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STEREOSELECTIVE SYNTHESIS AND STRUCTURE OF 3,4-*trans*-6-AMINO-4-ARYL-3-CARBAMOYL-5-CYANO-1,2,3,4-TETRAHYDROPYRIDIN-2(1H)-THIONES

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*Condensation of thiocarbamoylacetamide with arylidenemalononitrile or the three-component condensation of thiocarbamoylacetamide with aldehydes and malononitrile in the presence of triethylamine occurred regioselectively to give triethylammonium 6-amino-4-aryl-3-carbamoyl-5-cyano-1,4-dihydropyridine-2-thiolates. Protonation of the latter occurred stereoselectively to give 3,4-*trans*-6-aryl-3-carbamoyl-5-cyano-1,2,3,4-tetrahydropyridin-2(1H)-thiones. The ^1H NMR spectrum and single x-ray crystallography indicate that the dihydropyridine ring has the sofa conformation with *trans*-pseudodiaxial orientation of the Ar and $CONH_2$ groups and *trans*-pseudoequatorial orientation of atoms 3-H and 4-H.*

Thiocarbamoylacetamide (I) is used in the synthesis of functionally substituted 3-carbamoylpyridin-2(1H)-thiones [1, 2] from which 3-oxo-2,3-dihydroisothiazolo[5,4-*d*]pyridines with a wide range of biological activities can be obtained [3-6]. 6-Amino-4-aryl-3-carbamoyl-5-cyano-2-pyridine-2-thiols have been synthesized by the reaction of the amide I with arylidenemalononitriles in boiling ethanol in the presence of triethylamine [7].

We have developed a successful stereoselective method for the synthesis of substituted 3,4-*trans*-3-carbamoyl-1,2,3,4-tetrahydropyridin-2(1H)-thiones (III) by the reaction of thiocarbamoylacetamide I with unsaturated nitriles (II). We have established that when amide I is heated for a short while with the arylidenemalononitriles IIa-e at 40-50°C in absolute ethanol in the presence of triethylamine, the product is the salt of the corresponding 1,4-dihydropyridine-2(1H)-thiolate (IVa-e) (method A) and not the dehydrogenated substituted pyridine-2-thiol as shown earlier [7]. The yield of the salt is 63-77% under these conditions. The regioselectivity of the reaction is determined by the intermediate Michael adduct (V). It is probable that the thiocarbamoyl is the most nucleophilic and reacts with one of the cyano groups in closing the pyridine ring and forming the salt IV. It is interesting to note that 4-aryl-2,6-diamino-3,5-dicyano-4H-thiopyranes are formed from arylidenemalononitriles and cyanothioacetamide under analogous conditions, products in which the sulfur atom of the thioacetamide group rather than the nitrogen atom is included in the ring [8].

Salts IVa and IVb were also obtained in excellent yields (81 and 78% respectively) under analogous conditions by the three component condensation of compound I with malononitrile (VI) and the corresponding aldehyde (VIIa and VIIb) (method B). The required pyridines (IIIa-e) were obtained either by acidifying the salts IVa-e in ethanol or by directly acidifying the reaction mixture (compounds Ia, IVc, IVe) with 10% hydrochloric acid. Protonation of the salts occurred stereoselectively to give the 3,4-*trans*-isomers of substituted 1,2,3,4-tetrahydropyridin-2(1H)-thiols III.

The structures of compounds III and IV were confirmed by physicochemical methods (Tables 1 and 2). The IR spectra of the salts IV contained deformation vibrations of the amino group and also cyano and carbonyl absorptions shifted to low frequency in comparison with the corresponding bands in the IR spectra of compounds III. This probably results in delocalization of electron density in the pyridine ring and increased conjugation with these functional groups.

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TABLE 1. Yield and Characteristics of 1,4-Dihydropyridin-2-thiolates IVa-e

Compound	Molecular formula	(Found, %) (Calc, %)			mp, °C	IR Spectrum, ν, cm^{-1}	^{1}H NMR Spectrum, δ, ppm, J, Hz							Yield, % (method)
		C	H	N			4-H, s, 1H	NH_2 s, 2H	$CONH_2$ s, 2H	Ar	CH_3 t, 9H	CH_2 q, 6H	N^+H s, 1H	
IVa	$C_{19}H_{27}N_5OS$	60,84 61,10	6,93 7,29	18,61 18,75	179...181	3435, 3335, 3245 (N^+H, NH_2), 2167 (CN), 1634, 1595	4,62	5,35	6,12 , 7,45	7,12...7,18 m	1,09	2,83	10,21	73 (A), 81 (B)
IVb	$C_{19}H_{26}BrN_5OS$	50,12 50,44	5,44 5,79	15,05 15,48	173...175	3480, 3397, 3320, 3245 (N^+H, NH_2), 2178 (CN), 1645, 1605	4,58	5,46	5,93, 7,55	7,09 d (2H), 7,35 d (2H)	1,12	2,96	10,25	63 (A), 78 (B)
IVc	$C_{19}H_{26}FN_5OS$	58,07 58,29	6,52 6,69	17,73 17,89	185...187	3455, 3368, 3215 (N^+H, NH_2), 2177 (CN), 1635, 1600	4,92	5,43	6,05, 7,63	6,95...7,96 m	1,14	3,00	10,30	77 (A)
IVd	$C_{17}H_{25}N_5OS_2$	53,96 53,80	6,40 6,64	18,05 18,45	184...186	3449, 3335, 3235 (N^+H, NH_2), 2178 (CN), 1635, 1600	4,89	5,60	5,60, 7,63	6,66 d (1H, 3'-H), 6,70 m (1H, 4'-H), 7,08 d (1H, 5'-H)	1,14	3,00	10,17	72 (A)

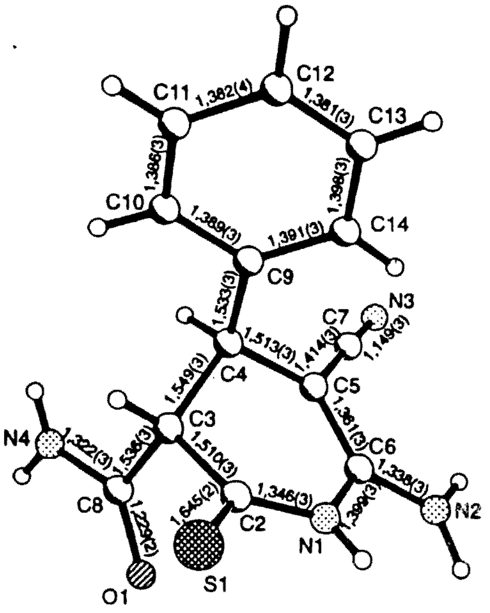
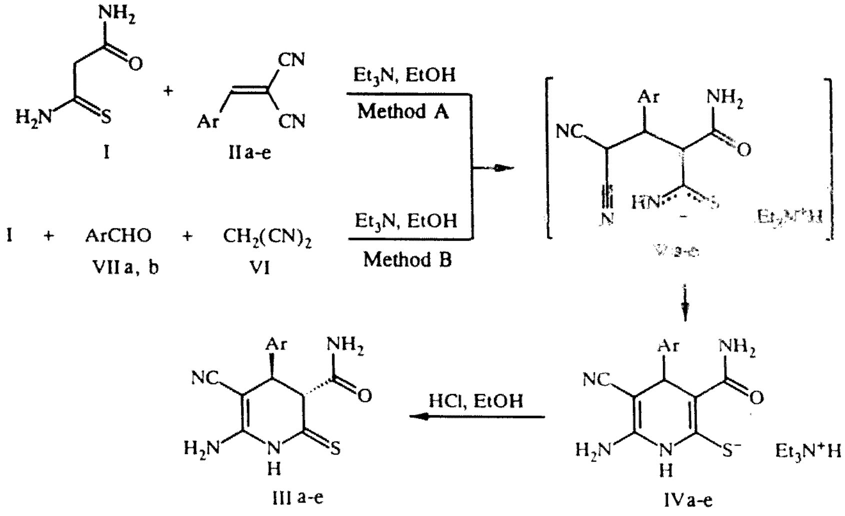


Fig. 1. Overall view and bond lengths for molecule IIIa.



II–V, VII a Ar = Ph, b Ar = 4-BrC$_6$H$_4$, c Ar = 2-FC$_6$H$_4$, d Ar = 2-C$_4$H$_3$S, e Ar = 2,4-Cl$_2$C$_6$H$_3$

Signals for NH and Ar protons are present in the ^{1}H NMR spectra of salts IV (Table 1). The signal for 4-H is a singlet in the range 4.58-4.92 ppm. Resonances for 3-H and 4-H in compounds III appear as two doublets 3.88-4.06 and 3.96-4.29 ppm with $^3J_{H3,H4}$ = 3.3-3.8 Hz. Calculations of the torsion angles $\varphi C_{(3)}H\text{-}C_{(4)}H$ from these coupling constants using the Karplus-Conroy equation [9] gives two possible values, 62-68° and 108-112°. Hence the 3-H and 4-H atoms are in either pseudoaxial-equatorial or pseudoequatorial conformations. In order to establish the structure of the pyridines III unequivocally we carried out an x-ray crystallographic study of compound IIIa. The general shape of the molecule and the bond lengths are shown in Fig. 1 and the bond angles are given in Table 3.

The heterocyclic ring has a distorted sofa conformation: atom $C_{(3)}$ is 0.622 Å out of the $C_{(2)}N_{(1)}C_{(6)}C_{(5)}C_{(4)}$ plane (planar with a precision of ±0.052 Å). Rotation of the pseudoaxial phenyl substituent relative to the planar part of the heterocycle by 86.9° is probably due to intramolecular steric non-bonding interactions: $C_{(3)}\ldots C_{(10)}$ 3.046(3) Å and $C_{(5)}\ldots C_{(14)}$ 2.967(3) Å (twice the van der Waal's radius of the carbon atom is 3.40 Å [10]). Fig. 2 shows the Newman projection of the molecule along the $C_{(3)}-C_{(4)}$ bond from which it is seen that the phenyl substituent is *trans* to the carbamoyl group (torsion

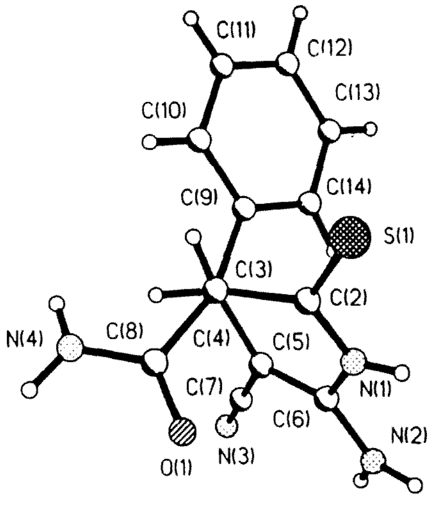


Fig. 2. Newman projection of molecule IIIa along the $C_{(3)}-C_{(4)}$ bond.

angle $C_{(8)}C_{(3)}C_{(4)}C_{(9)}$ 159.6°). The latter is oriented perpendicular to the plane of the heterocycle (torsion angle $N_{(1)}C_{(2)}C_{(3)}C_{(8)}$ 82.0°). Atoms 3-H and 4-H are *trans*-pseudoequatorial (torsion angle $H_{(3)}C_{(3)}C_{(4)}H_{(4)}$ −73.1°), displaced from the planar section of the ring by 0.43 and 0.49 Å respectively.

Conjugation in the $S_{(1)}{=}C_{(2)}-N_{(1)}-C_{(6)}{=}C_{(5)}$ unit, coupled to the CN and NH_2 groups, is evident from the variation in bond lengths from standard values.

The intermolecular hydrogen bonds $N_{(2)} - H_{(2,2)}\ldots O_{(1)}$ $(2 - x, y, 1.5 - z)$($N_{(2)}\ldots O_{(1)}$ 2.863(3), $N_{(2)} - H_{(2,2)}$ 0.90(3), $H_{(2,2)}\ldots O_{(1)}$ 1.99(3) Å, angle $N_{(2)} - H_{(2,2)}\ldots O_{(1)}$ 164(2)°) and $N_{(4)} - H_{(4,2)}\ldots O_{(1)}$ $(2 - x, 1 - y, 1 - z)$ ($N_{(4)}\ldots O_{(1)}$ 3.051(3), $N_{(4)} - H_{(4,2)}$ 0.91(3), $H_{(4,2)}\ldots O_{(1)}$ 2.16(3) Å, angle $N_{(4)} - H_{(4,2)}\ldots O_{(1)}$ 168(2)°) knit the molecules of compound IIIa into a three-dimensional network.

Hence it is established that the Ar and $CONH_2$ substituents are disposed *trans*-diaxially and atoms 3-H and 4-H have a *trans*-equatorial orientation in compounds III.

EXPERIMENTAL

Melting points were determined with a Kofler hot stage, IR spectra were recorded in KBr disks on a Perkin-Elmer 457 spectrometer, ^1H NMR spectra were recorded in DMSO-D_6 with a Bruker WM-250 spectrometer and elemental analysis for C, H and N was carried out with a Perkin-Elmer C, H, N analyzer.

Single Crystal X-Ray Diffraction Study of Compound IIIa. Crystals of compound IIIa are monoclinic: at −85°C $a = 13.866(2)$, $b = 10.466(3)$, $c = 17.896(4)$ Å, $\beta = 107.79(2)°$, $V = 2468$ Å^3, $d_{calc} = 1.472$ g cm^{-3}, $Z = 8$, space group C2/c. Cell parameters and the intensities of 3951 independent reflexions were measured on a Syntex P21 four-circle automatic diffractometer (λMoK_α, β filter, $\theta/2\theta$ scanning to $\theta_{max} = 27°$). Structure solution by direct methods revealed all nonhydrogen atoms and refinement was carried out by full matrix least squares in the anisotropic approximation for all nonhydrogen atoms using 2130 reflexions with $I > 3\sigma(I)$. All hydrogen atoms appeared in difference syntheses and were refined isotropically. The final residual factor was $R = 0.040$ ($R_w = 0.040$). Calculations were carried out with the SHELXTL PLUS program (PC version). Atomic coordinates are given in Table 4 (thermal factors for the atoms can be obtained from the authors).

Triethylammonium 6-Amino-4-aryl-3-carbamoyl-5-cyano-1,4-dihydropyridine-2-thiolates (IVa-e). A. Triethylamine (1.4 cm^3, 10 mmol) was added to a suspension of an arylmethylenemalononitrile 10 mmol) and thiocarbamoylacetamide (1.18 g, 10 mmol) in absolute ethanol (30 cm^3) and the mixture was heated to 40-50°C with stirring until the starting materials had dissolved. Crystals of IV began to form on the walls of the flask within 5-10 min. The crystals were filtered off and washed with ethanol and hexane.

B. Triethylamine (1.4 cm^3, 10 mmol) was added to a suspension of malononitrile VI (0.7 g, 10 mmol), aldehyde VIIa or VIIb (10 mmol) and amide I (10 mmol) in absolute ethanol (30 cm^3). Further treatment was as in method A.

TABLE 2. Yields and Characteristics of 3,4-*trans*-1,2,3,4-Tetrahydropyridin-2(1H)-thiones IIIa-e

Compound	Molecular formula	(Found, %) (Calc., %) C	H	N	mp, °C	IR Spectrum, ν, cm^{-1}	^{1}H NMR Spectrum, δ, ppm, J, Hz 3-H d, 1H	4-H d, 1H	NH_2 s, 2H	$CONH_2$ s, s, 2H	Ar	NH s, 1H	Yield, % (method)
IIIa	$C_{13}H_{12}N_4OS$	56,82 57,34	3,95 4,44	20,08 20,57	221...223	3480, 3350, 3230 (NH, NH$_2$), 2186 (CN), 1687, 1650	3,88 J = 3,5	3,96 J = 3,5	6,05	7,01, 7,45	7,20...7,38 m	11,50	49 (A) 51 (B)
IIIb	$C_{13}H_{11}BrN_4OS$	43,85 44,46	2,84 3,16	15,53 15,95	204...205	3460, 3365, 3245 (NH, NH$_2$), 2188 (CN), 1680 br.	3,85 J = 3,7	3,90 J = 3,7	6,27	7,31, 7,62	7,20 d (1H), 7,55 d (1H)	11,64	47 (A)
IIIc	$C_{13}H_{11}FN_4OS$	53,44 53,78	3,57 3,82	19,04 19,30	255...256	3465, 3365, 3230 (NH, NH$_2$), 2206 (CN), 1683, 1650	3,90 J = 3,3	4,16 J = 3,3	6,22	7,44*	7,09...7,38 m (5H, C_6H_4, NHCO)	11,70	43 (A) 74 (B)
IIId	$C_{11}H_{10}N_4OS_2$	47,05 47,47	3,34 3,62	19,82 20,13	237...239	3468, 3330, 3215 (NH, NH$_2$), 2188 (CN), 1645, 1610	4,06 J = 3,5	4,12 J = 3,5	6,26	7,20, 7,68	6,97 m (2H, 3'-H, 4'-H), 7,39 d (1H, 5'-H), 7,17 d (1H, 6'-H)	11,5	46 (A)
IIIe	$C_{13}H_{10}Cl_2N_4OS$	45,43 45,76	2,54 2,95	16,04 16,42	>250	3445, 3360, 3245 (NH, NH$_2$), 2189 (CN), 1670 br.	3,82 J = 3,8	4,29 J = 3,8	6,40	7,35, 7,40	7,48 d.d (1H, 5'-H), 7,68 d (1H, 3'-H)	11,82	69 (B)

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*Resonance overlapped by Ar proton resonances.

TABLE 3. Bond Angles ω in the Molecule of Compound IIIa

Angle	ω, (deg)	Angle	ω, (deg)
$C_{(2)}$—$N_{(1)}$—$C_{(6)}$	124,6(2)	$S_{(1)}$—$C_{(2)}$—$N_{(1)}$	122,7(2)
$S_{(1)}$—$C_{(2)}$—$C_{(3)}$	122,2(2)	$N_{(1)}$—$C_{(2)}$—$C_{(3)}$	115,1(2)
$C_{(2)}$—$C_{(3)}$—$C_{(4)}$	110,7(2)	$C_{(2)}$—$C_{(3)}$—$C_{(8)}$	111,0(2)
$C_{(4)}$—$C_{(3)}$—$C_{(8)}$	112,5(2)	$C_{(3)}$—$C_{(4)}$—$C_{(5)}$	108,0(1)
$C_{(3)}$—$C_{(4)}$—$C_{(9)}$	109,4(2)	$C_{(5)}$—$C_{(4)}$—$C_{(9)}$	116,0(2)
$C_{(4)}$—$C_{(5)}$—$C_{(6)}$	120,8(2)	$C_{(4)}$—$C_{(5)}$—$C_{(7)}$	120,9(2)
$C_{(6)}$—$C_{(5)}$—$C_{(7)}$	118,3(2)	$N_{(1)}$—$C_{(6)}$—$N_{(2)}$	114,6(2)
$N_{(1)}$—$C_{(6)}$—$C_{(5)}$	119,2(2)	$N_{(2)}$—$C_{(6)}$—$C_{(5)}$	126,1(2)
$N_{(3)}$—$C_{(7)}$—$C_{(5)}$	178,8(2)	$O_{(1)}$—$C_{(8)}$—$N_{(4)}$	122,7(2)
$O_{(1)}$—$C_{(8)}$—$C_{(3)}$	122,4(2)	$N_{(4)}$—$C_{(8)}$—$C_{(3)}$	114,9(2)
$C_{(4)}$—$C_{(9)}$—$C_{(10)}$	117,7(2)	$C_{(4)}$—$C_{(9)}$—$C_{(14)}$	123,3(2)
$C_{(10)}$—$C_{(9)}$—$C_{(14)}$	118,9(2)	$C_{(9)}$—$C_{(10)}$—$C_{(11)}$	120,9(2)
$C_{(10)}$—$C_{(11)}$—$C_{(12)}$	120,2(2)	$C_{(11)}$—$C_{(12)}$—$C_{(13)}$	119,5(2)
$C_{(12)}$—$C_{(13)}$—$C_{(14)}$	120,7(3)	$C_{(9)}$—$C_{(14)}$—$C_{(13)}$	119,8(2)

TABLE 4. Atomic Coordinates (× 10^4; × 10^3 for H) for Molecule IIIa

Atom	*x*	*y*	*z*
$S_{(1)}$	8591(1)	1744(1)	6725(1)
$O_{(1)}$	9768(1)	4532(2)	5969(1)
$N_{(1)}$	8689(1)	4111(2)	7243(1)
$N_{(2)}$	8860(2)	6075(2)	7855(1)
$N_{(3)}$	7236(2)	8230(2)	6508(1)
$N_{(4)}$	8609(2)	4794(2)	4795(1)
$C_{(2)}$	8449(2)	3305(2)	6627(1)
$C_{(3)}$	8031(2)	3937(2)	5834(1)
$C_{(4)}$	7247(2)	4980(2)	5857(1)
$C_{(5)}$	7726(2)	5859(2)	6542(1)
$C_{(6)}$	8416(2)	5404(2)	7204(1)
$C_{(7)}$	7447(2)	7164(2)	6519(1)
$C_{(8)}$	8888(2)	4455(2)	5542(1)
$C_{(9)}$	6252(2)	4340(2)	5857(1)
$C_{(10)}$	5741(2)	3616(2)	5205(1)
$C_{(11)}$	4841(2)	3002(2)	5166(1)
$C_{(12)}$	4425(2)	3128(2)	5772(1)
$C_{(13)}$	4912(2)	3871(2)	6415(1)
$C_{(14)}$	5831(2)	4472(2)	6466(1)
$H_{(1)}$	896(2)	381(3)	766(2)
$H_{(21)}$	869(2)	688(3)	788(2)
$H_{(22)}$	936(2)	574(3)	826(2)
$H_{(41)}$	805(2)	470(3)	453(2)
$H_{(42)}$	909(2)	511(3)	460(2)
$H_{(3)}$	770(2)	331(2)	548(1)
$H_{(4)}$	710(2)	549(2)	534(1)
$H_{(10)}$	601(2)	354(2)	478(1)
$H_{(11)}$	452(2)	250(2)	473(1)
$H_{(12)}$	374(2)	273(2)	572(1)
$H_{(13)}$	462(2)	398(3)	682(2)
$H_{(14)}$	620(2)	503(3)	688(2)

3,4-*trans*-6-Amino-4-aryl-3-carbamoyl-5-cyano-1,2,3,4-tetrahydropyridin-2(1H)-thiones (IIIa-e). A. A suspension of the corresponding salt IV (2 mmol) was heated to 40-50°C in ethanol (10 cm^3) and 10% hydrochloric acid (3 cm^3) was added. The initial precipitate dissolved and, after some time, the product precipitated and was filtered off and washed with ethanol and hexane.

B. Triethylamine (1.4 cm^3, 10 mmol) was added to a suspension of an arylmethylenemalononitrile, IIa-e, (10 mmol) amide I (1.18 g, 10 mmol) in absolute ethanol (30 cm^3) and the mixture was heated to 40-50°C with stirring until the starting materials dissolved. Ten percent Hydrochloric acid (2 cm^3) was added to the solution over 10-15 min. The precipitate of product III was filtered off and washed with ethanol and hexane.

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