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 $\text{ZCH}_2\text{Hal}$ or $\text{H}_2\text{NCOCH(Ph)}\text{Cl}$ to give substituted 2-$\text{ZCH}_2$thio or 2-$\text{H}_2\text{NCOCH(Ph)}$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 $\text{ZCH}_2\text{Hal}$ (VIIa-t) and $\text{H}_2\text{NCOCH(Ph)}\text{Cl}$ (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).

![Chemical Structures](image.png)
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 ¹H NMR spectra of DMSO-D₆ 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 cm³) 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). ¹H NMR spectrum: 9.24 (1 H, s, CONH), 8.09 (1 H, br. s., NH), 6.70-7.58 (8 H, m, Harom), 4.89 (1 H, s, 4-H), 3.76 (4 H, m, CH₂OCH₂), 3.09 (4 H, m, CH₂NCH₂), 2.72 (3 H, s, NCH₃), 2.07 ppm (3 H, s, 6-CH₃). Found, %: C 60.88, H 5.59, N 12.41, S 14.24. C₁₈H₁₅N₃O₃S₂. Calculated, %: C 60.77, H 5.76, N 12.32, S 14.11.

**6-Methyl-4-(2-thienyl)-5-phenylcarbamoyl-3-cyano-1,4-dihydropyridine-2-selenone (IV).** A suspension of anilide 17 (1.77 g, 10 mmol), aldehyde III (1.12 g, 10 mmol), cyanoacetamide V (1.47 g, 10 mmol) and N-methylmorpholine (1.51 g, 15 mmol) in absolute ethanol (20 cm³) 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 to give VI (2.83 g, 71%). mp 142-144°C. IR spectrum: 3210 (NH), 2220 (CN), 1650 cm⁻¹ (CONH). ¹H NMR spectrum: 10.63 (1 H, s, CONH), 7.00-7.85 (8 H, m, Harom), 2.60 ppm (3 H, s, CH₃). Found, %: C 54.11, H 3.08, N 10.64, S 8.16. C₁₈H₁₃N₃O₂S₂. Calculated, %: C 54.27, H 3.29, N 10.55, S 8.05.