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ALKALINE SCISSION OF A UREA UNIT IN 5-ALKYL-2-AMINO-N-UREIDO-3,4-DICYANOPYRROLES

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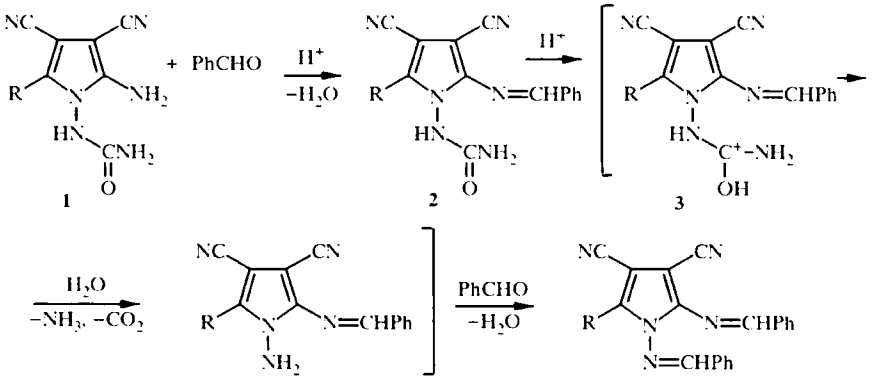
The scission of the urea group in 5-alkyl-2-amino-3,4-dicyano-N-ureidopyrroles on boiling in KOH solution in DMSO was observed to give 5-alkyl-1,2-diamino-3,4-dicyanopyrroles which were used for the synthesis of pyrrolo[1,2-b][1,2,4]triazepines by reaction with acetylacetone.

Keywords: diaminopyrroles, 1,2,4-triazepines, ureidopyrroles.

Organic polynitriles have found wide use in the synthesis of the majority of classes of polyfunctional substituted hetero- and alicycles, but their further conversion has not been used in practice with rare exceptions. We showed previously that when 5-alkyl-2-amino-3,4-dicyano-N-ureidopyrroles **1** are boiled with benzaldehyde in the presence of acetic acid the urea function is lost to give 5-alkyl-1,2-di(N-benzylideneamino)-3,4-dicyanopyrroles **5** [1]. It remained unclear if such scissions occur only on stabilization in the diazomethine compound **5** or are characteristic of N-ureidopyrroles **1**. Additional studies permit us to propose the following scheme. The reaction begins with the formation of the Schiff base **2** in which acid hydrolysis of the urea unit occurs, analogous to the hydrolysis of urea, to give pyrrole **4**. The latter reacts with another molecule of benzaldehyde to give 1,2-di(N-benzylideneamino)pyrroles **5a-c**.



1–5 a R = Me, **b** R = C_3H_7, **c** R = C_5H_{11}

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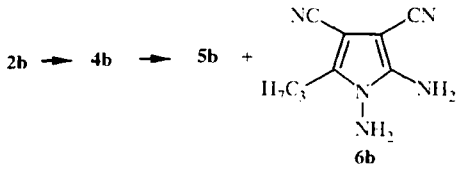
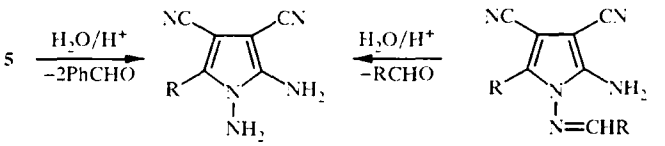
It was not possible to remove the urea fragment in the pyrroles **1** under conditions of acid hydrolysis. We associated this with protonation of the more basic amino group at position 2 of the heterocycle. This proposal, and also the proposal of the initial formation of the azomethine derivative **2** at this amino group is confirmed by the isolation of 2-(N-benzylideneamino)-3,4-dicyano-5-propyl-1-ureidopyrrole (**2b**) when the reaction was carried out in a mixture of benzaldehyde with acetic acid, the boiling point of which is evidently insufficient for scission of the urea fragment. The IR spectrum of **2b**, in contrast to that of the initial pyrrole, contains a C=N stretch at 1625 cm^{-1}. A compound which we identified as pyrrole **5b** was isolated from the reaction mixture from further scission of compound **2b** under conditions of acid catalysis. Its formation is possibly by an exchange reaction between two molecules of the expected 1-aminopyrrole **4** as a result of the greater nucleophilicity of the amino group attached to the nitrogen of the heterocycle. A similar scission occurs with base catalysis. The diaminopyrrole **6b**, which we were not able to isolate because of its great solubility, was observed in the reaction mixture by TLC. It was identified with a sample prepared by hydrolysis of bisazomethine **5b**.



6b



6a–f **7**

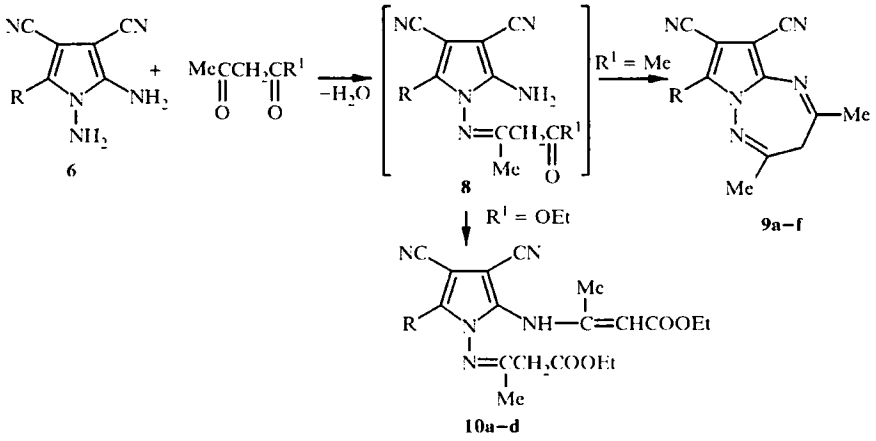
6, 7 a R = Me, **b** R = Pr, **c** R = C_5H_{11}, **d** R = Ph, **e** R = 4-$MeOC_6H_4$, **f** R = 2-Fu

Hydrolysis of pyrroles **7**, the products of the interaction of 1,1,2,2-tetracyanoethane with aldehyde azines [2], was used for synthesis of 5-aryl derivatives of 1,2-diamino-3,4-dicyanopyrrole **6d-f**. It was observed that the hydrolysis reaction was reversible and the equilibrium was shifted to the side of the starting compounds. By steam distillation of the aldehyde formed we were able to shift the equilibrium in the direction of formation of 1,2-diaminopyrroles **6a-f**. No C=N stretching bands were present in their IR spectra and, in contrast to the spectra of pyrroles **5**, bands appeared at 3460-3180 and 1660 cm^{-1}, characteristic of the NH bond (see Table 2).

The fact that compound **2b** was converted to pyrrole **5b** by base hydrolysis allowed the proposal that scission of the urea substituent in ureidopyrroles **1** might be possible under these conditions to synthesize 1,2-diaminopyrroles **6a-c**. It was shown that this conversion occurs on boiling compounds **1** in DMSO in the presence of KOH. Addition of a small (~ equimolar) amount of water, on the one hand, accelerates the reaction so that it is carried out in 2-4 h, but, on the other hand, because the requires a high temperature, an excess of water lowers the temperature of the reaction mixture which makes the hydrolysis impossible. It should be noted that prolonged boiling of compounds **1** in DMSO in the presence of alkali leads to the formation of large amounts of products from the decomposition of both the starting materials and the desired products, reducing the yield considerably. Hence from the preparative point of view diaminopyrroles **6** are more suitably made by hydrolysis of bisazomethines **5**.

The presence in pyrroles **6** of free amino groups provides the possibility to synthesize the pyrrolotriazepine structure. To this end we carried out reactions of compounds **6** with β-dicarbonyl compounds.

8,9-Dicyano-2,4-dimethyl-7-R-3H-pyrrolo[1,2-*b*][1,2,4]triazepines **9a-f** (Table 1) were synthesized by boiling pyrroles **6** in acetylacetone containing a catalytic amount of *p*-toluenesulfonic acid for 2-4 h. It is probable that interaction occurs at the more nucleophilic amino group bonded to the heterocyclic nitrogen to give azomethine **8** in which intramolecular cyclization of the second pair of amino and carbonyl groups occurs to give pyrrolotriazepine **9**. The IR spectra of compounds **9** differ from those of diaminopyrrole starting materials **6** in the absence of NH_2 absorption bands and the presence of C=N abssorptions at 1625 cm^{-1} [3].



9 a R =Me, **b** R =Pr, **c** R = C_5H_{11}, **d** R = Ph, **e** R = 4-$MeOC_6H_4$, **f** R = 2-Fu;
10 a R = Me, **b** R = C_5H_{11}, **c** R = Ph, **d** R = 2-Fu

TABLE 1. Characteristics of the Compounds Synthesized

Compound	R	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
			C	H	N		
2b	C_3H_7	$C_{17}H_{16}N_6O$	63.78 / 63.74	5.11 / 5.03	26.14 / 26.23	226-227	75
6a	CH_3	$C_7H_7N_5$	52.11 / 52.17	4.45 / 4.38	43.27 / 43.45	234-235	67 (52)*
6b	C_3H_7	$C_9H_{11}N_5$	57.18 / 57.13	5.81 / 5.86	37.09 / 37.01	303-304	65 (50)*
6c	C_5H_{11}	$C_{11}H_{15}N_5$	60.87 / 60.81	6.89 / 6.96	32.14 / 32.23	179-180	86 (42)*
6d	C_6H_5	$C_{12}H_9N_5$	64.64 / 64.56	4.12 / 4.06	31.29 / 31.37	168-169	95
6e	4-$H_3COC_6H_4$	$C_{13}H_{12}N_5O$	61.33 / 61.41	4.72 / 4.76	27.61 / 27.54	130-132	97
6f	2-Fu	$C_{10}H_7N_5O$	65.28 / 65.34	3.27 / 3.31	32.93 / 32.85	>210 (dec.)	96
9a	CH_3	$C_{12}H_{11}N_5$	64.02 / 63.99	4.98 / 4.92	31.02 / 31.09	230-232	88
9b	C_3H_7	$C_{14}H_{15}N_5$	66.35 / 66.38	5.94 / 5.97	27.71 / 27.65	119-120	50
9c	C_5H_{11}	$C_{16}H_{19}N_5$	68.34 / 68.30	6.83 / 6.81	24.80 / 24.89	104-105	55
9d	C_6H_5	$C_{17}H_{13}N_5$	71.03 / 71.07	4.58 / 4.56	24.29 / 24.37	236-238	52
9e	4-$H_3COC_6H_4$	$C_{18}H_{16}N_6O$	67.98 / 67.91	5.13 / 5.07	21.94 / 22.00	200-202 (dec.)	77
9f	2-Fu	$C_{15}H_{11}N_5O$	64.92 / 64.97	4.03 / 4.00	25.32 / 25.26	220-221	77
10a	CH_3	$C_{19}H_{23}N_5O_4$	59.23 / 59.21	6.05 / 6.01	18.05 / 18.17	161-162	48
10b	C_5H_{11}	$C_{23}H_{31}N_5O_4$	62.51 / 62.57	7.03 / 7.08	15.92 / 15.86	244-246	50
10c	C_6H_5	$C_{24}H_{25}N_5O_4$	64.44 / 64.42	5.66 / 5.63	15.58 / 15.65	169-170	45
10d	2-Fu	$C_{22}H_{23}N_5O_5$	60.36 / 60.40	5.27 / 5.30	16.12 / 16.01	210-212 (dec.)	49

* Yields by method B.

TABLE 2. IR Spectra of the Compounds Synthesized

Compound	NH_2	C≡N	C=N	δ NH
2b	3420, 3310, 3230	2220	1615	1640 (C=O); 1680
6a	3445, 3420, 3340	2235, 2205	—	1625
6b	3425, 3330, 2345, 3180	2225	—	1635
6c	3390, 3345, 3330, 3280	2220	-	1630
6d	3450, 3350, 3270	2230, 2205	—	1635
6e	3420, 3325, 3240	2220	—	1620
6f	3410, 3375, 3315, 3220	2230, 2215	—	1620
9a	—	2230	1625	—
9b	—	2230	1625	—
9c	—	2230	1620	—
9d	—	2230	1615	—
9e	—	2230	1605	—
9f	—	2230	1620	—
10a	3285	2230	1615	1720, 1695
10b	3380	2230	1635	1710, 1695
10c	3190, 3110	2235	1620	1720, 1690
10d	3200, 3150	2240	1620	1705, 1695

The absence of carbonyl group absorption band shows that the second azomethine unit is formed by an intramolecular reaction and not by condensation with a second molecule of the β-dicarbonyl compound. Apart from this, the ^{1}H NMR spectra contain two singlets, corresponding to the protons of the methyl groups in the triazepine ring, and a singlet at 3.45 ppm assigned to the protons of the methylene bridge.

In contrast to the symmetrical acetylacetone, 3,4-dicyano-1-(ethoxycarbonylisopropylideneamino)-2-(1-methyl-2-ethoxycarbonylvinylamino)-5-R-pyrroles **10a-d** were isolated from the reaction mixture as a result of the reaction with ethyl acetoacetate (Table 1). In this case, as with acetylacetone, it is probable that azomethines **8** were formed initially. However the subsequent attack of the second amino group did not occur intramolecularly at the ethoxycarbonyl group but at the more reactive carbonyl group of a second molecule of ethyl acetoacetate. The IR and mass spectra of these compounds are in complete agreement with the proposed structure (Table 2). According to the ^{1}H NMR spectrum of compound **10a**, the second azomethine unit isomerized into the enaminoethoxycarbonyl group.

EXPERIMENTAL

The course of reactions and the purity of the compounds synthesized were monitored by TLC on Silufol UV-254 strips with development with UV light and iodine vapor. IR spectra of nujol mulls were recorded on a UR-20 spectrometer. ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on Bruker WM-250 and AM-300 spectrometers.

2-(N-Benzylideneamino)-3,4-dicyano-5-propyl-1-ureidopyrrole (2d). Acetic acid (3 ml) was added to a suspension of pyrrole **1b** (1 g, 0.004 mol) in benzaldehyde (8 ml) and the mixture was boiled for 1 h. At the end of the reaction the mixture was cooled and diluted with an equal volume of isopropanol. The precipitate was filtered off, washed with isopropanol, and recrystallized from isopropanol (Table 1).

1,2-Di(N-benzylideneamino)-3,4-dicyano-5-propylpyrrole (5b). A drop of water and KOH (0.25 mmol) were added to a solution of pyrrole **2b** (0.5 g, 0.003 mol) in DMSO (10 ml) and the mixture was refluxed for 1 h. The reaction mixture was cooled and diluted with saturated sodium chloride solution. The precipitate was filtered off, washed with water, and recrystallized from isopropanol to give **5b** (0.26 g, 52%); mp 137-139°C.

1,2-Diamino-3,4-dicyano-5-R-pyrroles (6a-f). A. A suspension containing pyrrole **5** or **7** (0.004 mol), water (30 ml), and 15% sulfuric acid (1 ml) was heated and the benzaldehyde evolved was removed by steam distillation. The reaction mixture was then neutralized with sodium carbonate, the precipitate was filtered off, washed with water (10 ml) and isopropanol (5 ml), and recrystallized from isopropanol (Table 1).

B. A mixture of pyrrole **2a-c** (0.002 mol), DMSO (10 ml), a drop of water, and KOH (0.25 mmol) was boiled for 1-2 h. To isolate compounds **6a-c** the reaction mixture was diluted with saturated sodium chloride solution. The precipitate formed was filtered off, washed with water and isopropanol, and recrystallized.

8,9-Dicyano-2,4-dimethyl-7-R-3H-pyrrolo[1,2-*b*][1,2,4]triazepines (10a-f). A mixture of pyrrole **6** (0.002 mol), acetylacetone (2-3 ml), and 2-3 crystals of *p*-toluenesulfonic acid was refluxed for 1-2 h. After completion of the reaction, the reaction mixture was cooled, diluted with isopropanol (6 ml), the precipitate was filtered off, washed with isopropanol, and recrystallized from isopropanol (Table 1). ^{1}H NMR spectrum: compound **9a**: 2.31 (3H, s, CH_3); 2.35 (3H, s, CH_3); 2.4 (3H, s, CH_3); 3.45 ppm (2H, s, CH_2). Compound **9b**: 0.9 (3H, t, CH_3); 1.65 (2H, m, CH_2); 2.76 (2H, t, CH_2); 2.32 (3H, s, CH_3); 2.38 (3H, s, CH_3); 3.45 ppm (2H, s, CH_2).

3,4-Dicyano-1-(Ethoxycarbonylisopropylideneamino)-2-(1-methyl-2-ethoxycarbonylisopropylideneamino)-5R-pyrroles (10a-d). A mixture of pyrrole **6** (0.004 mol), ethyl acetoacetate (2-4 ml), and 2-3 crystals of *p*-toluenesulfonic acid was boiled for 2-3 h. The reaction mixture was cooled and diluted with a 2:1 isopropanol–hexane mixture. The precipitate was filtered off, washed with the same mixture, and recrystallized from isopropanol (Table 1). ^{1}H NMR spectrum of compound **10a**: 1.22 (6H, t, $2CH_3$); 1.56 (3H, s, $=C-CH_3$); 2.26 (3H, s, CH_3); 2.31 (3H, s, CH_3); 2.69 (2H, s, CH_2CO); 4.15 (4H, m $2CH_2O$); 4.32 (1H, s, =CH); 6.95 ppm (1H, s, NH). Mass spectrum of compound **10a**, *m/z*: 385 (97), 339 (44), 298 (78), 297 (95), 225 (89), 221 (89), 185 (47), 184 (100), 130 (26), 110 (41), 55 (51) (molecular ion and the 10 most intense fragment ions).

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