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TORP–ZIEGLER CYCLIZATION IN THE SYNTHESIS OF 3-AMINO-4-CYANOPYRROLE DERIVATIVES

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Polyfunctional derivatives of 3-aminopyrrole have been synthesized from several substituted β-enamino nitriles using Torp–Ziegler cyclization. These compounds are starting materials for further conversions, particularly for the synthesis of pyrrolo[3,2-d]- and pyrrolo[3,4-d]pyrimidines.

Keywords: 3-amino-4-cyanopyrrole, β-enamino nitriles, pyrrolo[3,2-*d*]pyrimidines, pyrrolo[3,4-*d*]-pyrimidines, intramolecular cyclization, Torp–Ziegler cyclization.

We previously developed methods for synthesizing 1,5-polymethylene derivatives of 3-aminopyrrole based on Torp–Ziegler cyclization [1-4]. These compounds are basic structures for closing a pyrimidine ring and for obtaining heterocyclic systems of the pyrrolo[3,2-*d*]- and pyrrolo[3,4-*d*]pyrimidine series. These methods, based on the N-alkylation of β,β-enaminonitriles, were used for the first time by K. Gewald [5,6], and included the treatment of the initial compounds with various α-halo ketones in anhydrous DMF using K_2CO_3 as alkaline reagent.

Enamino nitriles **1a-e** were selected as the initial subjects for the present work and were readily synthesized by the transamination of the dimethylamino derivative **2*** [7]. It had been shown previously that dehydration of the β-carbamoyl function of type **1a-e** enamines occurs smoothly under the action of the Vilsmeier reagent [7]. However in the case of the carbamide derivative **1c***[2], in addition to the desired dinitrile derivative **3c** (68% yield), 3-cyano-4-phenylamino-1,2-dihydropyrid-2-one (**4**) (8% yield) was isolated as a contaminant. Extremely high yields were achieved in the dehydration of the initial carbamides **1a-e** under the action of phosphorus oxychloride in dry acetonitrile (Scheme 1).

The following were selected as alkylating agents having an active methylene group necessary to carry out the subsequent intramolecular cyclization: bromoacetic acid ester, α-bromoacetophenone, and some *para*-substituted derivatives of it. It turned out that in practically all cases the alkylation was accompanied by a spontaneous Torp–Ziegler cyclization. The alkylation of enamino dinitrile **3d** (R = CH_2Ph) with methyl bromoacetate was an exception. In this case the process stopped at the stage of forming intermediate **5** and the use of sodium methylate as catalyst was required for the subsequent cyclization. As expected, compounds having an

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* According to the data of ^{1}H NMR spectra compound **2** exists in DMSO-d_6 solution as two geometric *cis* and *trans* isomers. Predominant isomer (60%): 2.20 (CH_3); 2.94 (NMe_2); 6.55 ppm (NH_2); other isomer (40%): 2.36 (CH_3); 3.14 (NMe_2); 6.53 ppm (NH_2).

*[2] According to the data of ^{1}H NMR spectra, compound **1c** exists in DMSO-d_6 solution as one geometric isomer which is stabilized by an intramolecular hydrogen bond: 2.20 (3H, s, CH_3); 7.00, 7.20 two equally broadened signals of 1H each, NH_2); 7.25 (3H, m), 7.42 (2H, m, Ph); 12.74 ppm (1H, br. signal, NH).

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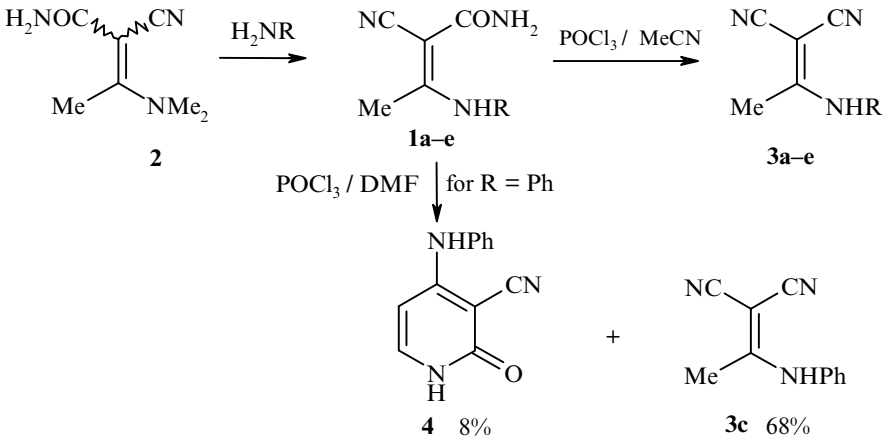
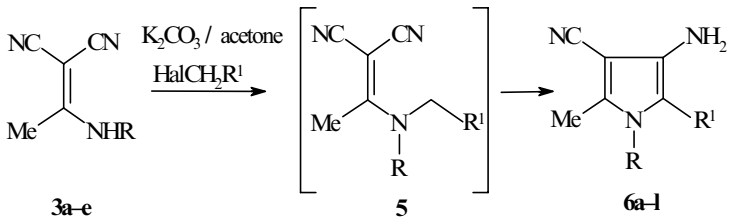
Scheme 1



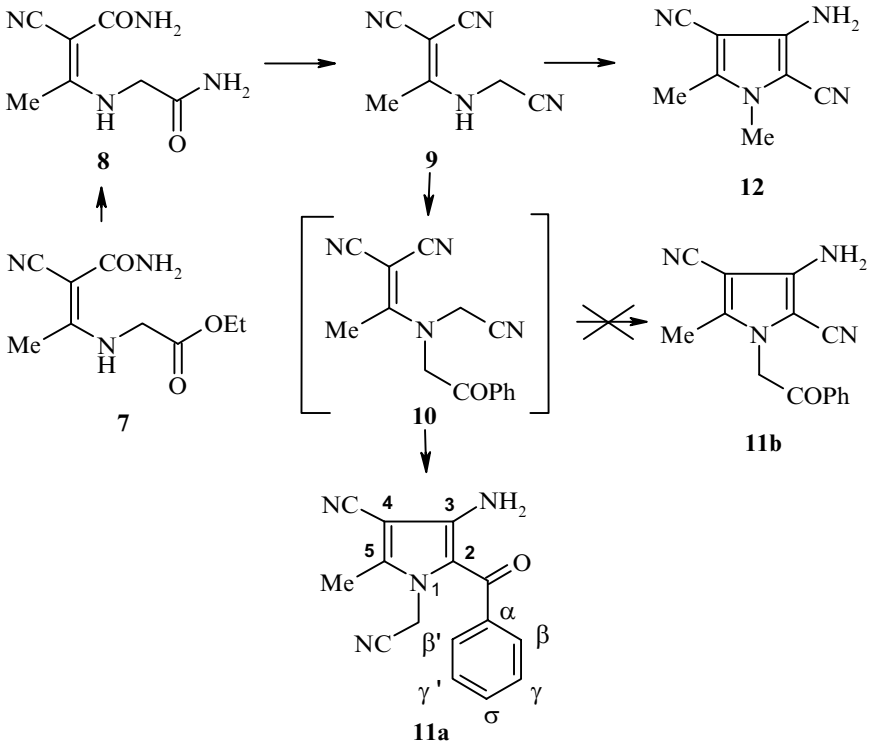
a R = Me; **b** R = CH_2Ph; **c** R = Ph; **d** R = C_6H_4–Br-*p*; **e** R = C_6H_4–Cl-*p*

aryl substituent in the amino fragment of the enamine group were the best for alkylating and undergoing subsequent intramolecular cyclization. This group facilitates the formation of the N-anion necessary on the one hand for the initial alkylation and on the other aids the formation of the subsequent carbanion for the cyclization involving the cyano group. In these cases the reaction as a rule takes place at room temperature and the desired 3-aminopyrrole derivatives **6** are obtained in completely satisfactory yield. Enamino nitriles **3a,b** having a benzyl or methyl substituent at the nitrogen atom require more forcing and extended conditions to effect the processes being studied. This leads to a reduction in yield of the final product due to some resinification of the reaction mixture.



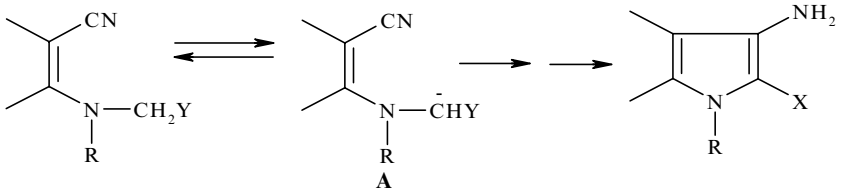
3 a R = Me; **b** R = CH_2Ph; **c** R = Ph; **d** R = C_6H_4Br-*p*; **e** R = C_6H_4Cl-*p*; **6 a** R = Me, R^1 = COPh;
b R = Me, R^1 = CO_2Me; **c** R = CH_2Ph, R^1 = COPh; **d** R = CH_2Ph, R^1 = CO_2Me; **e** R = Ph, R^1 = COPh;
f R = Ph, R^1 = CO_2Me; **g** R = Ph, R^1 = COC_6H_4Br-*p*; **h** R = C_6H_4Br-*p*, R^1 = COPh; **i** R = C_6H_4Br-*p*, R^1 = CO_2Et;
j R = C_6H_4Br-*p*, R^1 = COC_6H_4Br-*p*; **k** R = C_6H_4Cl-*p*, R^1 = CO_2Et; **l** R = C_6H_4Cl-*p*, R^1 = COC_6H_4Br-*p*

In order to study the effect of the substituent located at the active CH_2 group on the direction of the Torp–Ziegler reaction, we attempted to synthesize an intermediate having two functionally substituted methylene fragments at the nitrogen atom. For this purpose carbamide **8** was synthesized from the previously described α-cyano-β-ethoxycarbonyl-β-methylacrylamide (**7**) [8] by reaction with ammonia. In its turn carbamide **8** was readily transformed into nitrile **9**. Alkylation of the latter with α-bromoacetophenone leads initially to the formation of the intermediate enamine **10**, theoretically capable of being cyclized according to Torp–Ziegler in two directions, by attack of the β-enamino CN group at the CH_2 group linked directly with the cyano or acyl substituent (compounds **11a** and **11b**). It turned out that in the present case cyclization exclusively involved the methylene fragment at the benzoyl group and the final 3-amino-2-benzoyl-4-cyano-1-cyanomethyl-5-methylpyrrole (**11a**) was isolated in 60% yield. The structure of this compound was difficult to demonstrate unequivocally by ^{1}H NMR spectroscopy and a choice between structures **11a** and **11b** was effected by ^{13}C NMR spectra. In the ^{13}C NMR spectrum of structure **11a,** taken without suppression of proton coupling, the signal for the carbon atom of the CN group of the NCH_2CN fragment must be a triplet due to coupling with the protons of the neighboring



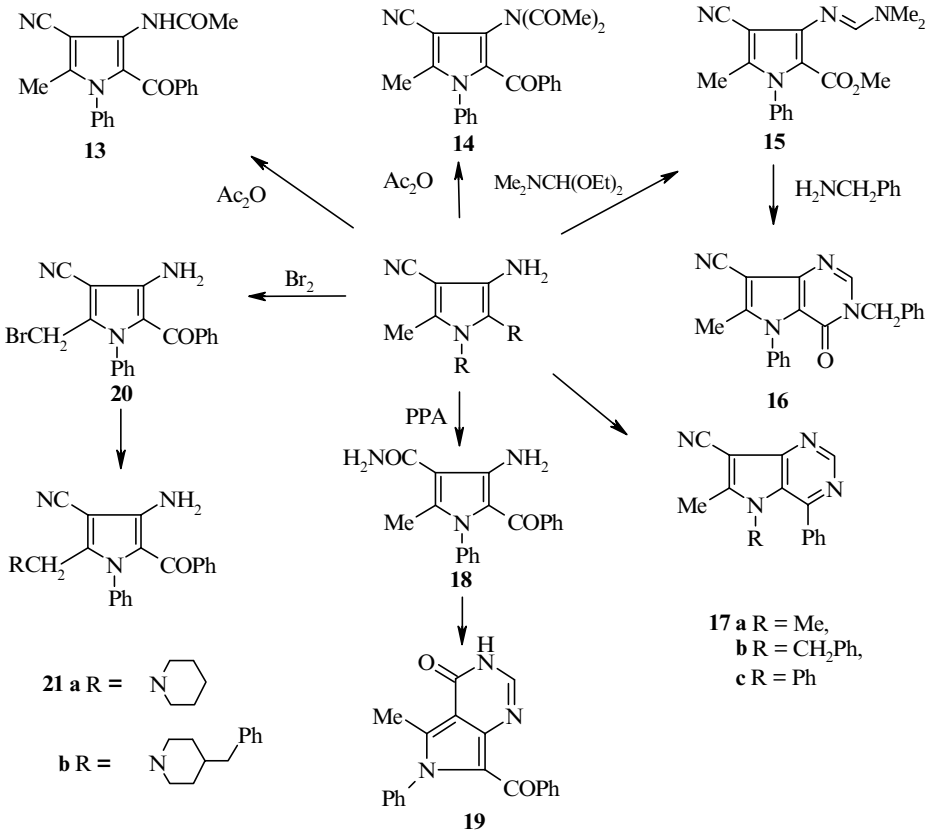
CH_2 group. The signal of the carbonyl carbon in this structure will interact only with the *ortho* protons of the neighboring phenyl ring. The situation is the reverse for structure **11b**. The signal for the ketonic carbon atom must experience an interaction both with the β,β-protons of the aromatic ring and with the protons of the neighboring methylene group. At the same time the signal of the carbon atom of the CN group in position 2 must be displayed in the spectrum as a singlet. The spectral data are as follows (DMSO-d_6), δ, ppm: 11.6 (CH_3); 34.7 (CH_2); 84.4 (C_4); 114.4 (4-CN); 114.7 (C_3); 116.7 (CH_2CN); 128.0 ($C_\beta C_{\beta 1}$); 129.5 ($C_\gamma C_{\gamma 2}$); 132.0 (C_δ); 139.7 (C_α); 146.0 (C_5); 146.6 (C_2); 183.1 (CO). The signal of the carbon atom at 116.7 ppm in the spectrum plotted without proton quenching is a triplet with CC 8.4 Hz. Plotting the spectrum in the selective decoupling mode showed that on quenching the signal of the CH_2 group (5.22 ppm) the triplet at 116.7 ppm is converted into a singlet. This signal may therefore be unequivocally assigned to the CN group carbon atom. In addition no coupling was observed of the ketonic carbon signal (183.1 ppm) with the CH_2 group protons, it only interacted with the *ortho* protons of the phenyl ring. Consequently both these facts unequivocally agree with structure **11a** for the studied compound. In order to clarify whether this reaction does not proceed by the second possible route with the formation of compound **11b** a ^{1}H NMR spectrum (DMSO-d_6) was taken for the reaction mixture, judging by which the sample being analyzed was a mixture of compounds **11a** and **9**, 18 : 1. No signals of the second possible compound **11b** were recorded in the sample.

It is necessary to consider the mechanism of the closure of the pyrrole ring according to Torp–Ziegler. The first stage of cyclization is the formation of a carbanion, the stability of which determines the rate and direction of the ring closure [9]. Anion **A** is stabilized mainly by the electron-withdrawing substituent **Y**, which may be assessed quantitatively by comparing the σ_R constants. It is known that the σ_R constant of the CN group is extremely small (σ_R = 0.08), which reflects the low level of the direct polar conjugation of this substituent with the carbonyl reaction center. Calculation of the σ_R constant of the benzoyl group was made by Charton's method [10] in [11] and its size was significantly greater (σ_R = 0.174). Consequently when selecting a direction for the process towards R–CH$^-$–CN or R–CH$^-$–COPh the formation of the more stable anion containing X = COPh is preferred. This circumstance explains the cyclization exclusively in the direction of forming compound **11a** and the absence in the reaction mixture of the pyrrole derivative **11b**.



A

We recorded previously that enamino nitriles of type **3**, having a secondary NH group, are not subject to Torp–Ziegler cyclization without protective acylation of the initial molecule [12]. In our case simple methylation of the cyano derivative **9** is safely followed by intramolecular cyclization and by the formation of 3-amino-2,4-dicyano-1,5-dimethylpyrrole (**12**).



13 **14** **15** **16** **17 a** R = Me, **b** R = CH_2Ph, **c** R = Ph **18** **19** **20** **21 a** R = **b** R =

The derivatives of 3-amino-4-cyanopyrrole synthesized in this way are extremely polyfunctional compounds containing an interesting set of substituents. The 3-amino group, although having electronegative substituents in the neighboring *ortho* positions, nonetheless retains basic properties and is readily acylated with acetic anhydride with the formation of the monoacetyl **13** and under more forcing conditions the diacetyl derivative **14**. The reaction of compound **6f** with the diethyl acetal of DMF also occurs readily, as a result of which amidine **15** was synthesized in good yield. On reacting amidine **15** with benzylamine a pyrimidine cyclization occurs with the formation of a bicyclic compound **16** of the pyrrolo[3,2-*d*]pyrimidine series. In this case the methoxycarbonyl group in position 2 of the pyrrole ring but not the 4-cyano group participatates in cyclization, which is in good agreement with literature date [3,4]. A similar closure of the pyrimidine ring using a benzoyl substituent in the synthesis of bicyclic derivatives **17a-c** was successfully effected on heating compounds **6a,c,e** in a HCOOH–$HCONH_2$–DMF mixture. Bicyclic derivatives of another type, the pyrrolo[3,4-*d*]pyrimidines, were obtained on transforming the CN group in position 4. For this the 4-cyanopyrrole **6e** was subjected to hydrolysis with polyphosphoric acid, as a result of which the carbamide derivative **18** was isolated, which by the action of DMF acetal or formic acid as standard one-carbon components was readily converted into the bicyclic compound **19**.

TABLE 1. Physicochemical Characteristics of the Synthesized Compounds

Compound	Empirical formula	Found, % / Calculated, %			R	R^1	mp, °C (solvent for recrystallization)	Yield %
		C	H	N				
1	2	3	4	5	6	7	8	9
1a	$C_6H_9N_3O$	51.79 / 51.79	6.64 / 6.52	30.38 / 30.20	Me	—	196-198 (ethanol)	56
3a	$C_6H_7N_3$	59.48 / 59.49	5.74 / 5.82	35.00 / 34.69	Me	—	149-152 (toluene)	62
3b	$C_{12}H_{11}N_3$	73.03 / 73.07	5.60 / 5.62	21.42 / 21.30	CH_2Ph	—	104-106 (aq. ethanol)	83
3c	$C_{11}H_9N_3$	72.23 / 72.11	5.06 / 4.95	22.88 / 22.94	Ph	—	194-197* (ethanol)	95
3d	$C_{11}H_8N_3Br$	50.36 / 50.40	3.02 / 3.08	16.34 / 16.03	C_6H_4Br-*p*	—	238-240 (acetonitrile)	83
3e	$C_{11}H_8N_3Cl$	60.44 / 60.70	3.70 / 3.70	19.32 / 19.31	C_6H_4Cl-*p*	—	219-220 (ethanol)	78
6a	$C_{14}H_{13}N_3O$	70.31 / 70.27	6.00 / 5.98	17.40 / 17.56	Me	COPh	165-167 (2-propanol)	33
6b	$C_9H_{11}N_2O_2$	55.74 / 55.95	5.87 / 5.74	21.77 / 21.75	Me	CO_2Me	187-187.5 (methanol)	27
6c	$C_{20}H_{17}N_3O$	76.25 / 76.14	5.49 / 5.43	13.06 / 13.32	CH_2Ph	COPh	167-169 (toluene)	45
6d	$C_{15}H_{15}N_3O_2$	67.00 / 66.90	5.60 / 5.61	15.52 / 15.60	CH_2Ph	CO_2Me	116-118 (ethanol)	46
6e	$C_{19}H_{15}N_3O$	75.20 / 75.68	5.09 / 5.01	13.73 / 14.00	Ph	COPh	192-195 (aq. DMF)	83
6f	$C_{14}H_{13}N_3O_2$	65.00 / 64.85	5.30 / 5.05	16.31 / 16.21	Ph	CO_2Me	126-127 (methanol)	40

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
6g	$C_{19}H_{14}N_3BrO$	60.28 60.01	3.80 3.71	11.14 11.05	Ph	COC_6H_4Br-*p*	170-172 (methanol)	64
6h	$C_{19}H_{14}N_3BrO$	60.06 60.01	3.69 3.71	11.00 11.05	C_6H_4Br-*p*	COPh	165-167 (acetonitrile)	84
6i	$C_{15}H_{14}N_3O_2Br$	51.92 51.74	4.12 4.05	11.95 12.07	C_6H_4Br-*p*	CO_2Et	171-172 (aq. DMF)	56
6j	$C_{19}H_{13}N_3Br_2O$	49.80 49.70	2.73 2.85	9.18 9.15	C_6H_4Br-*p*	COC_6H_4Br-*p*	245-247 (aq. DMF)	59
6k	$C_{15}H_{14}N_3O_2Cl$	59.48 59.31	4.63 4.65	13.98 13.83	C_6H_4Cl-*p*	CO_2Et	154-155 (DMF)	54
6l	$C_{19}H_{13}N_3ClBrO$	56.21 56.24	4.02 3.86	11.85 11.93	C_6H_4Cl-*p*	COC_6H_4Br-*p*	250-251 (DMF–ethanol)	61
8	$C_7H_{10}N_4O_2$	46.27 46.15	5.54 5.53	31.10 30.75	—	—	255-258 (aq. ethanol)	54
9	$C_7H_6N_4$	57.24 57.52	4.39 4.14	38.08 38.34	—	—	114-117 (ethyl acetate–heptane)	40
11	$C_{15}H_{12}N_4O$	68.15 68.17	4.82 4.58	21.27 21.20	—	—	134-136 (2-propanol)	60
12	$C_8H_8N_4$	59.87 60.00	5.07 5.03	34.97 34.97	—	—	266-268 (methanol)	45
13	$C_{21}H_{17}N_3O_2$	73.33 73.41	4.98 4.99	12.37 12.29	—	—	156-157 (2-propanol)	52
14	$C_{23}H_{19}N_3O_3$	71.98 71.67	5.11 4.97	10.73 10.90	—	—	169-170 (ethanol)	64
15	$C_{17}H_{18}N_4O_2$	65.79 65.61	5.85 5.94	18.05 18.15	—	—	131-132 (methanol)	64

TABLE 1 (continued)

1	2	3	4	5	6	7	8	9
16	$C_{21}H_{16}N_4O$	74.28 74.10	4.64 4.74	16.59 16.46	—	—	188-189 (2-propanol)	81
17a	$C_{15}H_{11}N_4$	72.50 72.86	4.96 4.48	22.71 22.66	Me	—	184-186 (methanol)	70
17b	$C_{21}H_{16}N_4$	77.85 77.78	4.88 4.97	17.24 17.26	CH_2Ph	—	134-135 (2-propanol)	69
17c	$C_{20}H_{14}N_4$	77.25 77.40	4.62 4.55	18.18 18.05	Ph	—	230-233 (DMF–methanol)	72
18	$C_{19}H_{17}N_3O_2$	71.31 71.45	5.27 5.37	13.17 13.16	—	—	255-258 (DMF–methanol)	53
19	$C_{20}H_{15}N_3O_2$	72.63 72.93	4.68 4.59	12.71 12.76	—	—	254-255 (DMF–ethanol)	67
20	$C_{19}H_{14}N_3OBr$	60.37 60.01	4.09 3.71	11.07 11.05	—	—	140 decomp. (benzene–heptane)	89
21a	$C_{24}H_{24}N_4O$	74.97 74.97	6.25 6.29	14.73 14.57	—	—	159-161(methanol)	50
22	$C_{31}H_{30}N_4O$	78.33 78.45	6.42 6.37	11.89 11.80	—	—	133-134 (ethanol)	37
1a	$C_{27}H_{22}N_6SO$	67.61 67.76	4.48 4.63	17.30 17.56	—	—	249-251 (acetic acid)	63
3a	$C_{27}H_{22}N_6SO$	67.57 67.76	4.69 4.63	17.39 17.56			285 decomp. (DMF)	90

* mp 194-195°C [15].

TABLE 2. ^{1}H NMR Spectra of the Synthesized Pyrroles (δ, ppm)*

Com-pound	R	R^1	NXY*[2]	R^2
6a	3.22 s (CH_3)	7.48-7.58 m (COPh)	5.90	2.27 s (CH_3)
6e	7.10-7.20 m (Ph + COPh)		6.64	2.11 s (CH_3)
6i	7.25 m, 7.65 m (C_6H_4Br-*p*)	0.91 t ($\underline{CH_3}CH_2$); 3.95 q ($CH_3\underline{CH_2}$)	5.96	2.02 s (CH_3)
6j	7.02-7.10 m, 7.26-7.36 m (C_6H_4Br-*p* + COC_6H_4Br-*p*)		6.60	2.11 s (CH_3)
6k	7.32 m, 7.52 m (C_6H_4Cl-*p*)	0.90 t ($\underline{CH_3}CH_2$); 3.92 q ($CH_3\underline{CH_2}$)	5.96	2.02 s (CH_3)
6l	7.04-7.30 m (C_6H_4Cl-*p* + COC_6H_4Br-*p*)		6.80	2.11 s (CH_3)
11a	5.22 s (CH_2CN)	7.50-7.65 m (COPh)	5.26	2.39 s (CH_3)
12	3.42 s (CH_3)	—	5.84	2.23 s (CH_3)
13	7.32-7.63 m (Ph + COPh)		1.53 s ($COCH_3$) 9.63 s (NH)	2.18 s (CH_3)
14	7.33-7.56 m (Ph + COPh)		2.17 s (2 $COCH_3$)	2.29 s (CH_3)
21	7.06-7.22 m (Ph + COPh)		6.52	4.38 s (CH_2); 3.14 s (NMe_2); 6.57 d (=CH); 7.93 d (=CH)
22a	7.06-7.22 m (Ph + COPh)		6.50	3.20 s (CH_2); 1.20-1.40 m (6H); 2.20 br. s (4H), (NC_5H_{10})
22b	7.04-7.28 m (Ph + COPh)*[3]		6.50	1.00 m (2H), 1.40 m (3H); 1.80 m (2H), 2.60 m (2H) (NC_5H_9); 2.44 d ($^3J_{CH_2CH}$ = 6.8 Hz) ($\underline{CH_2}$Ph); 3.20 s (CH_3); 7.04-7.28 (Ph)*[3]

* Solvent DMSO-d_6.

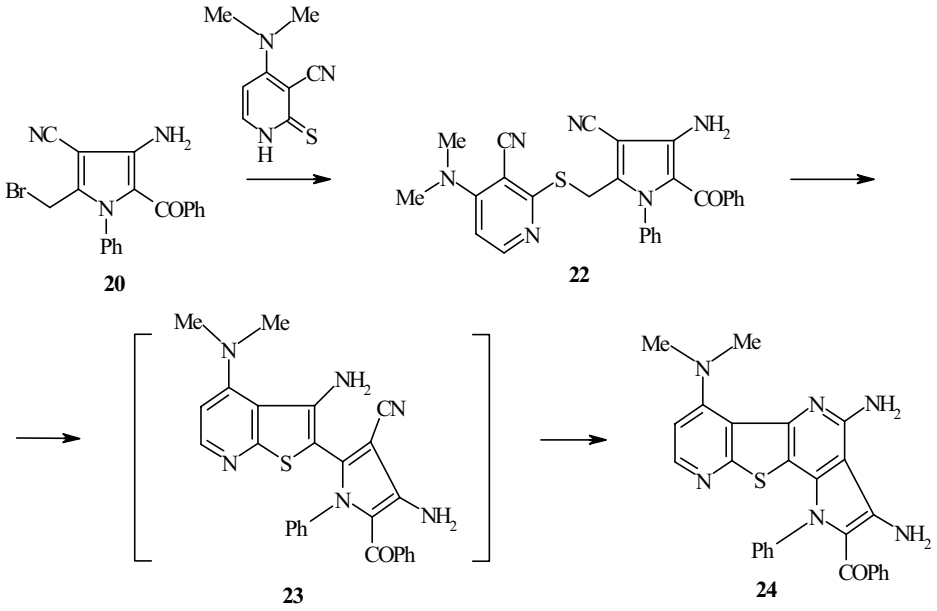
*[2] 3-NH_2-protons are represented in the spectrum as a broad singlet of intensity 2H.

*[3] For compound **22b** the intensity of the multiplet for the aromatic protons in the range 7.04-7.28 ppm corresponded to 15H (Ph + COPh + CH_2Ph).

TABLE 3. The IR Spectra of the Synthesized Compounds

Compound	C=C, C=O	CN	NH_2, NH
1a	1590, 1625, 1650	2150	3150, 3350
3a	1600 br.	2190 br.	3275
3b	1600 br.	2210 br.	3260
3c	1610	2195, 2205	3210
3d	1565	2195 br.	3220
3e	1575	2200 br.	3240
6a	1590, 1610	2200	3200, 3310, 3410
6b	1610, 1660	2200	3320, 3415
6c	1570, 1610	2210	3320, 3430
6d	1625, 1690	2210	3350, 3490
6e	1590, 1610	2200	3310, 3410
6f	1620, 1670	2200	3210, 3330, 3420
6g	1590	2200	3300, 3405
6h	1600	2215	3320, 3430
6i	1610, 1660	2200	3310, 3410
6j	1590	2200	3280, 3390
6k	1600, 1650	2190	3300, 3400
6l	1590	2205	3280, 3400
8	1600 br., 1650, 1675	2180	3100-3425
9	1550 br.	2200	3300
11	1600, 1640	2200	3230, 3330, 3430
12	1630	2190, 2200	3220, 3320, 3400
14	1640, 1695, 1720	2205	—
15	1670, 1690	2200	—
16	1680	2220	—
17a	1570, 1600	2205	—
17b	1560, 1605	2210	—
18	1600, 1660	—	3150 br., 3340, 3430
19	1600, 1680	—	3290
20	1605, 1625	2220	3195, 3290, 3400
21a	1600 br.	2190, 2210	3310, 3420
21b	1600 br.	2190	3260, 3320, 3380, 3420
22	1600	2200	3360, 3460

Compound **6e** is readily brominated by the action of molecular bromine in acetic acid with the formation of the bromo derivative **20**. The halogen atom in this compound is extremely labile and compounds **21a,b** are readily formed on N-alkylation of piperidine and 4-benzylpiperidine. The S-alkylation of 3-cyano-4-dimethylamino-1,2-dihydropyridin-2-thione [13] proved to be of interest, from which the heterylthio derivative **22** was isolated. The electronegativity of the pyridine fragment of this molecule proved to be sufficient to provide a further intramolecular Torp–Ziegler cyclization under the action of sodium ethylate. The thienopyridine intermediate **23** formed in this way undergoes further cyclization in the course of the reaction with the participation of the pyrrole CN group and the amino group of the thiophene ring. The structure of the resulting tetracyclic compound **24** was confirmed unequivocally by IR spectral data, from which the nitrile absorption band at 2200 cm^{-1} was absent, and by data of ^1H NMR spectra (in DMSO-d_6). In these spectra a singlet was observed at 3.08 ppm for the dimethylamino group, two doublets for the protons of the pyridine ring at 7.50 and 8.13 ppm, and also a broad signal for amino group protons at 6.90 ppm and a multiplet at 7.09-7.28 ppm of intensity 12 protons, assigned to the second amino group and the two phenyl substituents.



EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 400 MHz spectrometer, internal standard was TMS, and solvent DMSO-d_6. The IR spectra were obtained on a Perkin-Elmer 457 spectrometer. A check on the progress of reactions and the purity of substances was effected with Kieselgel 60 F_{254} plates (Merck). Melting points were determined on a Boetius hot stage.

1-Carbamoyl-1-cyano-2-methylaminopropene (1a). A mixture of enamino amide **2** (15.3 g, 0.1 mol) and 20% methylamine in methanol solution (100 ml) was heated in an autoclave for 6 h. The precipitated crystals were filtered off and washed with a small quantity of ethanol.

2-Benzylamino-1-carbamoyl-1-cyanopropene (1b) was obtained by the method of [14].

2-Amino-1-carbamoyl-1-cyano-substituted Propenes 1c,d,e were obtained by the method of [7].

General Method for Obtaining 2-Amino-substituted 1,1-Dicyanopropenes 3a-e. The appropriate carbamide **1a-e** (0.03 mol) was added to a solution of phosphorus oxychloride (6.1 g, 0.04 mol) in dry acetonitrile (50 ml) and the mixture boiled with stirring for 2 h. The reaction mixture was poured into a mixture of ice and water and the precipitated crystals were filtered off.

Reaction of 1-Carbamoyl-1-cyano-2-phenylaminopropene 1c with the Vilsmeier Reagent. Phosphorus oxychloride (12 ml, 0.137 mol) was added at 5°C to a mixture of DMF (11.7 ml) and acetonitrile (150 ml) and the mixture was stirred for 40 min. Enamine **1c** (23.2 g, 0.125 mol) was then added and the mixture boiled for 2 h. The reaction mixture was poured into a mixture of ice and water, and the precipitated solid filtered off. Compound **4** (2.1 g, 8%) with M^+ 211 and dicyano enamine **3c** (15.4 g, 68%) were isolated by recrystallization from alcohol.

General Method for Obtaining Derivatives of 3-Amino-4-cyano-5-methylpyrroles 6a-l, 11a, and 12. Potassium carbonate (20.7 g, 0.15 mol) was added to a solution of the initial enamine (0.1 mol) in acetone (150 ml). The alkylating agent (0.12 mol) was then added and the reaction mixture was stirred with boiling for 1-3 h. The inorganic solid was filtered off, and the final aminopyrroles were isolated by the usual methods. In the case of compound **3d** the reaction mixture was evaporated in vacuum, a solution of sodium methylate in methanol was added, and the mixture boiled for 30 min. The precipitated solid was filtered off.

1-Carbamoyl-2-carbamoylmethylamino-1-cyanopropene (8). Enamine **7** (1.0 g, 0.047 mol) was added to a mixture of methanol (10 ml) and 25% aqueous ammonia solution (10 ml). The mixture was stirred for 5 h, cooled, and the precipitated solid filtered off. ^{1}H NMR spectrum, δ, ppm: 2.12 (3H, s, CH_3); 4.00 (2H, d, $^{3}J_{CH_2,NH}$ = 5.6 Hz, CH_2); 6.68 (2H, strongly br. signal, NH_2); 7.55 (2H, two strongly br. signals, NH_2); 10.84 (1H, t, NH).

1,1-Dicyano-2-cyanomethylaminopropene (9). Phosphorus oxychloride (50.5 g, 0.33 mol) was added to a suspension of carbamide **8** (25.0 g, 0.137 mol) in dry acetonitrile (150 ml) and the mixture stirred and boiled for 1.5 h. The reaction mixture was then poured onto ice and the solution neutralized to pH 7 with sodium carbonate. The solution was then extracted with ethyl acetate, the extract dried over Na_2SO_4, the solvent removed in vacuum, the residue was triturated with 2-propanol, and the precipitated solid filtered off. ^{1}H NMR spectrum, δ, ppm, *J* (Hz): 2.27 (3H, s, CH_3); 4.49 (2H, d, $^3J_{CH2,NH}$ = 6.0, CH_2); 9.09 (1H, br. t, NH).

3-Acetylamino-2-benzoyl-4-cyano-5-methyl-1-phenylpyrrole (13). Compound **6e** (1.7 g, 0.0056 mol) was added to acetic anhydride (10 ml), the mixture was heated for 10 min at 100°C, cooled, and the precipitated crystals filtered off.

2-Benzoyl-4-cyano-3-diacetylamino-5-methyl-1-phenylpyrrole (14) was obtained analogously to compound **13** but the reaction mixture was boiled for 1 h.

4-Cyano-3-dimethylaminomethinamino-2-methoxycarbonyl-5-methyl-1-phenylpyrrole (15). DMF dimethylacetal (8.24 g, 0.07 mol) was added to a solution of pyrrole **6f** (8.83 g, 0.035 mol) in toluene (60 ml) and the mixture boiled for 7 h. The reaction mixture was cooled, and the precipitated solid filtered off.

3-Benzyl-7-cyano-6-methyl-5-phenyl-3,4-dihydropyrrolo[3,2-*d*]pyrimid-4-one (16). Benzylamine (1.25 g, 0.012 mol) and *p*-toluenesulfonic acid (0.01 g) were added to a solution of amidine **15** (1.82 g, 0.006 mol) in toluene (40 ml). The reaction mixture was boiled for 7 h, and the precipitated solid filtered off. ^{1}H NMR spectrum, δ, ppm: 2.26 (3H, s, CH_3); 5.11 (2H, s, CH_2); 7.22-7.53 (10H, m, $2C_6H_5$); 8.55 (1H, s, 4-CH).

5-Methyl, 5-Benzyl, and 5-Phenyl Derivatives of 7-Cyano-6-methyl-4-phenylpyrrolo[3,2-*d*]-pyrimidines 17a-c. The appropriate pyrrole **6a,c,e** (0.008 mol) was added to a mixture (25 ml) of DMF–HCOOH–$HCONH_2$, 15 : 5 : 2 and the mixture boiled for 6 h. The reaction mixture was poured into water, the precipitated solid was filtered off, and washed with 2-propanol. Compound **17b**: ^{1}H NMR spectrum, δ, ppm: 2.60 (3H, s, CH_3); 5.21 (2H, s, CH_2); 6.42 (2H, m); 7.15 (3H, m); 7.35 (4H, m); 7.50 (10H, m, $2C_6H_5$); 8.98 (1H, s, 4-CH). Compound **17c**: ^{1}H NMR spectrum, δ, ppm: 2.49 (3H, s, CH_3); 7.00-7.30 (10H, m, $2C_6H_5$); 9.05 (1H, s, 4-CH).

3-Amino-2-benzoyl-4-carbamoyl-5-methyl-1-phenylpyrrole (18). Phosphoric anhydride (25 g) was added to *ortho*-phosphoric acid (25 ml) and the mixture stirred at 100-110°C for 1 h. Compound **6e** (7.0 g, 0.023 mol) was then added and the mixture maintained at 100°C for 1 h. The reaction mixture was poured onto ice, and the precipitated solid filtered off.

7-Benzoyl-5-methyl-6-phenyl-3,4-dihydropyrrolo[3,4-*d*]pyrimid-4-one (19). A mixture of compound **18** (7.0 g, 0.023 mol) and formic acid (100 ml) was heated at the boiling point with stirring for 4 h. The reaction mixture was evaporated in vacuum, and the residue triturated with 2-propanol.

3-Amino-2-benzoyl-5-bromomethyl-4-cyano-1-phenylpyrrole (20). Bromine (3.34 g, 0.021 mol) was added dropwise to a suspension of compound **6e** (6.02 g, 0.02 mol) in acetic acid (100 ml) at 20°C during 1 h, and the mixture then stirred at this temperature for 15 min. The reaction mixture was poured into water, and the precipitated solid filtered off.

3-Amino-2-benzoyl-4-cyano-5-piperidinomethyl-1-phenylpyrrole (21a). A mixture of bromo derivative **20** (1 g, 0.0026 mol) and piperidine (25 ml) was heated at 70°C for 2 h. The reaction mixture was evaporated in vacuum, and the residue crystallized.

3-Amino-2-benzoyl-5-(4-benzylpiperidino)methyl-4-cyano-1-phenylpyrrole (21b) was obtained analogously to compound **21a**.

3-Amino-2-benzoyl-4-cyano-5-(3-cyano-4-dimethylamino-2-pyridyl)mercaptomethyl-1-phenylpyrrole (22). Dimethylformamide (DMF) (40 ml) was added to a solution of KOH (0.5 g, 0.009 mol) in water (4 ml) and then 3-cyano-4-dimethylamino-1,2-dihydropyridine-2-thione [13] (1.5 g, 0.0084 mol) was added. After complete solution a solution of bromo derivative **20** (3.35 g, 0.088 mol) in DMF (15 ml) was added dropwise at 20°C. The reaction mixture was stirred for 15 min and the precipitated solid filtered off.

3,4-Diamino-2-benzoyl-6-dimethylamino-1-phenylpyrrolo[3,2-*c*]dipyrido[*b,d*]thiophene (24). Compound **21** (0.82 g, 0.0017 mol) was added to a solution of sodium ethylate, obtained from sodium (0.23 g, 0.01 mol) and ethyl alcohol (20 ml). The reaction mixture was boiled for 10 min, the precipitated solid was filtered off, and washed with ethanol. ^{1}H NMR spectrum, δ, ppm: 3.08 (6H, s, NMe_2); 6.90 (2H, br. s, NH_2); 7.50 (1H, d, 7-H); 7.09-7.28 (12H, m, NH_2 + $2C_6H_5$); 8.13 (1H, d, 8-H).

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