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SYNTHESIS OF 1-R-2-AMINO-3-[2-(BENZ)AZOLYL]-4(5H)-KETOPYRROLES

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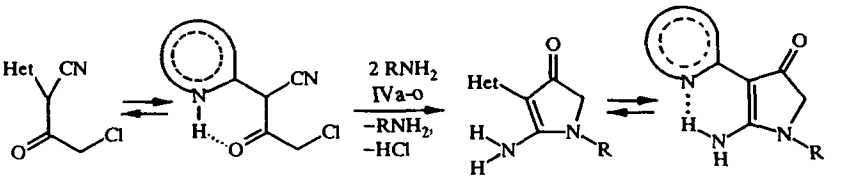
A study has been made of the interaction of 2-[2-(benz)azolyl]3-keto-4-chlorobutanenitriles with primary aliphatic amines. This is a convenient method for the synthesis of 2-amino-3-[2-(benz)azolyl]-4(5H)-ketopyrroles.

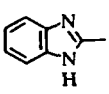
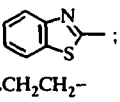
We had previously reported the preparation of 2-(2-azahetaryl)-3-keto-4-chlorobutanenitriles (I, II) by the acylation of 2-cyanomethylazaheterocycles with chloroacetyl chloride [1, 2]. We also studied the interaction of compounds I and II with primary amines, proceeding in two directions: (a) Alkylation of the amine, with subsequent intramolecular addition of the secondary amino group at the nitrile group to form 1-R-2-amino-3-(2-azahetaryl)-4(5H)-ketopyrroles, or (b) intramolecular alkylation under the influence of the amine as a base to obtain pyrrolo[1,2-a]azaheterocycles [2].

Here we are reporting new examples of the interaction of compounds I and II, and also the interaction of a previously unstudied nitrile (III), with aliphatic amines (IVa-n) to obtain 1-R-2-amino-3-(2-azahetaryl)-4(5H)-ketopyrroles (V-VII respectively).

Scheme 1



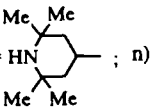
I–III Vb-f,h-o; VIb-e,h-m; VIIa-h,j,k,n

I,V Het =  ; II,VI Het =  ; III,VII Het = 

IV–VII a) R = $PhCH_2$–; b) R =  ; c) R = $C_{12}H_{23}$-cyclo;

d) R = 3,4-$(MeO)_2C_6H_3CH_2CH_2$–; e) R =  ; f) R = C_6H_{11}-cyclo;

g) R = $PhCH_2CH_2$–; h) R = iso-Pr; i) R = n-C_6H_{13}; j) R = sec-Bu;

k) R =  ; l) R =  ; m) R =  ; n) R = $H_2N(CH_2)_5$;

o) R = tert-Bu

We found that with any of the three nitriles, in n-butanol medium with a twofold excess of the amine, the reaction proceeds smoothly, forming the 1-R-2-amino-3-[2-(benz)azolyl]-4(5H)-ketopyrroles Vb-f,h-o, VIb-e,h-m, and VIIa-h,j,k,n with

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TABLE 1. Characteristics of 1-R-2-Amino-3(benzimidazol-2-yl)-4(5H)-ketopyrroles Vb-f,h-o

Compound	Empirical formula	Found N, % / Calculated N, %	mp, °C	Solvent for recrystallization	Yield, %
Vb	$C_{21}H_{13}N_5O$	19,7 / 19,6	254	n-Butanol	72
Vc	$C_{23}H_{32}N_4O$	15,3 / 14,8	269	n-Butanol	70
Vd	$C_{21}H_{22}N_4O_3$	14,7 / 14,8	248	Acetonitrile	53
Ve*	$C_{15}H_{16}N_4O_3S$	12,8 / 12,6	>300	DMF	83
Vf	$C_{17}H_{20}N_4O$	19,5 / 18,9	>300	n-Butanol	74
Vh	$C_{14}H_{16}N_4O$		251	n-Propanol	67
Vi	$C_{17}H_{22}N_4O$	19,0 / 18,8	234	Dioxane	54
Vj	$C_{15}H_{18}N_4O$	20,4 / 20,7	259	Isopropanol	78
Vk	$C_{16}H_{20}N_4O_2$	18,6 / 18,8	255	Acetonitrile	58
Vl	$C_{16}H_{14}N_4O_2$	19,1 / 19,0	254	Methanol	52
Vm	$C_{20}H_{27}N_5O$	20,0 / 19,8	288	Dioxane	67
Vn·HCl†	$C_{16}H_{22}ClN_5O$	21,1 / 20,8	213	n-Butanol	85
Vo	$C_{15}H_{18}N_4O$	20,6 / 20,7	239	Toluene	51

*Found S 9.8%, calculated S 9.7%.

†Found Cl 10.6%, calculated Cl 10.6%.

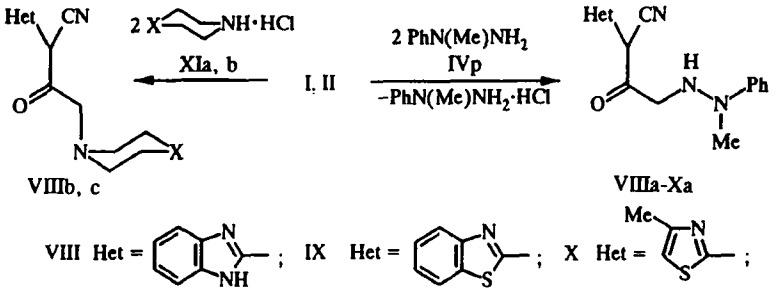
yields of 60-90% (Scheme 1). If the amine needed for this reaction is very expensive or difficult to prepare, the reaction can be performed successfully by using one equivalent of the amine, plus triethylamine to bind the HCl. When 4-amino-2,2,6,6-tetramethylpiperidine IVm is brought into reaction, the interaction proceeds through the primary amino group, since the secondary group carries an extremely high steric overload; however, in this case there is no need for a twofold excess of this diamine, since it acts simultaneously as a base on account of the secondary amino group. As a result, the corresponding aminoketopyrroles Vm and VIm are recovered from the reaction mixture; these are readily converted to the free base by treatment with a caustic solution. A similar picture is observed when using one equivalent of pentamethylenediamine VIn: The interaction involves only one of the amino groups, forming the hydrochlorides of the aminoketopyrroles Vn-VIIn. Similarly, the use of the sterically hindered tert-butylamine IVo gives the corresponding aminoketopyrrole Vo, but with a lower yield (51%). From all of the foregoing results, we can assume that this method for the synthesis of aminoketopyrroles is quite general.

As we had shown previously [3, 4], all of these compounds V-VII exist in the aminoketo form. In their PMR spectra in DMSO-d_6, in addition to the signals of the N-substituent and the 3-azahetaryl substituent, which are located in their respective characteristic regions, we observe a two-proton singlet of the cyclic methylene group in the 3.65-4.00 ppm region. The signals of the protons of the primary amino group are observed in the 8.30-8.60 ppm region in the form of two broadened one-proton signals as a result of nonequivalence of the amino-group protons, or in the form of a broad two-proton singlet as a result of rapid exchange. In the IR spectra of these aminoketopyrroles, there are two strong bands of stretching vibrations of the primary amino group in the 3340-3330 and 3150-3100 cm^{-1} regions, with no absorption in the 1700-1620 cm^{-1} region that is characteristic for a conjugated carbonyl group. Thus, the spectral characteristics indicate the presence of a β-enaminoketone fragment, supporting our interpretation of the structure of the synthesized compounds.

An interesting result was obtained in the action of N-methyl-N-phenylhydrazine IVp on the halonitriles I-III. In the IR spectra of the products, which were obtained with yields of 60-80%, there is a strong band of stretching vibrations of the conjugated nitrile group in the 2200-2280 cm^{-1} region. In their PMR spectra in DMSO-d_6, there is no primary amino-group signal, but there is a signal of the N-phenyl substituent in the form of a two-proton multiplet in the 7.1-7.0 region and a three-

proton multiplet in the 6.65-6.55 ppm region. The two-proton multiplet of the CH_2 group is observed in the 4.5-4.3 ppm region. It is evident that the interaction proceeds through the primary amino group of the hydrazine IVp, since its basicity is 10^5 times higher; however, since the basicity of the hydrazine is approximately one-tenth that of aliphatic amines, the reaction stops in the alkylation stage without subsequent intramolecular addition through the nitrile group. Thus, the products synthesized from compounds I-III and the hydrazine IVp do not have any ketopyrrole ring (VIIIa-Xa respectively) (Scheme 2). Like the nitriles I-III, they may have two tautomeric forms (see Scheme 1).

Scheme 2



VIIIb, IXb, XIa X = CH_2; VIIIc, IXc, XIb X = O

Up to now, the question of the sequence of stages in reactions of this type has remained controversial. Some investigators [5] have proposed initial alkylation of the amine with subsequent intramolecular addition of the secondary amino group through the nitrile group; others [6] have proposed the alternative sequence. Our isolation of the noncyclic products VIIIa-Xa suggests that the first stage of the reaction is alkylation. In order to confirm this hypothesis, we introduced secondary amine hydrochlorides (XIa,b) into the reaction; as a result, we identified the alkylation products VIIIb,c and IXc.

In the PMR spectra (taken in DMSO-d_6) of the noncyclic alkylation products that were obtained, we find a broad one-proton singlet (or two-proton in the case of benzimidazole derivatives) in the 11.0-13.0 region, from the strongly deshielded chelated proton, and also a two-proton singlet in the 3.8-4.6 ppm region, from the $C(O)CH_2N$ group. The protons of the other substituents absorb in their own characteristic regions. In the IR spectra of these compounds, we observe a strong absorption band in the 2200-2180 cm^{-1} region from stretching vibrations of the conjugated nitrile group; there is no absorption in the 1700-1620 cm^{-1} region that is characteristic for conjugated carbonyl groups.

EXPERIMENTAL

The course of the reaction was monitored by TLC on Silufol UV-254 plates in a 9/1 chloroform/methanol system. Infrared spectra were recorded on a Pye Unicam SP 3-300 instrument in KBr tablets. PMR spectra were recorded in DMSO-d_6 or CF_3CO_2D on a Bruker WP-100 SY instrument.

The elemental analyses of all of the synthesized compounds matched the calculated analyses (Tables 1-4). Spectral characteristics are listed in Table 5.

2-(4-Methylthiazol-2-yl)3-keto-4-chlorobutanenitrile III was obtained by a procedure given in [1]; mp 218°C (from dioxane). PMR spectrum (100 MHz, DMSO-d_6): 13.3 (1H, br.s, N−H...O); 6.86 (1H, s, S−CH=); 4.42 (2H, s, CH_2); 2.27 (3H, s, CH_3).

1-R-2-Amino-3-(benzimidazol-2-yl)-4(5H)-ketopyrroles (Vb-f,h-l,o). *A.* To 0.70 g (0.003 mole) of 2-(benzimidazol-2-yl)3-keto-4-chlorobutanenitrile I in 25 ml of n-butanol, 0.0065 mole of the appropriate amine IVb-l,o was added, and the reaction mixture was refluxed 6-10 h, until the original nitrile I had disappeared as indicated by TLC. Then the reaction mass was cooled, and the precipitate *1* was filtered off, washed with n-butanol and water, and recrystallized from an appropriate solvent (see Table 1). The filtrate was evaporated to dryness under vacuum in a rotary evaporator; the residue was drenched with water and triturated. The resulting crystals were filtered off and recrystallized from the same solvent as that used for the precipitate *1*. The two portions of purified crystals were combined. Yields of the products V are indicated in Table 1.

TABLE 2. Characteristics of 1-R-2-Amino-3(benzothiazol-2-yl)-4(5H)-ketopyrroles VIb-e,h-m

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Solvent for recrystallization	Yield, %
		N	S			
VIb	$C_{21}H_{18}N_4OS$	11,9 / 11,7	8,6 / 8,9	281	THF	67
VIc	$C_{23}H_{31}N_3OS$	10,4 / 10,6	8,3 / 8,1	287	n-Butanol	69
VId	$C_{21}H_{21}N_3O_3S$	11,4 / 11,0	8,7 / 8,4	271	DMF	76
VIe	$C_{15}H_{15}N_3O_3S_2$	12,0 / 12,0	18,1 / 18,4	>300	DMF	64
VIh	$C_{14}H_{15}N_3OS$	15,2 / 15,4	11,5 / 11,7	267	n-Butanol	73
VIi	$C_{17}H_{21}N_3OS$	13,4 / 13,3	10,3 / 10,2	246	Dioxane	75
VIj	$C_{15}H_{17}N_3OS$	14,9 / 14,6	11,0 / 11,6	257	Acetonitrile	64
VIk	$C_{16}H_{17}N_3O_2S$	13,8 / 14,0	10,5 / 10,7	232	Acetonitrile	69
VIl	$C_{16}H_{13}N_3O_2S$	13,7 / 13,5	10,8 / 10,3	249	Methanol	88
VIm	$C_{20}H_{26}N_4OS$	15,0 / 15,1	8,1 / 8,6	262	Dioxane	60

TABLE 3. Characteristics of 1-R-2-Amino-3(4-methylthiazolyl-2-yl)-4(5H)-ketopyrroles VIIa-h,j,k,n

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Solvent for recrystallization	Yield, %
		N	S			
VIIa	$C_{15}H_{15}N_3OS$	15,6 / 15,5	11,9 / 11,9	247	n-Butanol	64
VIIb	$C_{18}H_{18}N_4OS$	16,6 / 16,6	9,7 / 9,5	268	DMF	63
VIIc	$C_{20}H_{31}N_3OS$	11,9 / 11,6	8,8 / 8,9	255	n-Butanol	91
VIId	$C_{18}H_{21}N_3O_3S$	12,0 / 12,2	9,5 / 9,3	241	n-Butanol	69
VIIe	$C_{12}H_{15}N_3O_3S_2$	13,5 / 13,4	20,2 / 20,4	>300	DMF	53
VIIf	$C_{14}H_{19}N_3OS$	15,3 / 15,2	11,6 / 11,6	260	Acetonitrile	63
VIIg	$C_{16}H_{17}N_3OS$	14,0 / 14,0	10,9 / 10,7	250	n-Butanol	79
VIIh	$C_{11}H_{15}N_3OS$	17,9 / 17,7	13,5 / 13,5	247	Acetonitrile	80
VIIj	$C_{12}H_{17}N_3OS$	16,6 / 16,7	12,4 / 12,8	210	Ethyl acetate	84
VIIk	$C_{13}H_{17}N_3O_2S$	15,3 / 15,0	11,6 / 11,5	198	Acetonitrile	48
VIIn·HCl*	$C_{13}H_{21}ClN_4OS$	17,9 / 17,7	10,3 / 10,1	267	n-Butanol	72

*Found Cl 11.6%, calculated Cl 11.2%.

B. To 0.70 g (0.003 mole) of the nitrile I in 25 ml of n-butanol, 0.003 mole of an amine IVb-l,o and 0.45 ml (0.0035 mole) of triethylamine were added. The subsequent procedure was the same as in Method A.

1-R-2-Amino-3-(benzothiazol-2-yl)-4(5H)-ketopyrroles (VIb-e,h-l). To 0.75 g (0.003 mole) of 2-(benzothiazol-2-yl)-3-keto-4-chlorobutanenitrile II in 10 ml of n-butanol, 0.0065 mole of an amine IVb-f,h-l was added. The subsequent procedure

TABLE 4. Characteristics of 4-R-2-(2-azahetaryl)-3-ketobutanenitriles VIIIa-c, IXa,c, and Xa

Compound	Empirical formula	Found, % / Calculated, %		mp, °C	Solvent for recrystallization	Yield, %
		N	S			
VIIIa	$C_{18}H_{17}N_5O$	21,7 / 21,9	—	237	Toluene	60
VIIIb	$C_{16}H_{18}N_4O$	19,6 / 19,9	—	236	n-Butanol	18
VIIIc	$C_{15}H_{16}N_4O_2$	19,9 / 19,7	—	253	THF	30
IXa	$C_{18}H_{16}N_4OS$	16,9 / 16,7	9,6 / 9,5	224	n-Butanol	77
IXc	$C_{15}H_{15}N_3O_2S$	14,2 / 13,9	10,3 / 10,6	244	n-Butanol	17
Xa	$C_{15}H_{16}N_4OS$	18,1 / 18,7	10,5 / 10,6	183	n-Octane	58

TABLE 5. Spectral Characteristics of Compounds V-X

Compound	IR spectrum, cm^{-1}	PMR spectrum (DMSO-d_6), δ, ppm; and SSCC (J), Hz
1	2	3
Vb	3310, 3160 (NH_2)	11,84 (1H, br. s, NH_{Het}); 10,88 (1H, s, NHR); 8,39 (2H, s, NH_2); 7,7...6,9 (9H, m, $4H_{Het}$ & $5H_{arom}R$); 3,81 (4H, s, t, J = 8,0, $COCH_2$ & NCH_2R); 3,04 (2H, t, J = 8,0, CCH_2R)
Vc	3300, 3150 (NH_2)	11,9 (1H, br. s, NH); 8,37 (2H, s, NH_2); 7,45 (2H, m, H_{Het}); 7,04 (2H, m, H_{Het}); 4,02 (1H, m, CHR); 3,82 (2H, s, $COCH_2$); 1,34 (22H, m, $11CH_2R$)
Vd	3320, 3180 (NH_2)	11,8 (1H, br. s, NH); 8,38 (2H, s, NH_2); 7,47 (2H, m, H_{Het}); 7,04...6,85 (5H, m, $2H_{Het}$ & $3H_{arom}R$); 3,78 (4H, s, distorted at base, $COCH_2$ & NCH_2R); 3,74 & 3,71 (6H, two s, OCH_3); 2,83 (2H, t, CCH_2R)
Ve*	3300, 3140 (NH_2)	7,8...7,6 (4H, m, H_{Het}); 5,14 (1H, m, NCHR); 4,56 (2H, s, $COCH_2$); 4,1...3,3 (4H, m, $2SCH_2R$); 3,0...2,6 (2H, m, CCH_2R)
Vf	3280, 3180 (NH_2)	11,6 (1H, br. s, NH); 8,38 (2H, s, NH_2); 7,46 (2H, m, H_{Het}); 7,03 (2H, m, H_{Het}); 3,80 (3H, s, distorted at base, $COCH_2$ & NCHR); 1,75...1,39 (10H, m, $5CH_2R$)
Vh	3300, 3120 (NH_2)	11,55 (1H, s, NH); 8,42 (2H, s, NH_2); 7,43 (2H, m, H_{Het}); 7,02 (2H, m, H_{Het}); 4,23 (1H, m, NCH); 3,78 (2H, s, $COCH_2$); 1,19 (6H, d, $2CH_3$)
Vi	3280, 3175 (NH_2)	10,90 (1H, s, NH); 8,16 (2H, s, NH_2); 7,45 (2H, m, H_{Het}); 7,07 (2H, m, H_{Het}); 3,85 (2H, s, $COCH_2$); 3,46 (2H, t, NCH_2R); 1,63...1,34 (8H, m, $4CH_2R$); 0,90 (3H, t, CH_3)
Vj	3310, 3120 (NH_2)	11,60 (1H, s, NH); 8,68 (1H, s, N...HNH_2); 8,22 (1H, s, N...HNH_2); 7,46 (2H, m, H_{Het}); 7,03 (2H, m, H_{Het}); 4,01 (1H, m, NCH); 3,76 (2H, s, $COCH_2$); 1,56 (2H, m, CH_2R); 1,16 (3H, d, CH_3); 0,86 (3H, t, CH_3)
Vk	3290, 3130 (NH_2)	11,75 (1H, br. s, NH); 8,38 (2H, s, NH_2); 7,47 (2H, m, H_{Het}); 7,04 (2H, m, H_{Het}); 4,05...3,33 (7H, m, $COCH_2$, OCHR, OCH_2R & NCH_2R); 2,11...1,44 (4H, m, $2CH_2R$)
Vl	3320, 3160 (NH_2)	11,9 (1H, br. s, NH); 8,61 (2H, s, NH_2); 7,67 (1H, distorted s, OCHR); 7,50 (2H, m, H_{Het}); 7,08 (2H, m, H_{Het}); 6,46 (2H, distorted s, 2CCHR); 4,75 (2H, s, CH_2R); 3,81 (2H, s, $COCH_2$)
Vm	3350, 3180 (NH_2)	11,58 (1H, br. s, NH_{Het}); 8,67 (1H, s, N...HNH_2); 8,28 (1H, s, N...HNH_2); 7,45 (2H, m, H_{Het}); 7,04 (2H, m, H_{Het}); 4,33 (1H, m, NCHR); 3,76 (2H, s, $COCH_2$); 3,45 (1H, br. s, NHR); 1,57 (4H, d, d, $2CH_2R$); 1,28 (6H, s, CH_3); 1,12 (6H, s, CH_3)
Vn·HCl	3300, 3060 (NH_2)	11,71 (1H, br. s, NH); 8,48 (2H, s, NH_2); 7,94 (3H, br. s $NH_3^+Cl^-$); 7,45 (2H, m, H_{Het}); 7,03 (2H, m, H_{Het}); 3,88 (2H, s, $COCH_2$); 3,37 (2H, t, NCH_2); 2,77 (2H, t, $CH_2NH_3^+Cl^-$); 1,57 (6H, m, $3CH_2R$)
Vo	3360, 3200 (NH_2)	11,57 (1H, br. s, NH); 8,38 (2H, s, NH_2); 7,45 (2H, m, H_{Het}); 7,05 (2H, m, H_{Het}); 3,99 (2H, s, CH_2); 1,47 (9H, s, t-Bu)
VIb	3300, 3140 (NH_2)	10,52 (1H, s, NH); 8,41 (2H, s, NH_2); 7,9...6,9 (9H, m, $4H_{Het}$ & $5H_{arom}R$); 3,84 (4H, s, t, J = 8,0, $COCH_2$ & NCH_2R); 3,00 (2H, t, J = 8,0, CCH_2R)
VIc	3290, 3120 (NH_2)	8,54 (2H, s, NH_2); 7,85 (2H, m, H_{Het}); 7,30 (2H, m, H_{Het}); 4,04 (1H, m, NCHR); 3,87 (2H, s, $COCH_2$); 1,35 (22H, m, $11CH_2R$)

TABLE 5 (continued)

1	2	3
VId	3320, 3160 (NH_2)	8,1 ...9,0 (2H,br. s, NH_2); 7,80 (2H, m, H_{Het}); 7,30 (2H, m, H_{Het}); 6,85...6,95 (3H, two distorted s, $H_{arom}R$; 3,79 (4H, s, distorted at base, $COCH_2$ & NCH_2R); 3,73...3,71 (6H, two s, OCH_3); 2,94 (2H, t, J = 7,0, CCH_2R)
VIe	3290, 3120 (NH_2), 1300, 1110 (SO_2)	8,71 (2H, s, NH_2); 7,85 (2H, m, H_{Het}); 7,30 (2H, m, H_{Het}); 4,92 (1H, m, NCHR); 3,95 (2H, s, $COCH_2$); 3,44 (4H, m, $2SCH_2R$); 2,4 (2H, m, CCH_2R)
VIh	3310, 3170 (NH_2)	8,50 (2H,br. s, NH_2); 7,8 (2H, m, H_{Het}); 7,3 (2H, m, H_{Het}); 4,27 (1H, m, NCH); 3,81 (2H, s, $COCH_2$); 1,21 (6H, d, J = 10,0, $2CH_3$)
VIi	3320, 3150 (NH_2)	8,46 (2H,br. s, NH_2); 7,80 (2H, m, H_{Het}); 7,28 (2H, m, H_{Het}); 3,85 (2H, s, $COCH_2$); 3,45 (2H, t, J = 7NCH_2R); 1,57...1,29 (8H, m, $4CH_2R$); 0,87 (3H, t, CH_3)
VIj	3310, 3160 (NH_2)	8,54 (2H,br. s, NH_2); 7,85 (2H, m, H_{Het}); 7,23 (2H, m, H_{Het}); 4,05 (1H, m, NCHR); 3,76 (2H, s, $COCH_2$); 1,53 (2H, m, CH_2R); 1,17 (3H, d, J = 8,0, CH_3); 0,86 (3H, t, CH_3)
VIk	3295, 3120 (NH_2)	8,47 (2H, s, NH_2); 7,85 (2H, m, H_{Het}); 7,25 (2H, m, H_{Het}); 4,2...3,4 (7H, m, $COCH_2$, OCHR, OCH_2R & NCH_2R); 2,11...1,44 (4H, m, $2CH_2R$)
VIl	3255, 3055 (NH_2)	8,74 (2H,br. s, NH_2); 7,7 (3H, m, $2H_{Het}$ & OCHR); 7,3 (2H, m, H_{Het}); 6,47 (2H, distorted s, 2CCHR); 4,77 (2H, s, CH_2R); 3,79 (2H, s, $COCH_2$)
VIm	3340, 3170 (NH_2)	8,60 (2H,br. s, NH_2); 7,8 (2H, m, H_{Het}); 7,4 (2H, m, H_{Het}); 4,38 (1H, m, NCHR); 3,77 (2H, s, $COCH_2$); 3,56 (1H,br. s, NH); 1,57 (4H, d.d, $2CH_2R$); 1,26 (6H, s, $2CH_3$); 1,09 (6H, s, $2CH_3$)
VIIa	3300, 3160 (NH_2)	8,54 (2H, s, NH_2); 7,32 (5H, distorted s, Ph); 6,75 (1H, s, H_{Het}); 4,72 (2H, s, CH_2R); 3,69 (2H, s, $COCH_2$); 2,33 (3H, s, CH_3)
VIIb	3240, 3090 (NH_2)	10,87 (1H, s, NH); 8,33 (2H, s, NH_2); 7,7...6,9 (5H, m, H arom R); 6,72 (1H, s, H_{Het}); 3,74 (4H, s, t, J = 10,5, $COCH_2$ & NCH_2R); 3,00 (2H, t, J = 10,5, CCH_2R); 2,31 (3H, s, CH_3)
VIIc	3320, 3160 (NH_2)	8,3 (2H,br. s, NH_2); 6,8 (1H, s, H_{Het}); 4,0 (1H, m, NCHR); 3,8 (2H, s, $COCH_2$); 3,3 (3H, s, CH_3); 1,9...1,2 (22H, m, $11CH_2$)
VIId	3320, 3170 (NH_2)	8,29 (2H, br. s NH_2); 6,85 (3H, distorted d, $H_{arom}R$; 6,72 (1H, s, H_{Het}); 3,68 (2H, t, J = 7,5, NCH_2); 3,73...3,71 (8H, 3 s, $COCH_2$ & $2OCH_3$); 2,81 (2H, t, J = 7,5, $ArCH_2$); 2,31 (3H, s, CH_3)
VIIe	3290, 3145 (NH_2), 1310, 1120 (SO_2)	8,51 (2H,br. s, NH_2); 6,77 (1H, s, H_{Het}); 4,87 (1H, m, CHR); 3,87 (2H, s, $COCH_2$); 3,41 (6H, m, $3CH_2R$); 2,31 (3H, s, CH_3)
VIIf	3300, 3160 (NH_2)	8,31 (2H, s, NH_2); 6,73 (1H, s, H_{Het}); 3,73 (3H, s, distorted at base, $COCH_2$ & CHR); 2,30 (3H, s, CH_3); 1,73...1,37 (10H, m, $5CH_2R$)
VIIg	3295, 3120 (NH_2)	8,28 (2H, s, NH_2); 7,29 (5H, s, Ph); 6,70 (1H, s, H_{Het}); 3,69 (4H, s, t, J = 7, $COCH_2$ & NCH_2); 2,89 (2H, t, J = 7,0, $PhCH_2$); 2,30 (3H, s, CH_3)
VIIh	3300, 3040 (NH_2)	8,3 (2H,br. s, NH_2); 6,70 (1H, s, H_{Het}); 4,20 (1H, m, NCH); 3,70 (2H, s, CH_2); 2,30 (3H, s, CH_3); 1,17 (6H, d, J = 7,5, CH_3)
VIIi	3310, 3170 (NH_2)	8,29 (2H, br. s, NH_2); 6,72 (1H, s, H_{Het}); 3,77 (2H, s, $COCH_2$); 3,39 (2H, t, J = 10,0, NCH_2); 1,54...1,27 (8H, m, $4CH_2$); 2,30 (3H, s, $CH_{3\ Het}$); 0,87 (3H, t, CH_3R)
VIIj	3310, 3130 (NH_2)	8,30 (2H,br. s, NH_2); 6,70 (1H, s, H_{Het}); 3,97 (1H, m, NCHR); 3,66 (2H, s, $COCH_2$); 2,30 (3H, s, $CH_{3\ Het}$); 1,54 (2H, m, CH_2R); 1,14 (3H, d, CH_3R); 0,84 (3H, t, CH_3R)
VIIk	3300, 3160 (NH_2)	8,29 (2H, s, NH_2); 6,73 (1H, s, H_{Het}); 4,2...3,2 (7H, m, $COCH_2$ + OCHR + OCH_2R + NCH_2R); 2,31 (3H, s, CH_3); 2,0...1,4 (4H, m, $2CH_2R$)
VIIn·HCl	3300, 3160 (NH_2)	8,33 (2H, s, NH_2); 6,70 (1H, s, H_{Het}); 3,77 (2H, s, $COCH_2$); 3,44 (5H, s, t, J = 7,0, NCH_2 + $NH_3^+Cl^-$); 2,74 (2H, t, J = 8,0, $CH_2NH_3^+Cl^-$); 2,31 (3H, s, CH_3); 1,54 (6H, m, $3CH_2$)
VIIIa	2180 (CN)	12,87 (2H, s, NH_{Het}); 7,45 (2H, m, H_{Het}); 7,04 (4H, m, $2H_{Het}$ & $2m$-H_{Ph}); m, 6,65 (3H, m, $2o$- & $1p$-H_{Ph}); 4,41 (2H, s, CH_2); 3,7 (1H, s, NH); 3,06 (3H, s, NCH_3)
VIIIb	2190 (CN)	7,43 (2H, m, H_{Het}); 7,08 (2H, m, H_{Het}); 3,82 (2H, s, $COCH_2$); 2,93 (4H, t, $2CH_2N$); 1,62 (6H, m, 3CH)
VIIIc	2200 (CN)	12,7 (2H,br. s, NH); 7,47 (2H, m, H_{Het}); 7,20 (2H, m, H_{Het}); 3,58 (4H, t, $2CH_2O$); 3,34 (2H, s, $COCH_2$); 2,54 (4H, t, $2CH_2N$)
IXa	2185 (CN)	13,5 (1H, s, NH...O); 7,0...8,0 (6H, m, $4H_{Het}$ & $2m$-H_{Ph}); 6,6 (3H, m, $2o$- & $1p$-H_{Ph}); 4,49 (2H, s, CH_2); 3,7 (1H, s, NH); 3,04 (3H, s, NCH_3)
IXc	2185 (CN)	10,55 (1H, br. s, NH); 7,0...7,6 (4H, m, H_{Het}); 4,95 (2H, s, $COCH_2$); 3,93 (4H, t, $2CH_2O$); 3,40 (4H, t, $2CH_2N$)
Xa	2195 (CN)	13,1 (1H, s, NH—O); 7,13 (2H, d.d, J = 7,0 & J = 8,0, m-H_{Ph}); 6,59 (3H, m, $2o$- & $1p$-H_{Ph}); 4,37 (2H, s, CH_2); 3,3 (1H,br. s, NH); 3,01 (3H, s, NCH_3); 2,26 (3H, s, $CH_{3\ Het}$)

*PMR spectrum taken in CF_3CO_2D.

was the same as shown for Method A. The products VI can also be obtained by Method B. The recrystallization solvents and the product yields are listed in Table 2.

1-R-2-Amino-3-(4-methylthiazol-2-yl)-4(5H)-ketopyrroles (VIIa-h,j,k). To 0.65 g (0.003 mole) of 2-(4-methylthiazol-2-yl)-3-keto-4-chlorobutanenitrile III in 5 ml of n-butanol, 0.0065 mole of an amine IVa-h,j,k was added. The subsequent procedure was the same as shown for Method A. The products VII can also be synthesized by Method B. The recrystallization solvents and the product yields are listed in Table 3.

1-(2,2,6,6-Tetramethylpiperidin-4-yl)-4(5H)-ketopyrrolesandl-(5-aminoamyl)-2-amino-3-[2-(benz)azolyl]-4(5H)-ketopyrroles (Vm,n, VIm, VIIn). To 0.003 mole of a 2-(2-azahetaryl)-3-keto-4-chlorobutanenitrile I-III in 25, 10, or 5 ml of n-butanol, respectively, 0.40 ml (0.0035 mole) of cadaverine IVn or 0.55 ml (0.0035 mole) of 4-amino-2,2,6,6-tetramethylpiperidine IVm was added. The mixture was refluxed 8-12 h until the original nitrile I-III had disappeared as indicated by TLC. The mixture was cooled, and the precipitate was filtered off and washed with n-butanol. The resulting crystals were suspended in water, and a 2% aqueous NaOH solution was added until the mixture gave an alkaline reaction. Then the suspension was heated to boiling and cooled. If the reaction was still alkaline, the crystals were filtered off and washed with water; otherwise, the treatment with 2% NaOH solution was repeated. The product yields are shown in Tables 1-3.

4-R-2[2-(Benz)azolyl]-3-ketobutanenitriles (VIIIa-c, IXa,c, Xa). To 0.003 mole of a nitrile I-III in 25, 10, or 5 ml of n-butanol, respectively, there was added 0.0065 mole of N-methyl-N-phenylhydrazine IVp, the hydrochloride XIa, or piperidine XIb.* The mixture was refluxed 7-10 h until the original nitrile I-III had disappeared as indicated by TLC. Subsequently, Method A was followed. The recrystallization solvents and product yields are listed in Table 4.

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*As in Russian original; piperidine is identified as XIa in Scheme 2 — Translator.