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SYNTHESIS OF N-METHYLMORPHOLINIUM 6-METHYL-4-(2-THIENYL)-5-PHENYLCARBAMOYL-3-CYANO-1,4-DIHYDROPYRIDINE-2-THIOLATE AND ITS REACTION WITH VARIOUS FUNCTIONALLY SUBSTITUTED METHYL HALIDES

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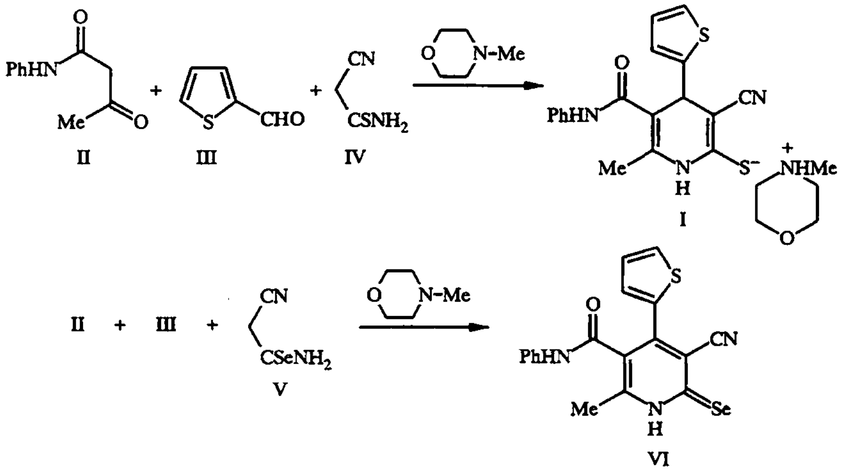
Condensation of the anilide of acetoacetic acid, thiophene aldehyde, cyanothioacetamide and N-methylmorpholine gave N-methylmorpholinium 6-methyl-4-(2-thienyl)-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-thiolate which reacted with various halides ZCH_2Hal *or* $H_2NCOCH(Ph)Cl$ *to give substituted 2-*ZCH_2*-thio or 2-*$H_2NCOCH(Ph)$*-thio-1,4-dihydropyridines.*

Thienyl substituted 1,4-dihydropyridines are known to be pharmacologically active [1]. With the objective of preparing new biologically active compounds of this series we have developed a method for the synthesis of N-methylmorpholinium 6-methyl-4-(2-thienyl)-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-thiolate (I) which involves a three component condensation of the anilide of acetoacetic acid (II), thiophene aldehyde (III) and cyanothioacetamide (IV) in ethanol at 20°C in the presence of N-methylmorpholine. When cyanoselenoacetamide (V) was used in place of compound IV the product was the selenone (VI) rather than the selenolate.

Reaction of salt (I) with the halides ZCH_2Hal (VIIa-t) and $H_2NCOCH(Ph)Cl$ (VIII) gave the corresponding 2-thio-1,4-dihydropyridines substituted at the sulfur atom (IXa-t and X). The 4,7-dihydrothieno[2,3-*b*]pyridines (XIa and b) were prepared from compounds IXa and b under the conditions of the Thorpe–Ziegler synthesis.

Treatment of salt I with dilute hydrochloric acid converted it to the thione (XII) which reacted with 3-bromoacetylcoumarin (VIIu) and 1-iodohexane (VIIv) in basic media to give the corresponding sulfides (XIIIa and b).



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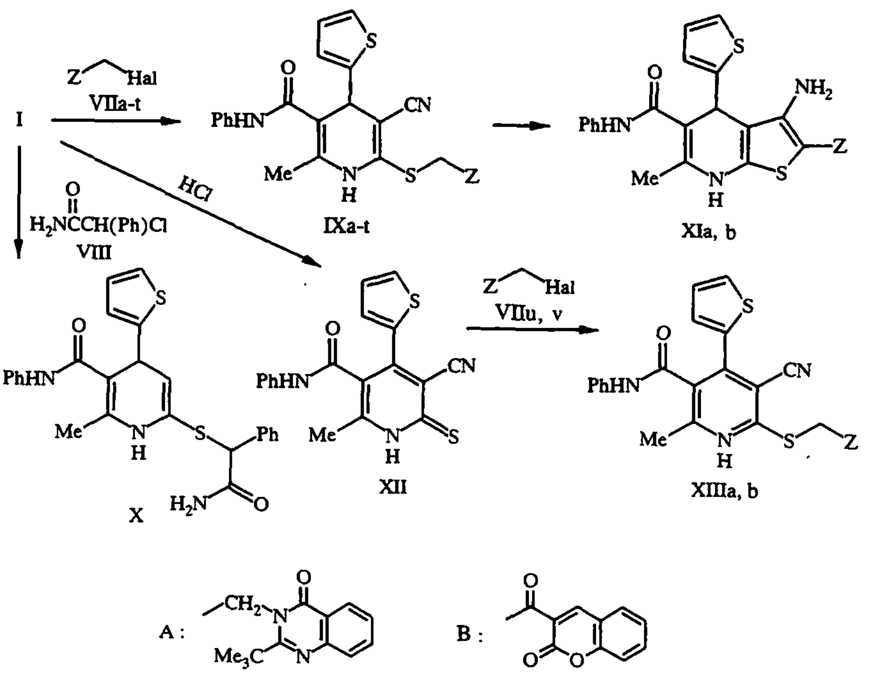

VII, IX, XI a Hal = Br, Z = p-ClC$_6$H$_4$CO; b Hal = Br, Z = p-BrC$_6$H$_4$NHCO; c Hal = Br, Z = CH$_2$ = CH; d Hal = Br, Z = p-ClC$_6$H$_4$; e Hal = Cl, Z = COOH; f Hal = Cl, Z = Ph; g Hal = I, Z = CH$_3$(CH$_2$)$_4$; h Hal = I, Z = Me; i Hal = Br, Z = Et; j Hal = I, Z = H; k Hal = Cl, Z = PhNHCO; *l* Hal = Br, 2-thienoyl; m Hal = Br, Z = p-BrC$_6$H$_4$CO; n Hal = Cl, Z = COOMe; o Hal = Cl, Z = COOEt; p Hal = Br, Z = PhCO; q Hal = Cl, Z = CONH$_2$; r Hal = Br, Z = p-MeC$_6$H$_4$CO; s Hal = Cl, Z = CN; t Hal = Cl, Z = A, VIIu, XIIIa Hal = Br, Z = B; VIIv, XIIIb Hal = I, Z = CH$_3$(CH$_2$)$_4$

The spectroscopic characteristics of compounds I, VI, IXa-t, X, XIa and b, XII and XIIIa and b confirmed their structures (see Table 1 and Experimental section). The IR spectra contain bands corresponding to a conjugated CN group at 2190-2220 and an NH group in the 3200-3350 cm^{-1} region. The H NMR spectra contain singlets of the hydrogens of the dihydropyridine ring at 5.05-5.20 (CH) and 9.23-9.70 ppm (NH) as well as signals of hydrogen atoms of the substituents.

EXPERIMENTAL

IR spectra of Nujol mulls were recorded with an IRS-29 spectrometer, and ^{1}H NMR spectra of DMSO-D$_6$ solutions with TMS as internal standard were recorded with a Bruker WP-100 SY (10 MHz) instrument.

Characteristics of the compounds synthesized are presented in Table 2.

N-Methylmorpholinium 6-Methyl-4-(2-thienyl)-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-thiolate (I). A mixture of anilide II (1.77 g, 10 mmol), aldehyde III (1.12 g, 10 mmol), cyanothioacetamide IV (1.00 g, 10 mmol) and N-methylmorpholine (1.51 g, 15 mmol) in ethanol (20 cm^3) was stirred at 20°C for 6 h. The precipitate of compound I was filtered off and washed with ethanol and acetone. Yield 3.54 g (78%). mp 142-144°C. IR spectrum: 3255 (NH), 2190 (CN), 1650 cm^{-1} (CONH). ^{1}H NMR spectrum: 9.24 (1 H, s, CONH), 8.09 (1 H, br. s., NH), 6.70-7.58 (8 H, m, H$_{\rm arom}$), 4.89 (1 H, s, 4-H), 3.76 (4 H, m, CH$_2$OCH$_2$, 3.09 (4 H, m, CH$_2$NCH$_2$), 2.72 (3 H, s, NCH$_3$), 2.07 ppm (3 H, s, 6-CH$_3$). Found, %: C 60.88, H 5.59, N 12.41, S 14.24. C$_{18}$H$_{15}$N$_3$OS$_2$·C$_5$H$_{11}$NO. Calculated, %: C 60.77, H 5.76, N 12.32, S 14.11.

6-Methyl-4-(2-thienyl)-5-phenylcarbamoyl-3-cyanopyridine-2(1H)-selenone (VI). A suspension of anilide II (1.77 g, 10 mmol), aldehyde III (1.12 g, 10 mmol), cyanoselenoacetamide V (1.47 g, 10 mmol) and N-methylmorpholine (1.51 g, 15 mmol) in absolute ethanol (20 cm^3) was stirred for 6 h at 20°C in an atmosphere of argon after which the pH was adjusted to 3 by addition of 10% aqueous hydrochloric acid. The precipitate was filtered off and washed with ethanol and hexane togive VI (2.83 g, 71%), mp 284-286°C. IR spectrum: 3210 (NH), 2220 (CN), 1650 cm^{-1} (CONH). ^{1}H NMR spectrum: 10.63 (1 H, s, CONH), 7.00-7.85 (8 H, m, H$_{\rm arom}$), 2.60 ppm (3 H, s, CH$_3$). Found, %: C 54.11, H 3.08, N 10.64, S 8.16. C$_{18}$H$_{13}$N$_3$OSSe. Calculated, %: C 54.27, H 3.29, N 10.55, S 8.05.

TABLE 1. ^{1}H NMR Spectra and IR Spectra of Compounds IXa-t, X and XIIIa and b

Compound	IR spectra, ν, cm^{-1}			^{1}H NMR spectrum, δ, ppm						
	NH	CN	CONH	6-CH_3, s	NH, s	CONH, s	4-H, s	SCH_2	H_{arom}, m	other protons
1	2	3	4	5	6	7	8	9	10	11
IX a	3300	2200	1674	2,09	9,26	9,67	5,10	4,76 s	6,80...8,01	—
IX b	3272	2205	1654	2,10	9,57	10,50	5,12	3,96 s	6,86...7,57	9,70 s (NH)
IX c	3330	2200	1670	2,10	9,28	9,67	5,09	3,69 m	6,80...7,57	5,20 m (CH_2=); 5,80 m (CH=)
IX d	3210	2190	1662	2,13	9,39	9,67	5,06	4,30 s	6,66...7,70	—
IX e	3300	2218	1650	2,06	9,69	10,60	5,09	4,01 s	6,75...7,52	—
IXe	3330	2190	1650	2,11	9,36	9,64	5,04	4,30 d	6,67...7,56	—
IX g	3335	2218	1675	2,09	9,30	9,66	5,09	3,02 m	6,80...7,57	0,86 t (CH_3); 1,26 m ((CH_2)$_4$)
IX h	3378	2220	1650	2,09	9,31	9,69	5,10	3,03 t	6,75...7,58	1,22 t (CH_3)
IX i	3264	2204	1677	2,09	9,30	9,68	5,10	2,99 m	6,80...7,57	0,97 t (CH_3); 1,57 m (CH_2)
IX j	3328	2195	1644	2,10	9,23	9,68	5,05	2,52 s	6,80...7,70	—
IX k	3330	2218	1655	2,11	9,65	9,70	5,14	3,98 s	6,87...7,59	10,39 s (CONH)
IX*l*	3295	2204	1660	2,07	9,30	9,69	5,10	4,65 s	8,07 т; 6,80...7,56	—
IX m	3315	2210	1688	2,08	9,27	9,67	5,09	4,75 s	6,80...7,92	—
IX n	3300	2220	1650	2,06	9,29	9,67	5,09	3,96 s	6,80...7,55	3,63 s (OCH_3)
IX o	3300	2200	1650	2,10	9,33	9,68	5,12	4,04 m*	6,91...7,54	4,04 m (OCH_2)*; 1,18 t (CH_3)

TABLE 1 (continued)

Compound	IR spectra, ν, cm^{-1}			^1H NMR spectrum, δ, ppm						
	NH	CN	CONH	6-CH_3, s	NH, s	CONH, s	4-H, s	SCH_2	H_{arom}, m	other protons
1	2	3	4	5	6	7	8	9	10	11
IX p	3270	2190	1660	2,10	9,25	9,67	5,11	4,82 s	6,80...8,02	—
IX q	3375	2190	1684	2,11	9,67	10,12	5,12	3,72 d	6,80...7,57	7,91 br. s (NH_2)
IX r	3280	2205	1650	2,08	9,26	9,68	5,08	4,77	6,85...9,70	2,37 s (CH_3)
IX s	3314	2222, 2260	1682	2,11	9,49	9,76	5,20	4,27 s	6,91...7,58	—
IX t	3284	2192	1648	2,16	9,50	9,66	5,17	4,39 t*	6,85...8,10	4,39 t (CH_2N)*; 1,47 s ($(CH_3)_3$)
X	3300	2190	1670	2,04	9,59	10,55	5,03	5,34 s	6,47...7,70	7,95 br. s (NH_2)
XIII a	—	2222	1675	2,36	—	10,53	—	4,89 s	8,77 s; 7,00...8,10	—
XIII b	—	2217	1650	2,58	—	10,54	—	3,31 t	7,00...7,60; 7,79 d	0,87 t (CH_3), 1,34...1,71 m ($(CH_2)_4$)

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*Signal overlap.

TABLE 2. Characteristics of the Synthesized Compounds IXa-t, X and XIa and b

Compound	Molecular formula	(Found, %)/ (Calculated, %) C	H	N	S	mp, °C (solvent for crystallization)	Yield, %
IXa	$C_{26}H_{20}ClN_3O_2S_2$	61.60 61,71	4.15 3,98	8.41 8,30	12.54 12,67	200...202 (AcOH)	74
IXb	$C_{26}H_{21}BrN_4O_2S_2$	55.15 55,22	3.80 3,74	10.01 9,91	11.19 11,34	248...250 (1-butanol)	68
IXc	$C_{21}H_{13}N_3OS_2$	63.88 64,09	4.90 4,87	10.55 10,68	16.41 16,30	110...112 (ethanol	69
IXd	$C_{25}H_{20}ClN_3OS_2$	62.73 62,81	4.11 4,22	8.88 8,79	13.50 13,41	164...166 (1-butanol)	78
IXe	$C_{20}H_{17}N_3O_3S_2$	58.42 58,38	4.20 4,16	10.01 10,21	15.69 15,58	178...180 (AcOH)	72
IXf	$C_{25}H_{21}N_3OS_2$	67.80 67,69	4.59 4,77	9.30 9,47	14.54 14,46	177...179 ethanol	78
IXg	$C_{24}H_{27}N_3OS_2$	65.92 65,87	6.33 6,22	9.54 9,60	14.51 14,65	112...114 ethanol	71
IXh	$C_{20}H_{19}N_3OS_2$	63.11 62,96	4.90 5,02	10.88 11,01	16.92 16,81	124...126 ethanol	86
IXi	$C_{21}H_{21}N_3OS_2$	63.59 63,77	5.42 5,35	10.70 10,62	16.12 16,21	160...162 ethanol	83
IXj	$C_{19}H_{17}N_3OS_2$	61.95 62,10	4.70 4,66	11.29 11,43	17.50 17,45	174...176 methanol	72
IXk	$C_{26}H_{22}N_4O_2S_2$	64.02 64,18	4.62 4,56	11.43 11.51	13.07 13,18	250...252 (1-butanol)	73
IXi	$C_{24}H_{19}N_3O_2S_3$	60.11 60,35	3.92 4,01	8.94 8,80	20.20 20,14	186...188 (1-butanol)	80
IXm	$C_{26}H_{20}BrN_3O_2S_2$	56.60 56,73	3.58 3,66	7.72 7,63	11.59 11,65	182...184 (1-butanol)	86
IXn	$C_{21}H_{19}N_3O_3S_2$	59.33 59,27	4.41 4,50	10.00 9,88	14.86 15,07	182...184 ethanol	69
IXo	$C_{22}H_{21}N_3O_3S_2$	59.98 60,12	4.76 4,82	9.65 9,56	14.70 14,59	126...128 ethanol	78
IXp	$C_{26}H_{21}N_3O_2S_2$	66.11 66,22	4.60 4,49	9.03 8,91	13.54 13,60	185...187 (AcOH)	77
IXq	$C_{20}H_{18}N_4O_2S_2$	58.40 58,52	4.31 4,42	13.78 13,65	15.80 15,62	250...252 (1-butanol)	76
IXr	$C_{27}H_{23}N_3O_2S_2$	66.66 66,78	4.84 4,77	8.72 8,65	13.15 13,21	189...191 ethanol	73
IXs	$C_{20}H_{16}N_4OS_2$	61.11 61,20	4.20 4,11	14.33 14,27	16.28 16,34	190...192 ethanol	82
IXt	$C_{32}H_{31}N_5O_2S_2$	66.20 66,07	5.42 5,37	11.95 12,04	10.88 11,02	216...218 (1-butanol)	77
X	$C_{26}H_{22}N_4O_2S_2$	64.04 64,18	4.39 4,56	11.68 11,51	13.30 13,18	189...191 (1-butanol)	70
XIIIa	$C_{29}H_{19}N_3O_4S_2$	64.85 64,79	3.49 3,56	7.77 7,82	12.05 11,93	224...226 (DMF)	78
XIIIb	$C_{24}H_{25}N_3OS_2$	66.29 66,17	5.60 5,78	9.54 9,65	14.89 14,72	118...120 ethanol	74

6-Methyl-2-Z-methylthio-4-(2-thienyl)-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridines (IXa-t, X). 10 mmol of the halides VII or VIII were added with stirring to a suspension of the salt I (4.55 g, 10 mmol) in ethanol (20 cm^3), the reaction mixture was stirred for 4 h and then diluted with water (10 cm^3). The precipitated product was filtered off and washed with water, ethanol, and hexane.

3-Amino-6-methyl-4-(2-thienyl)-5-phenylcarbamoyl-2-(4-chlorobenzoyl)-4,7-dihydrothieno[2,3-*b*]pyridine (XIa). Potassium hydroxide (5.6 cm^3, 10 mmol, 10% aqueous solution) was added with stirring to a solution of compound IXa (5 g, 10 mmol) in DMF (15 cm^3), the mixture was stirred for 6 h and then diluted with water (10 cm^3). The precipitate was filtered off and washed with water, ethanol, and hexane to give compound XIa (3.64 g, 72%). mp 134-136°C. IR spectrum: 3190-3385 (NH, NH$_2$), 1665 cm^{-1} (CONH). ^{1}H NMR spectrum: 10.44 (1 H, br s, CONH), 9.60 (1 H, br s, NH), 6.80 (2 H, br. s, NH$_2$), 7.10-7.92 (12 H, m, H$_{arom}$), 5.55 (1 H, s, 4-H), 2.10 ppm (3 H, s, CH$_3$). Found, %: C 61.80, H 4.12, N 8.19, S 12.70. $C_{26}H_{20}ClN_3O_2S_2$. Calculated, %: C 61.71, H 3.98, N 8.30, S 12.67.

3-Amino-2-(4-bromophenylcarbamoyl)-6-methyl-4-(2-thienyl)-5-phenylcarbamoyl-4,7-dihydrothieno[2,3-*b*]pyridine (XIb). Product XIb was prepared as described above for compound XIa. Yield 3.83 g (68%). mp 248-250°C (1-butanol). IR spectrum: 3210-3450 (NH, NH_2), 1680 cm^{-1} (CONH). ^1H NMR spectrum: 10.46 (1 H, s, 5-CONH), 9.58 (1 H, s, 2-CONH), 9.00 (1 H, s, NH), 6.54-7.75 (12 H, m, H_{arom}), 6.04 (2 H, br. s, NH_2), 5.54 (1 H, s, 4-H), 2.15 ppm (3 H, s, CH_3). Found, %: C 55.49, H 3.33, N 10.02, S 11.19. $C_{26}H_{21}BrN_4O_2S_2$. Calculated, %: C 55.22, H 3.74, N 9.91, S 11.34.

6-Methyl-4-(2-thieno)-5-phenylcarbamoyl-3-cyanopyridine-2(1H)-thione (XII). (10%) Aqueous hydrochloric acid was added with stirring to a suspension of salt I (4.55 g 10 mmol) in ethanol (15 cm^3) until the pH reached 3 and the solution was filtered. The precipitate of compound XII which developed over 24 h was separated and washed with ethanol and hexane to give a yield of 2.53 g (72%). mp 301-303°C. IR spectrum: 3305 (NH), 2220 (CN), 1650 cm^{-1} (CONH). ^1H NMR spectrum: 14.36 (1 H, s, NH), 10.42 (1 H, s, CONH), 7.00-7.83 (8 H, m, H_{arom}), 2.45 (3 H, s, CH_3). Found, %: C 61.66, H 3.81, N 11.85, S 18.10. $C_{18}H_{13}N_3OS_2$. Calculated, %: C 61.52, H 3.73, N 11.96, S 18.25.

2-ZCH$_2$-6-methyl-4-(2-thienyl)-5-phenylcarbamoyl-3-cyanopyridines (XIIIa and b). To a suspension of thione XII (3.51 g, 10 mmol)in DMF (10 cm^3) 10% aqueous KOH (5.6 cm^3, 10 mmol) was added with stirring and then 10 mmol of the corresponding halide VII was added in 1 min. The mixture was then stirred for 4 h and diluted with water (10 cm^3). The precipitated product was filtered off and washed with water, ethanol, and hexane.

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