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SYNTHESIS OF 6-ALKYLTHIO-5-CARBAMOYL-3-CYANO-4-PHENYL-3,4-DIHYDROPYRIDIN-2(1H)-ONES*

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Condensation of ethyl benzylidenecyanoacetate with thiocarbamoylacetamide in the presence of an equimolar amount of piperidine produces piperidinium 5-carbamoyl-3-cyano-2-oxo-4-phenyl-3,4-dihydropyridine-6(1H)-thiolate, which is then used in synthesis of the corresponding 6-alkylthiosubstituted 3,4-dihydropyridin-2(1H)-ones.

Condensation of benzylidenemalononitrile with thiocarbamoylacetamide in the presence of an equimolar amount of piperidine produces in high yields 6-amino-3-carbamoyl-5-cyano-1,4-dihydropyridine-2(3H)-thiolates [1, 2], which are of interest as reactive intermediates for the preparation of hydrogenated 7H-thiazolo[3,2-*a*]-pyridines [3]. On the other hand, condensation of a chalcone with thiocarbamoylacetamide under similar conditions produces 3-thiocarbamoyl-3,4,5,6-tetrahydropyridin-2(1H)-one [4]. Four products are possible from the condensation of ethyl benzylidenecyanoacetate (I) with thiocarbamoylacetamide (II). These are 5-carbamoyl-3-cyano-6-mercapto-4-phenyl-3,4-dihydropyridin-2(1H)-one (V), 3-cyano-6-hydroxy-4-phenyl-5-thiocarbamoyl-3,4-dihydropyridin-2(1H)-one (VII), 6-amino-5-ethoxycarbonyl-4-phenyl-3-thiocarbamoyl-3,4-dihydropyridin-2(1H)-one (VIII), and 6-amino-3-carbamoyl-5-ethoxycarbonyl-4-phenyl-3,4-dihydropyridine-2(1H)-thione (IX).

We demonstrated that this reaction is regioselective and produces a pyridin-2(1H)-one of type V. This means that the thioamide and ester groups are involved in the intramolecular cyclization of the intermediate 3-carbamoyl-1-cyano-1-ethoxycarbonyl-2-phenyl-3-thiocarbamoylpropane (III). Condensation of ethyl benzylidenecyanoacetate I with thiocarbamoylacetamide II in the presence of an equimolar amount of piperidine gives piperidinium 5-carbamoyl-3-cyano-2-oxo-4-phenyl-1,4-dihydropyridine-6-thiolate (IV), which converts to the 3,4-dihydropyridin-2(1H)-one V upon acidification with acetic acid. Piperidine reacts readily with V in the reverse reaction to give IV.

Treatment of thiolates IV with alkyl halides produces 6-alkylthio-5-carbamoyl-3-cyano-4-phenyl-3,4-dihydropyridin-2(1H)-ones VI. The PMR spectra of IV and V in solution show tautomeric equilibria between keto- and enol-forms and thione- and enthiol-forms in addition to a mixture of *cis* and *trans* stereoisomers. Their IR spectra contain absorption bands corresponding to C=O, C≡N, NH, NH_2, and OH groups. The solid-state structures of the compounds can be conveniently proved by estimating the stretching vibrations of the C≡N group. The presence of an absorption band at 2254-2272 cm^{-1} is characteristic of an unconjugated nitrile. For thiolate IV, this is the tautomer IVA. For pyridin-2(1H)-ones V, these are tautomers VA and VC. The PMR spectra suggest that the ratio of the tautomers IVA and IVB is 1:3. According to the literature [5, 6], $^3J_{3,4}$ = 1.8 Hz indicates a *trans* diequatorial arrangement of the 3-H and 4-H protons in IVA. The PMR spectrum of V in the region of 3.8-4.5 and 5.0-5.6 ppm is complicated, corresponds to three protons, and does not unambiguously exclude any of the four possible tautomers.

* Dedicated to Professor Henk van der Plas on his 70th birthday.

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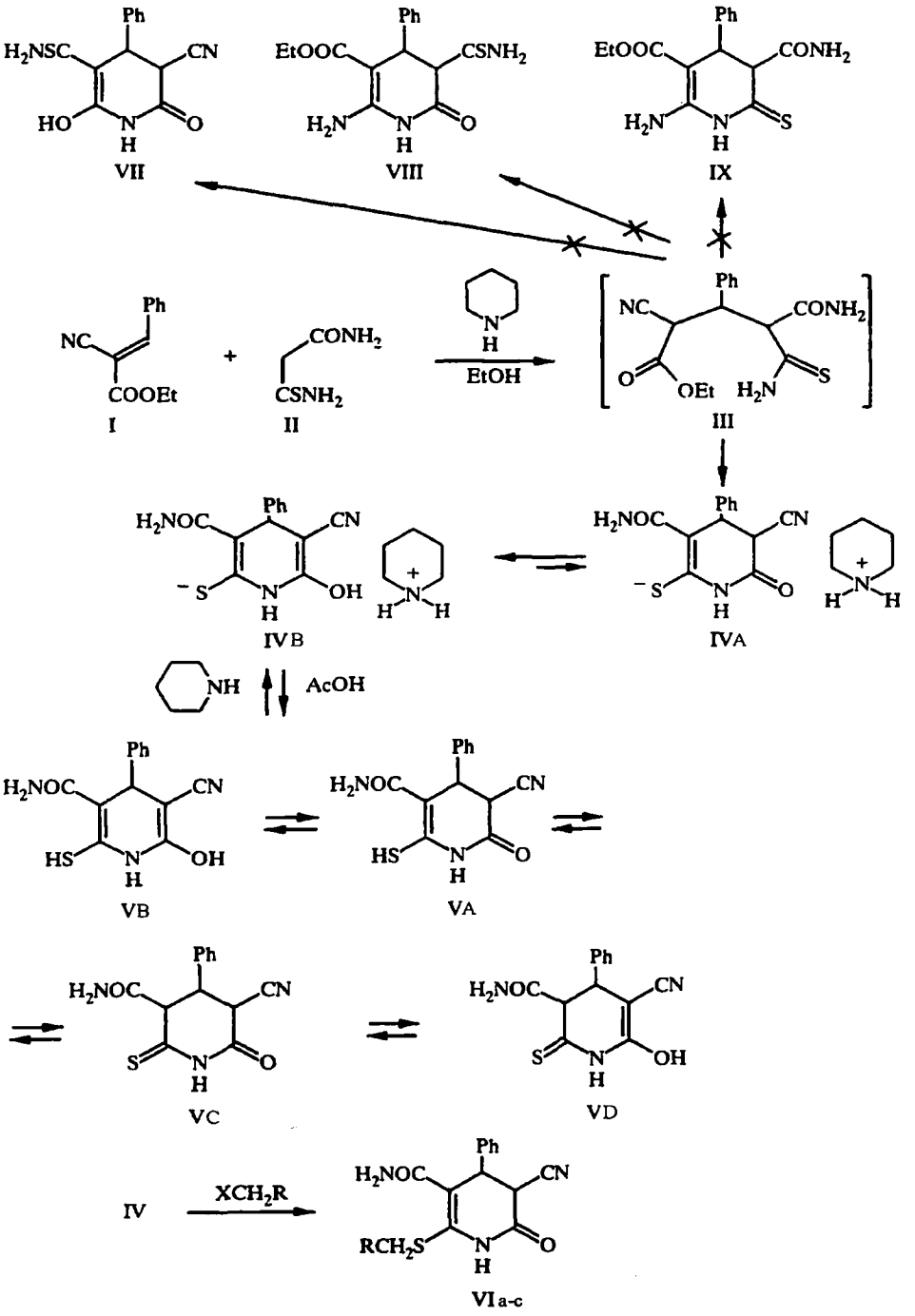

VI a R = H, b R = $CONH_2$, c R = COOEt, X = Br, I

The PMR spectra of 3,4-dihydropyridin-2(1H)-ones VI suggest that compounds VIa and VIb ($^3J_{3,4}$ = 6.2-6.5 Hz) are obtained exclusively as the *cis* stereoisomers whereas VIc is isolated as a 2:3 a mixture of the *cis* and *trans* stereoisomers. Splitting of the SCH_2R protons in VIb and VIc is explained by an interaction with the asymmetric atom 4-H.

Thus, stable 6-alkylthio-5-carbamoyl-3-cyano-4-phenyl-3,4-dihydropyridin-2(1H)-ones are synthesized for the first time. The corresponding 3,5-dicyanopyridin-2(1H)-ones were previously prepared by stabilizing them with *gem*-substituents in the 4-position [7, 8]. The higher reactivity of the thiocarbamoyl group compared with the carbamoyl in intramolecular cyclization with the δ-ester group is similar to that observed in cyclization with the δ-cyano group [1-3] but different from that observed in cyclization with the δ-benzoyl group [4].

EXPERIMENTAL

IR spectra were recorded on a Perkin–Elmer 580B spectrometer in nujol. PMR spectra were recorded on a WH 90/DC spectrometer in DMSO-d_6 (TMS as internal standard). The course of the reaction and purity of the compounds was monitored by TLC on Silufol UV-254 plates with hexane–chloroform–ethanol (5:5:2) as eluent.

Piperidinium 5-Carbamoyl-3-cyano-2-oxo-4-phenyl-3,4-dihydropyridine-6-thiolate (IV). A. A mixture of ethyl benzylidenecyanoacetate I (2.01 g, 10 mmol) and thiocarbamoylacetamide (1.18 g, 10 mmol) was dissolved upon gentle warming in ethanol (10 ml). Piperidine (1.0 ml, 10 mmol) was added and the mixture was stirred for 1 h at room temperature. The precipitate was filtered off and washed with cold ethanol (20 ml). Yield 2.51 g (70%) of IV; mp 181-184°C. IR spectrum: 1687, 1700 sh. (C=O), 2254 (C≡N), 2534 ($^+NH_2$), 3176, 3370 cm^{-1} (NH, NH_2, OH). PMR spectrum: 1.58 [6H, m, $(CH_2)_3$], 3.0 [4H, m, $(CH_2)_2N$], 3.76 (0.2H, d, J = 1.8 Hz, 3'-H), 4.58 (0.6H, s, 4-H), 4.76 (0.2H, d, J = 1.8 Hz, 4'-H), 6.24 (0.6H, br. s, OH), 7.1-7.3 (5H, m, 4-Ph), ~8.0 and ~8.2 (2H, br. s and br. s, 3-$CONH_2$), 8.70 (0.4H, br. s, N'H), 10.32 ppm (0.6H, br. s, NH). Found, %: C 60.29; H 6.26; N 15.73; S 9.03. $C_{18}H_{22}N_4O_2S$. Calculated, %: C 60.31; H 6.19; N 15.63; S 8.94.

B. Compound V (0.27 g, 1 mmol) is dissolved in ethanol (5 ml) and piperidine (0.15 ml, 1.5 mmol) is added. The precipitated product is filtered off and washed with cold ethanol (2 ml). Yield 0.29 g (82%) of IV; mp 182-184°C.

5-Carbamoyl-3-cyano-6-mercapto-4-phenyl-3,4-dihydropyridin-2(1H)-one (V). Thiolate IV (0.72 g, 2 mmol) was dissolved upon warming in acetic acid (4 ml) and ethanol (6 ml). Water (20 ml) was added gradually with stirring. The precipitate formed was separated after 1 h and washed with ethanol (5 ml) and water (20 ml). Yield 0.45 g (82%) of V; mp 131-133°C. IR spectrum: 1676, 1724 (C=O), 2260, 2272 (C≡N), 3186, 3368, 3460, 3500 cm^{-1} (NH, NH_2, OH). PMR spectrum: 3.8-4.5 and 5.0-5.6 (~3H, 3-H, 4-H, and 5-H of tautomers A, B, C, and D, *cis*- and *trans*-isomers), 6.9-7.7 (7H, 4-Ph and 3-$CONH_2$), 8.04, 8.3, 9.5, 10.73 and 11.68 ppm (1H, br. s, NH, OH, SH). Found, %: C 56.84; H 4.03; N 15.20; S 11.56. $C_{13}H_{11}N_3O_2S$. Calculated, %: C 57.13; H 4.06; N 15.37; S 11.73.

5-Carbamoyl-3-cyano-6-methylthio-4-phenyl-3,4-dihydropyridin-2(1H)-one (VIa). A mixture of IV (0.72 g, 2 mmol) and methyl iodide (0.62 ml, 10 mmol) in ethanol (30 ml) was heated for 10 min on a water bath, filtered hot, and cooled to 5°C. The precipitate formed was filtered off and washed with cold ethanol (10 ml) and water (20 ml). Yield 0.37 g (64%) of VIa; mp 193-195°C. IR spectrum: 1648, 1708 (C=O), 2256 (C≡N), 3200, 3344, 3420, 3452, 3500, 3576 cm^{-1} (NH, NH_2). PMR spectrum: 2.36 (3H, s, SCH_3), 4.46 (1H, d, J = 6.5 Hz, 4-H), 4.92 (1H, d, J = 6.5 Hz, 3-H), 7.1-7.4 (7H, 4-Ph and 3-$CONH_2$), 10.20 ppm (1H, s, NH). Found, %: C 56.51; H 4.81; N 13.98; S 10.66. $C_{14}H_{13}N_3O_2S \cdot 0.5H_2O$. Calculated, %: C 56.74; H 4.76; N 14.18; S 10.82.

5-Carbamoyl-6-carbamoylmethylthio-3-cyano-4-phenyl-3,4-dihydropyridin-2(1H)-one (VIb). A mixture of IV (0.72 g, 2 mmol) and iodoacetamide (0.41 g, 2.2 mmol) in ethanol (20 ml) was heated for 10 min on a water bath, filtered hot, and cooled to 5°C. The precipitate formed was filtered off and washed with ethanol (5 ml) and water (20 ml). Yield 0.46 g (70%) of VIb; mp 183-185°C. IR spectrum: 1638, 1650, 1714 (C=O), 2260 (C≡N), 3220, 3346, 3358 cm^{-1} (NH, NH_2). PMR spectrum: 3.40 and 3.68 (2H, d and d, J = 15 Hz, SCH_2), 4.52 (1H, d, J = 6.2 Hz, 4-H), 4.90 (1H, d, J = 6.2 Hz, 3-H), 7.0-7.5 (7H, 4-Ph and 3-$CONH_2$), 7.65 and 7.98 (2H, 2 br. s, $SCH_2CO\underline{NH_2}$), 11.40 ppm (1H, s, NH). Found, %: C 54.34; H 4.28; N 16.82; S 9.66. $C_{15}H_{14}N_4O_3S$. Calculated, %: C 54.53; H 4.27; N 16.96; S 9.71.

5-Carbamoyl-3-cyano-2-ethoxycarbonylmethylthio-4-phenyl-3,4-dihydropyridin-2(1H)-one (VIc) was prepared from mixture of IV (2 mmol) and ethylbromoacetate (2.2 mmol) as described for VIb. Yield 0.56 g (78%); mp 194-196°C. IR spectrum: 1654, 1700, 1722 (C=O), 2258 (C≡N), 3196, 3300, 3366, 3432 cm^{-1} (NH, NH_2). PMR spectrum: 1.19 (3H, t, $CH_2\underline{CH_3}$), 3.86 (0.6H, d, J ~ 2 Hz, 3-H), 3.9-4.4 (4H, SCH2 and $\underline{CH_2}CH_3$), 4.50 (0.6H, d, J ~ 2 Hz, 4-H), 4.52 (0.4H, d, J = 6.5 Hz, 4-H'), 4.78 (0.4H, d, J = 6.5 Hz, 3-H'), 7.1-7.6 (7H, 4-Ph and $CONH_2$), 10.34 (0.4H, s, N'H), 10.40 ppm (0.6H, s, NH). Found, %: C 56.73; H 4.75; N 11.68; S 8.93. $C_{17}H_{17}N_3O_4S$. Calculated, %: C 56.81; H 4.77; N 11.69; S 8.92.

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