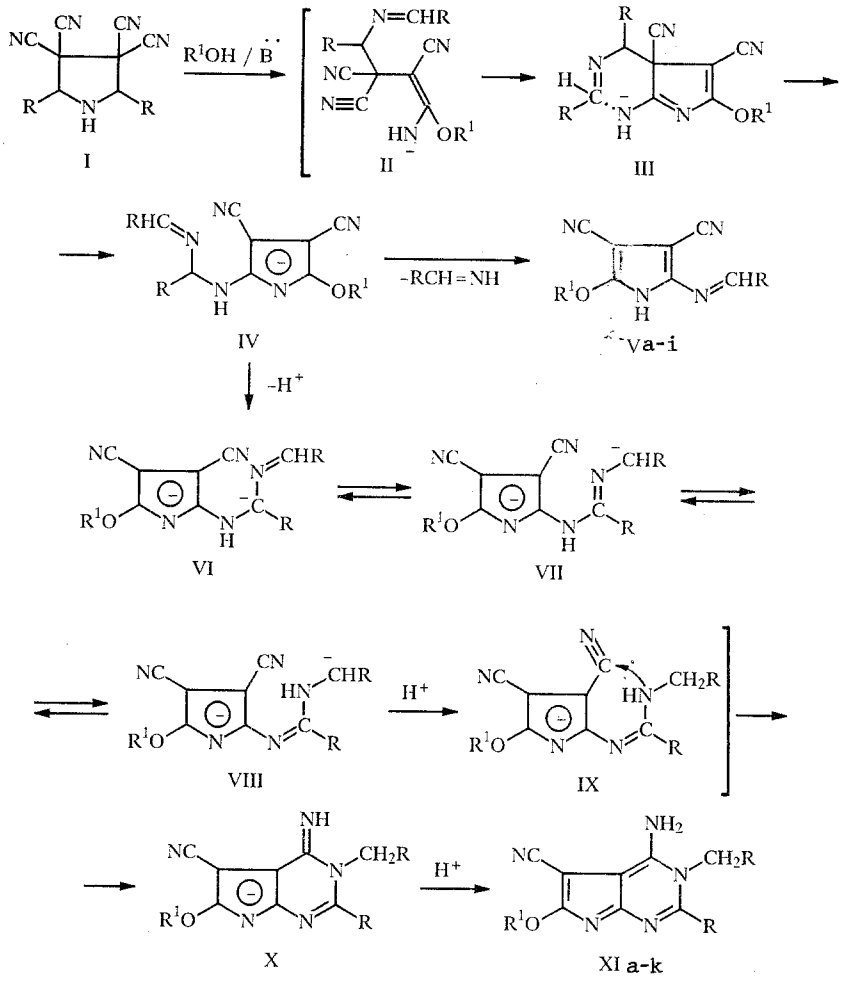


Fig. 1. Molecule of 4-amino-6-propoxy-2-(2-furyl)-3-furfuryl-5-cyano-3H-pyrrolo[2,3-d]pyrimidine (XIc).

Chuvash State University, Cheboksary 428015. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1472-1476, November, 1992. Original article submitted November 4, 1991.

0009-3122/92/2811-1255$12.50

Scheme 1



mixture or after isolation as a suspension in isopropanol is converted to 2,3-disubstituted 6-alkoxy-4-amino-5-cyano-3H-pyrrolo[2,3-d]pyrimidines XIa-k.

These reactions proved very sensitive to changes in the molar ratio of the initial reagents and the nature of the substituent in tetracyanopyrroles I.

In a number of experiments it was shown that a change in molar ratio of the reagents leading to an increase in alkali content results in the formation of pyrrolopyrimidines XI, which corresponds to the scheme put forward by us. In fact, it is likely that an increase in KOH content assists the removal of a proton and the formation of anion VI. At the same time elimination of aldimine to give pyrrole V is suppressed. Thus, in reactions of 2,5-diphenyl-3,3,4,4-tetracyanopyrrolidine with the same ratio of compound I to KOH (1:2), on changing from ethanol to 1-propanol and then 1-butanol the following occurs. When the weight contents of these alcohols is virtually the same, their molar ratio decreases from 1:2:35 (with ethanol) to 1:2:27 (with 1-propanol) and 1:2:22 (with 1-butanol). When the reactions are carried out under the same conditions, only 5-ethoxy-2-(N-benzylidenamino)-3,4-dicyanopyrrole is isolated in the first case [2], with 1-propanol a mixture of pyrrole Va and pyrrolopyrimidine XIf is obtained with a predominance of the latter, while with 1-butanol only compound XIg is obtained. An increase in quantity of the respective alcohols, namely, initial dilution of the reaction mixtures by a factor of 2-4 (Table 1), the equilibrium is fully shifted in favor of alkoxypyrroles Va and Vb. At the same time isolation of the final products becomes somewhat difficult, since their solubility is improved in the higher alcohols. On the other hand, when the alkali content is increased, only compounds XI (Table 2) are formed.

Another factor that governs the reaction route is the substituent effect in pyrrolidines I. In fact, starting from a pyrrolidine with a furyl substituent in various alcohols other than methanol, pyrrolopyrimidines XI were obtained even with a twofold excess of alkali (see Table 2).

TABLE 1. Properties of 5-Alkoxy-2-(N-arylidenamino)-3,4-dicyanopyrroles Va-i

Compound	Empirical formula	R	R^1	mp, °C	Ratio of I:KOH: R^1OH	IR spectrum, cm^{-1}		Yield, %
						ν NH	νC≡N	
Va	$C_{16}H_{14}N_4O$	C_6H_5	n-C_3H_7	211...212 (decomp)	1 : 2 : 53	3220	2230	43
Vb	$C_{17}H_{16}N_4O$	C_6H_5	n-C_4H_9	172...173	1 : 2 : 90	3200, 3125	2245, 2225	38
Vc	$C_{16}H_{13}FN_4O$	4-FC_6H_4	n-C_3H_7	203...204	1 : 2 : 27	3240, 3180	2230	87
Vd	$C_{16}H_{14}N_4O_2$	4-$H_3COC_6H_4$	C_2H_5	216...218	1 : 10 : 34	3190	2240, 2220	69
Ve	$C_{17}H_{16}N_4O_2$	4-$H_3COC_6H_4$	n-C_3H_7	230...232 (decomp)	1 : 10 : 27	3200	2240, 2220	63
Vf	$C_{18}H_{18}N_4O_2$	4-$H_3COC_6H_4$	n-C_4H_9	211...213 (decomp)	1 : 10 : 22	3200	2235, 2220	58
Vg	$C_{15}H_{11}BrN_4O$	4-BrC_6H_4	C_2H_5	250...251 (decomp)	1 : 2 : 51	3210	2245, 2225	76
Vh	$C_{16}H_{14}N_4O$	4-$H_3CC_6H_4$	C_2H_5	236...237 (decomp)	1 : 6 : 34	3200	2240, 2225	53
Vi	$C_{13}H_{10}N_4O_2$	2-Fu	C_2H_5	213...214 (decomp)	1 : 2 : 100	3220, 3170	2245, 2225	60

TABLE 2. Properties of 6-Alkoxy-4-amino-5-cyano-3H-pyrrolo[2,3,-d]pyrimidines XIa-k

Compound	Empirical formula	R	R^1	mp, °C	Ratio of I: KOH: R^1OH	IR spectrum, cm^{-1}			Yield, %
						ν NH	νC≡N	δ NH	
XIa	$C_{17}H_{13}N_5O_3$	2-Fu	CH_3	255...257 (decomp)	1 : 6 : 50	3430	2195	1650	79
XIb	$C_{18}H_{15}N_5O_3$	2-Fu	C_2H_5	208...210 (decomp)	1 : 2 : 34	3435, 3335, 3285	2195	1650	64
XIc	$C_{19}H_{17}N_5O_3$	2-Fu	n-C_3H_7	168...169	1 : 2 : 40	3435, 3335, 3290	2190	1655	73
XId	$C_{20}H_{19}N_5O_3$	2-Fu	n-C_4H_9	151...152	1 : 2 : 22	3415	2190	1640	37
XIe	$C_{22}H_{19}N_5O$	C_6H_5	C_2H_5	232...233 (decomp)	1 : 6 : 34	3430, 3320, 3285	2200	1640	35
XIf	$C_{23}H_{21}N_5O$	C_6H_5	n-C_3H_7	240...241	1 : 6 : 27	3435, 3325, 3290	2211	1650	41
XIg	$C_{24}H_{23}N_5O$	C_6H_5	n-C_4H_9	235...236	1 : 2 : 22	3440, 3330, 3290	2210	1650	59
XIh	$C_{23}H_{19}F_2N_5O$	4-FC_6H_4	n-C_3H_7	233...234	1 : 8 : 35	3430, 3325, 3290	2210	1640	72
XIi	$C_{22}H_{17}Br_2N_5O$	4-BrC_6H_4	C_2H_5	244...245	1 : 6 : 34	3420, 3325, 3285	2210	1635	81
XIj	$C_{25}H_{25}N_5O$	4-$H_3CC_6H_4$	n-C_3H_7	247...248	1 : 6 : 27	3440, 3410, 3310. 3285	2200	1635	49
XIk	$C_{26}H_{27}N_5O$	4-$H_3CC_6H_4$	n-C_4H_9	221...222	1 : 6 : 22	3430, 3315, 3285	2200	1625	47

In a number of aryl-substituted pyrrolidines I, depending on the nature of the substituent in the benzene ring it is necessary to increase the alkali content to a sixfold excess in order to obtain pyrrolopyrimidines XI. With a p-methoxyphenyl substituent, pyrrolopyrimidines XI are not formed even when a tenfold excess of KOH is used (see Table 1).

TABLE 3. Coordinates of Nonhydrogen Atoms in Molecule XIc

Atom	x	y	z	Atom	x	y	z
O(1)	0,3040 (4)	-0,0329 (2)	0,4628 (3)	C(10)	0,3272 (7)	0,1883 (4)	0,4384 (5)
O(2)	0,8589 (4)	0,2644 (3)	0,2415 (3)	C(11)	0,2280 (6)	0,0160 (4)	0,5382 (4)
O(3)	0,6906 (5)	0,1121 (3)	-0,0411 (3)	C(12)	0,1597 (7)	-0,0586 (4)	0,6013 (5)
N(1)	0,4309 (5)	-0,0320 (3)	0,3216 (4)	C(13)	0,0753 (8)	-0,0110 (5)	0,6826 (5)
N(2)	0,5569 (5)	0,0121 (3)	0,1780 (4)	C(14)	0,6712 (6)	0,2500 (4)	0,1057 (4)
N(3)	0,2927 (7)	0,2520 (4)	0,4824 (5)	C(15)	0,8290 (6)	0,2490 (4)	0,1423 (4)
N(4)	0,4874 (5)	0,2878 (3)	0,2609 (4)	C(16)	0,9530 (6)	0,2373 (4)	0,0974 (5)
N(5)	0,5853 (5)	0,1756 (3)	0,1547 (4)	C(17)	1,0713 (7)	0,2452 (5)	0,1721 (6)
C(2)	0,3656 (6)	0,0169 (3)	0,3921 (4)	C(18)	1,0116 (7)	0,2613 (5)	0,2587 (6)
C(3)	0,4848 (6)	0,0330 (3)	0,2603 (4)	C(19)	0,6887 (6)	0,0575 (3)	0,0431 (4)
C(5)	0,6051 (6)	0,0826 (3)	0,1278 (4)	C(20)	0,7682 (7)	-0,0215 (4)	0,0306 (5)
C(7)	0,5072 (6)	0,1980 (3)	0,2362 (4)	C(21)	0,8229 (7)	-0,0147 (5)	-0,0665 (5)
C(8)	0,4535 (6)	0,1243 (3)	0,2904 (4)	C(22)	0,7750 (7)	0,0666 (4)	-0,1056 (5)
C(9)	0,3750 (6)	0,1147 (3)	0,3789 (4)				

The results confirm the validity of assuming that removal of a proton determines the course of the reaction in a similar manner to the formation of an active anion in the benzoin condensation, for which it is known that many substituted benzaldehydes that usually contain electron-donating substituents do not undergo this condensation [3, 4].

EXPERIMENTAL

The course of the reactions and purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates; ethyl acetate–hexane (1:1) was eluent; iodine vapor and UV light were used for development.

The IR spectra were recorded on a UR-20 instrument in a thin film.

X-Ray Diffraction Analysis of Pyrrolo[2,3-d]pyrimidine (XIc). The main crystallographic data were a = 9.032(6), b = 14.322(5), c = 13.313(6) Å, β = 94.47(3)°, space group $P2_1/c$, Z = 4, V = 1717.1 Å^3, $C_{19}H_{17}N_5O_3$. Of the 2558 nonzero reflections, 1908 greater than $3\sigma_I$ were used for refinement of the positional and thermal parameters of the molecule, whose motif was determined using direct methods carried out with the program MULTAN as part of the SDP program package. Refinement of the parameters of the nonhydrogen atoms was carried out as an anisotropic full-matrix approximation (Table 3). The positions of the hydrogen atoms were determined from Fourier syntheses and refined by isotropic approximation. The final value of R was 5.9%. X-ray diffraction analysis was conducted in a 4-circle automated Enraf–Nonius CAD-4 diffractometer, MoK_α radiation, ω scanning.

5-Alkoxy-2-(N-arylidenamino)-3,4-dicyanopyrroles (Va-i). To a solution of KOH in the respective alcohol at room temperature was added the initial 3,3,4,4-tetracyanopyrrolidine I in a single batch and the mixture was agitated until the latter had completely dissolved [the ratio of pyrrolidine I to KOH (1:2) was sufficient for this reaction and the content of alcohol had to be not less than that indicated in Table 1]. The resulting solution was heated to boiling and then cooled with water. After cooling, the reaction mixture was acidified with a twofold excess of acetic acid and again cooled with agitation. The precipitate that formed was filtered off and washed with isopropanol. Potassium acetate was removed by washing with a small quantity of water and the precipitate was washed again with isopropanol and recrystallized.

2-(N-Benzylidenamino)-5-butoxy-3,4-dicyanopyrrole (Ib). To a solution of 0.56 g (10 mmoles) of KOH in 41 ml of 1-butanol at room temperature was added 1.62 g (5 mmoles) of 2,5-diphenyl-3,3,4,4-tetracyanopyrrolidine and the mixture was agitated until the latter had dissolved. The mixture was then heated to boiling, cooled with water, and acidified with 1.2 g of acetic acid. Half of the alcohol was distilled off under vacuum and the potassium acetate that precipitated was removed by filtration. After this, about another 10 ml of 1-butanol was distilled off and the residue was cooled with water. The precipitate that formed was filtered off, washed with a small quantity of ether, then hexane, and recrystallized from acetic acid. Yield 0.55 g (38%) of product, mp 172-173°C.

2,3-Substituted 4-Amino-6-alkoxy-5-cyano-3H-pyrrolo[2,3-d]pyrimidines (XIa-k). To a solution of KOH in the respective alcohol at room temperature was added the initial 3,3,4,4-tetracyanopyrrolidine in a single batch in the proportions

shown in Table 2. On agitation the latter dissolved and the resulting solution was then heated to boiling. After this the mixture was cooled with water and acidified with excess acetic acid. The precipitate that formed was filtered off, washed with 2-propanol, the potassium acetate was removed by washing with water, and the precipitate washed again with 2-propanol and recrystallized. The final products XI were obtained in a purer state if the precipitate of the potassium derivative X was filtered before acidification. It was washed on the filter with a small quantity of 2-propanol, then suspended in 2-propanol and acidified with excess acetic acid. Potassium derivative X first dissolved, then compound XI precipitated out (see Table 2).

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