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SYNTHESIS OF PYRROLOPYRIMIDINES FROM 2,5-DIARYL-3,3,4,4-TETRACYANOPYRROLIDINES

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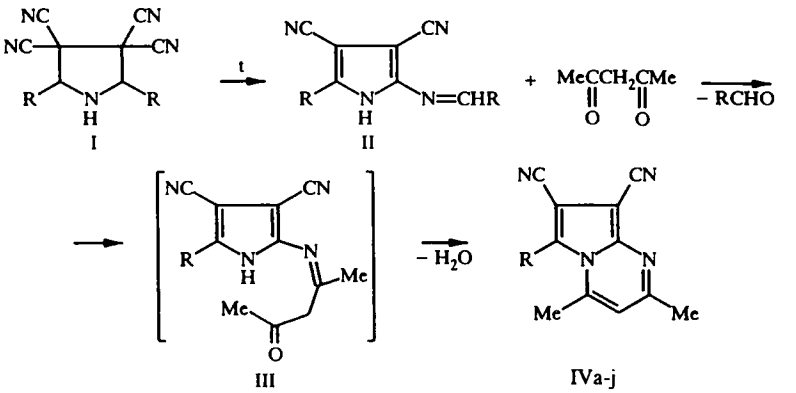
Feasibility has been demonstrated for the synthesis of pyrrolo[1,2-a]pyrimidines by the reaction of 2,5-diaryl-3,3,4,4-tetracyanopyrrolidines I with β-dicarbonyl compounds, which was carried out by the rearrangement of I to give 2-(N-arylidenamino)-5-aryl-3,4-dicaynopyrroles II. A different pathway was found for the reaction of pyrroles II with β-diketones and ethyl acetoacetate. The existence of a latent o-enaminonitrile fragment in these compounds permits their conversion to pyrrolo[2,3-d]pyrimidines.

In previous work [1], we showed that 2,5-disubstituted 3,3,4,4-tetracyanopyrrolidines are acylated at the amino fragment similar to secondary amines. We then attempted to use these compounds as amines. However, the product of the reaction with phenyl isocyanate could not be obtained, probably due to structural features of 2,5-diaryl-3,3,4,4-tetracyanopyrrolidines I, while an attempt to synthesize the corresponding acetylacetone enamine led to an unexpected result. Heating 2,5-diphenyl-3,3,4,4-tetracyanopyrrolidine Ia with acetylacetone in benzene in the presence of *p*-toluenesulfonic acid at reflux and subsequent distillation of the solvent from the decomposition products gave 2,4-dimethyl-6-phenyl-7,8-dicyanopyrrolo[1,2-*a*]pyrimidine IVa in low yield. The structure of Ia was determined by IR spectroscopy and mass spectrometry.



IV a R = Ph, b R = 4-MeOC$_6$H$_4$, c R = 4-FC$_6$H$_4$, d R = 3-ClC$_6$H$_4$, e R = 2-ClC$_6$H$_4$, f R = OMe, g R = OEt, h R = OC$_3$H$_7$-n, i R = OC$_4$H$_9$-n

Under the reaction conditions, pyrrolidine Ia probably undergoes partial rearrangement and the resultant pyrrole IIa undergoes exchange with acetylacetone. Intramolecular cyclization of III leads to pyrrolo[1,2-*a*]pyrimidine IV. The formation of the pyrrolo[1,2-*a*]pyrimidine structure is in accord with reported methods for the preparation of similar structures from 2-aminopyrroles [2, 3].

The assumption that rearrangement is the initial step in this reaction was checked by the reaction of acetylacetone with pyrroles II obtained according to our procedure [4]. A series of pyrrolo[1,2-*a*]pyrimidines IVa-IVe were obtained in yields up

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TABLE 1. Physical Indices of IVa-IVi, VIa-VId, and VIIa-VIIc

Compound	R	R^1	Chemical formula	Found, % / calculated			mp, °C	Yield, %
				C	H	N		
IVa	Ph	—	$C_{17}H_{12}N_4$	74,83 / 74,98	4,31 / 4,44	20,98 / 20,57	296...297	82
IVb	4-$MeOC_6H_4$	—	$C_{18}H_{14}N_4O$	71,39 / 71,51	4,78 / 4,67	18,41 / 18,53	253...254	73
IVc	4-FC_6H_4	—	$C_{17}H_{11}FN_4$	70,25 / 70,34	3,91 / 3,82	19,49 / 19,30	294...295 (dec.)	94
IVd	3-ClC_6H_4	—	$C_{17}H_{11}ClN_4$	66,64 / 66,56	3,69 / 3,61	18,14 / 18,26	305...306	83
IVe	2-ClC_6H_4	—	$C_{17}H_{11}ClN_4$	66,61 / 66,56	3,53 / 3,61	18,19 / 18,26	252...253	71
IVf	OMe	—	$C_{12}H_{10}N_4O$	63,71 / 63,67	4,46 / 4,49	24,76 / 24,65	249...251 (dec.)	74
IVg	OEt	—	$C_{13}H_{12}N_4O$	64,99 / 65,05	5,03 / 5,09	23,32 / 23,21	209...210	88
IVh	OC_3H_7-n	—	$C_{14}H_{14}N_4O$	66,21 / 66,13	5,59 / 5,55	21,95 / 22,03	187...188	84
IVi	OC_4H_9-n	—	$C_{15}H_{16}N_4O$	67,18 / 67,15	6,08 / 6,01	20,79 / 20,88	184...185	93
VIa	Ph	Ph	$C_{25}H_{20}N_4O_2$	73,42 / 73,51	5,06 / 4,94	13,88 / 13,72	257...258	12
VIb	OMe	Ph	$C_{20}H_{18}N_4O_2$	66,34 / 66,29	5,07 / 5,01	15,41 / 15,46	233...234	68
VIc	OMe	2-Fu	$C_{18}H_{16}N_4O_2$	61,42 / 61,36	4,66 / 4,58	15,81 / 15,90	241...242 (dec.)	43
VId	OEt	Ph	$C_{21}H_{20}N_4O_2$	67,11 / 67,01	5,44 / 5,36	14,75 / 14,88	216...217	56
VIIa	Ph	—	$C_{13}H_9N_5$	66,45 / 66,37	3,91 / 3,86	29,64 / 29,77	342...343 (dec.)	74
VIIb	4-$MeOC_6H_4$	—	$C_{14}H_{11}N_5O$	63,48 / 63,39	4,25 / 4,18	26,28 / 26,40	337...338	38
VIIc	4-BrC_6H_4	—	$C13H_8BrN_5$	49,75 / 49,70	2,44 / 2,57	22,37 / 22,29	357...358	72

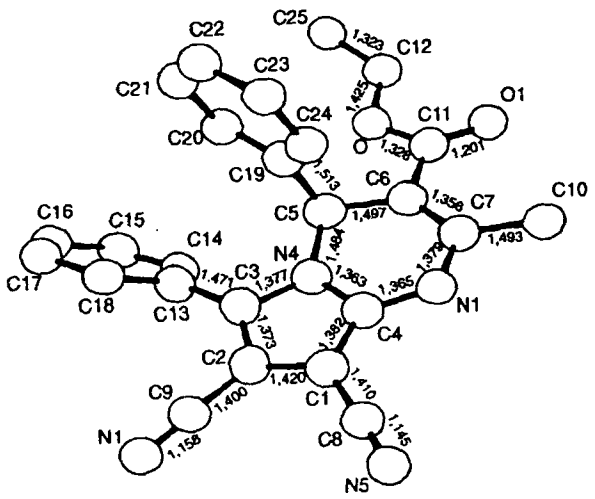


Fig. 1. Molecule of VIa without hydrogen atoms (bond lengths, Å).

to 94%. Analogous 5-alkoxypyrroles IIf-IIi synthesized by the reactions of pyrrolidines I with alcohols [5, 6] react readily with acetylacetone to give IV (Table 1). The spectral data of these compounds are in complete accord with the proposed structure (Table 2).

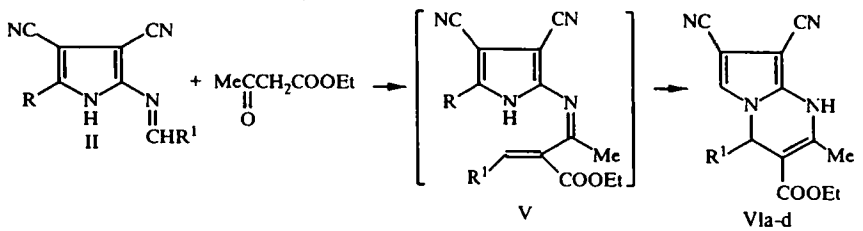
No loss of alcohol occurred in the reaction of pyrroles II when ethyl acetoacetate was used as the β-dicarbonyl compound as might have been expected assuming that the intramolecular cyclization occurs at the ethoxycarbonyl group as in

TABLE 2. IR and Mass Spectra of IVa-IVi, VIa-VId, and VIIa-VIIc

Compound	IR spectrum cm^{-1}			Mass spectrum, m/z (relative intensity, %)
	ν (=CH-)	ν (C ≡N)	ν (C=N)	
IVa	3070	2238	1620	272 (100), 271 (20), 270 (5), 257 (2), 256 (2), 244 (1)
IVb	3060	2238	1618	—
IVc	3060	2235, 2245	1618	290 (100), 289 (19), 288 (9), 182 (9), 145 (9), 81 (6), 69 (12), 67 (10), 57 (10), 44 (39), 42 (12)
IVd	3060	2230, 2245	1620	306 (100), 305 (9), 271 (13), 270 (16), 256 (9), 190 (24), 135 (25), 75 (14), 67 (19), 65 (15), 51 (12)
IVe	3080	2230, 2250	1628	306 (100), 271 (8), 270 (13), 269 (21), 190 (12), 135 (16), 109 (8), 85 (10), 69 (11), 55 (12), 43 (15)
IVf	3070	2220, 2235	1620	226 (15), 212 (17), 211 (100), 156 (8), 143 (8), 130 (7), 107 (12), 77 (8), 67 (18), 57 (10), 45 (15)
IVg	3065	2225, 2240	1620	—
IVh	3065	2230, 2235	1620	—
IVi	3055	2220, 2235	1605	—
	ν (NH)		ν (C=O)	
VIa	3305, 3260, 3215, 3155	2235	1700	408 (100), 362 (38), 335 (41), 334 (36), 331 (23), 232 (33), 165 (12), 128 (37), 103 (11), 77 (20) 45 (29)
VIb	3300, 3235, 3150	2230	1690	362 (100), 347 (55), 317 (15), 302 (69), 273 (24), 201 (15), 186 (34), 155 (29), 128 (41), 91 (6), 77 (22)
VIc	3300, 3230, 3145	2230	1690	352 (100), 347 (32), 323 (91), 307 (48), 291 (91), 263 (55), 186 (86), 130 (52), 108 (50), 91 (36), 44 (45)
VId	3300, 3225, 3145	2235	1690	376 (100), 348 (45), 347 (91), 303 (27), 302 (41), 276 (18), 274 (18), 270 (23), 155 (45), 129 (37), 128 (47)
			δ (NH)	
VIIa	3475, 3320, 3100	2230	1655	235 (100), 208 (41), 184 (22), 180 (9), 155 (10), 118 (6), 105 (12), 104 (22), 77 (26), 55 (8), 45 (98)
VIIb	3475, 3220, 3120	2230	1655	265 (48), 250 (19), 199 (10), 195 (13), 185 (25), 149 (27), 115 (33), 111 (42), 97 (60), 84 (59), 44 (100)
VIIc	3450, 3220, 3100	2225	1650	313 (100), 288 (16), 265 (26), 207 (40), 180 (16), 165 (14), 104 (23), 77 (30), 55 (16), 51 (11), 44 (89)

*The molecular ion peak and 10 strongest fragmentation ion peaks are given.

the synthesis of pyrazolinones. The reaction of these compounds gives 6-substituted 4-aryl-2-methyl-7,8- dicyano-3-ethoxycarbonyl-1,4-dihydropyrrolo[1,2-*a*]pyrimidines VIa-VId (Table 1). Their structure was determined by x-ray diffraction analysis of a monocrystal of IVa (Fig. 1, Table 3).



VI a R = Ph, R^1 = Ph; b R = OMe, R^1 = Et; c R = OMe, R^1 = 2-Fu; d R = OEt, R^1 = Ph

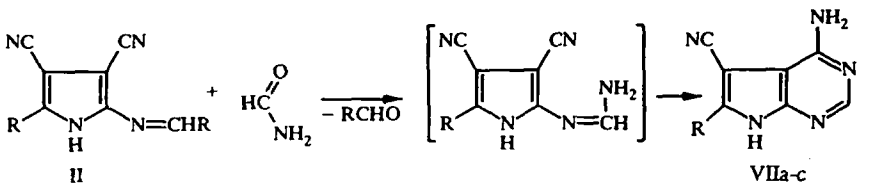
TABLE 3. Atomic Coordinates ($\times 10^4$, $\times 10^3$ for H) in VIa

Atom	x	y	z	Atom	x	y	z
O	7658(5)	-3545(4)	8762(3)	$C_{(19)}$	7306(6)	-1190(6)	7476(3)
$O_{(1)}$	8850(6)	-2430(5)	10166(3)	$C_{(20)}$	7265(7)	-2371(7)	6698(4)
$N_{(1)}$	6252(5)	1640(5)	9559(3)	$C_{(21)}$	8220(8)	-2390(8)	6021(4)
$N_{(4)}$	5087(4)	156(4)	8122(3)	$C_{(22)}$	9226(7)	-1239(8)	6143(4)
$N_{(5)}$	3798(6)	5422(6)	9065(4)	$C_{(23)}$	9303(7)	-64(8)	6915(5)
$N_{(6)}$	1419(6)	3084(5)	6356(3)	$C_{(24)}$	8332(6)	-40(7)	7596(4)
$C_{(1)}$	4239(6)	2601(5)	8345(4)	$C_{(25)}$	885(2)	-547(1)	8039(7)
$C_{(2)}$	3475(5)	1821(5)	7462(3)	$HN_{(1)}$	623(6)	263(6)	1006(3)
$C_{(3)}$	4032(5)	326(5)	7330(3)	$H_{(5)}$	581(5)	-203(5)	809(3)
$C_{(4)}$	5230(5)	1527(5)	8732(3)	$H_{(10)}$	793(6)	4(6)	1122(4)
$C_{(5)}$	6233(6)	-1137(5)	8198(3)	$H_{(14)}$	328(5)	-239(5)	734(3)
$C_{(6)}$	7051(6)	-976(6)	9201(3)	$H_{(15)}$	237(7)	-441(6)	591(4)
$C_{(7)}$	7100(6)	380(6)	9818(3)	$H_{(16)}$	258(6)	-421(6)	437(4)
$C_{(8)}$	4008(6)	4153(6)	8760(4)	$H_{(17)}$	311(6)	-172(6)	417(4)
$C_{(9)}$	2348(6)	2494(5)	6847(4)	$H_{(18)}$	368(7)	41(7)	552(4)
$C_{(10)}$	8010(7)	726(7)	10793(4)	$H_{(20)}$	647(7)	-302(7)	656(5)
$C_{(11)}$	7956(7)	-2341(6)	9455(4)	$H_{(21)}$	819(8)	-352(7)	533(5)
$C_{(12)}$	856(1)	-4958(7)	8866(5)	$H_{(22)}$	979(7)	-95(7)	557(4)
$C_{(13)}$	3609(6)	-925(5)	6522(3)	$H_{(23)}$	983(6)	85(6)	703(4)
$C_{(14)}$	3206(7)	-2353(6)	6648(4)	$H_{(24)}$	837(5)	79(5)	821(3)
$C_{(15)}$	2815(8)	-3503(7)	5876(4)	$H_{(101)}$	777(7)	188(6)	1112(4)
$C_{(16)}$	2815(9)	-3252(7)	4970(5)	$H_{(102)}$	899(6)	67(6)	1084(4)
$C_{(17)}$	3182(9)	-1832(7)	4838(4)	$H_{(121)}$	861(6)	503(6)	955(3)
$C_{(18)}$	3588(7)	-670(6)	5607(4)				

In light of the structure of VI, we may assume that formation of a C=N bond is followed by condensation of liberated benzaldehyde with the adduct of the Knoevenagel exchange reaction. Then, 1,4-addition of the conjugation system occurs to give final product VI.

The presence of benzaldehyde does not affect the yield of the final product, indicating a complex reaction. The exchange step, which probably proceeds through a four-center transition state [7], and the condensation step are virtually simultaneous. The reaction of pyrrole IIa of pyrrole IIa with ethyl benzylidenacetoacetate yields VIa but the low yield of this product is a function of the complexity of the reaction and difficulty in isolating the product. Pyrrolopyrimidines VIb-VId were more readily isolated. The IR and mass spectral data of VIb-VId are in accord with the corresponding data for VIa.

The interesting features of N-arylidenamine fragment used instead of the amino group to form the pyrrolo[1,2-*a*]-pyrimidine structure were employed to obtain pyrrolo[2,3-*d*]pyrimidines unsubstituted at position 7. Heating pyrroles II with formamide at reflux gave in a yield of 74% 4-amino-6-aryl-5-cyanopyrrolo[2,3-*d*]pyrimidines VIIa-VIIc



VII a R = Ph, b R = 4-$MeOC_6H_4$, c R = 4-BrC_6H_4

The IR spectra of VIIa-VIIc show NH stretching bands at 3475-3100 cm^{-1} and NH deformation bands at 1655-1650 cm^{-1} (Table 2). A broad band is found at 3125-3100 cm^{-1} characteristic for the pyrrole NH fragment. The conjugated cyano group gives rise to a strong band at 2230 cm^{-1}. The ^{13}C NMR spectral data for VIIa are in complete accord with the proposed structure. This spectrum shows a set of six carbon atom signals for the pyrrolo[2,3-*d*]pyrimidine structure at 78-156 ppm and a cyano group carbon signal at δ = 116.50 ppm in addition to the signals of the benzene ring carbon atoms.

Thus, original methods have been found for formation of pyrrolopyrimidine structures. Special practical interest may be found in pyrrolo[2,3-*d*]pyrimidines substituted at position 7, which are structural analogs of the aglycone of nucleoside antibiotics [8, 9].

EXPERIMENTAL

The reaction course and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with development by UV light or iodine vapor. The IR spectra were taken for Vaseline mulls on a UR-20 spectrometer. The mass spectra were taken on a Kratos MS 25PFA mass spectrometer with direct inlet of the sample into the ion source at 50 and 70 eV. The ^{13}C NMR spectra were taken on a Bruker WH-90 spectrometer at 22.63 MHz with HMDS as the internal standard. The x-ray diffraction structural analysis was carried out on an Enraf Nonius CAD-4 four-circle automatic diffractometer with MoK_α radiation and ω-scanning using a graphite monochromator.

2,4-Dimethyl-7,8-dicyano-6-phenylpyrrolo[1,2-*a*]pyrimidine (IVa). A reaction mixture consisting of 3.23 g (0.01 mole) 2,5-diphenyl-3,3,4,4,-tetracyanopyrrolidine, 5 ml acetylacetone, and 3-4 small crystals of *p*-toluenesulfonic acid was heated at reflux until the starting pyrrolidine disappeared. After cooling and the addition of 5 ml 2-propanol, the precipitate formed was filtered off, washed with 2-propanol, and recrystallized from methylcellosolve. Drying in the air gave 0.3 g (11%) IVa with mp 296-297°C.

6-Substituted 2,4-Dimethyl-7,8-dicyanopyrrolo[1,2-*a*]pyrimidines (IVa-IVi). Two or three small crystals of *p*-toluenesulfonic acid were added to a suspension of 10 mmoles starting 2-(N-arylidenamino)-3,4-dicyanopyrrole IIa-IIi in 8 ml acetylacetone and heated to reflux. The mixture was heated at reflux for 15-20 min until the starting pyrrole II disappeared. In several cases, a precipitate began to separate out. After cooling of the solution in a water bath, the precipitate formed was filtered off, washed with 2-propanol, and recrystallized. The indices of these products are given in Table 1.

2-Aryl-2-methyl-6-R-7,8-dicyano-3-ethoxycarbonyl-1,4-dihydropyrrolo[1,2-*a*]pyrimidines (VIa-VId). A sample of 10 mmoles 2-(N-arylidenamino)-5-R-3,4-dicyanopyrrole II in 8 ml ethyl acetoacetate in the presence of 2-3 small crystals of *p*-toluenesulfonic acid was heated at reflux until starting pyrrole II completely disappeared (~30 min). The reaction mixture was maintained after cooling for 1 h to give crystallization of the desired product. The mixture was maintained for 24 h in the case of VIa. Then, the precipitate formed was filtered off, washed with 1:1 water–2-propanol, and recrystallized from 2-propanol (Table 1).

X-Ray Diffraction Structural Analysis of VIa. The major crystallographic data: $a = 8.802(4)$, $b = 8.873(3)$, $c = 14.354(3)$ Å, $\alpha = 100.8(3)$, $\beta = 99.51(3)$, $\gamma = 86.15(3)°$, $V = 874.7$ Å^3, space group P1, $Z = 2$. A total of 3119 nonzero reflections were measured at $\theta \leq 25°$, of which 2238 with $I > 3\sigma(I)$ were used to refine the positional and temperature parameters. The structure was solved by the direct method using the SDP MULTAN program package. Refinement of the positional and temperature parameters of the nonhydrogen atoms was carried out in the anisotropic full-matrix approximation. The hydrogen atoms were localized from the Fourier maps and refined isotropically. The hydrogen atoms at $C_{(25)}$ and one of the hydrogen atoms at $C_{(12)}$ could not be localized (Fig. 1). The final $R_f = 6.4\%$. The molecule without hydrogen atoms is shown in Fig. 1, while the atomic coordinates are given in Table 3.

4-Amino-6-aryl-5-cyanopyrrolo[2,3-*d*]pyrimidines (VIIa-VIIc). A reaction mixture consisting of 10 mmoles 2-(N-arylidenamino)-5-aryl-3,4-dicyanopyrrole II in 8 ml formamide was heated at reflux until formation of a precipitate and disappearance of starting pyrrole II (50-80 min). The mixture was then heated at reflux for an additional 10 min and then cooled in a cold water bath. The precipitate formed was filtered off, washed with 2-propanol, and recrystallized from DMF (Table 1). ^{13}C NMR spectrum of VIIa in DMF: $C_{(2)}$ 153.37, $C_{(4)}$ 156.47, $C_{(4a)}$ 78.83, $C_{(5)}$ 102.61, $C_{(6)}$ 142.18, $C_{(7a)}$ 151.13, $C_{(CN)}$ 116.50.

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