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REGIOSELECTIVE SYNTHESIS OF METHYL 5,7-DIPHENYL-3-ETHOXYCARBONYLMETHYL-4,7-DIHYDROTHIAZOLO[3,2-*a*]PYRIDINE-8-CARBOXYLATE

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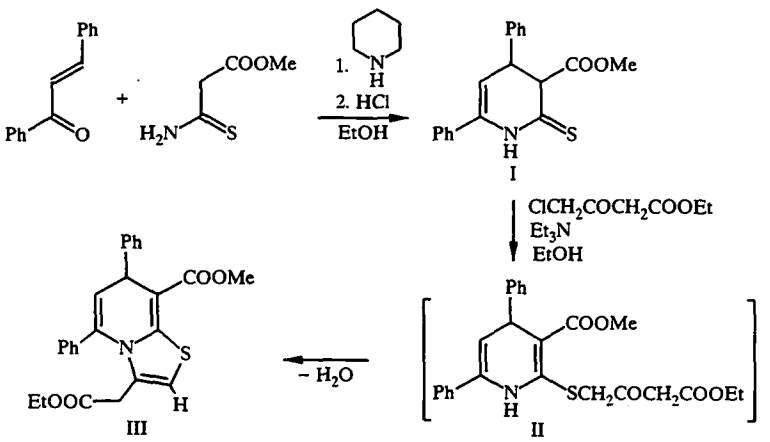
2-Alkylthio-5-carbamoyl-3-cyano-1,4-dihydropyridines [1], derivatives of 8-ethoxycarbonyl-5,6-dihydrothiazolo[2,3-*c*][1,4]thiazines [2] and 7-alkoxycarbonyl-2,3,5,6-tetrahydropyrrolo[2,1-*b*]thiazines [3] all show liver-protecting activity. Combination of the structural units responsible for activity in these substances in a single molecule may have promise.

We recently proposed a simple method for the synthesis of 3-oxo-2,3,4,7-tetrahydrothiazolo[3,2-*a*]pyridine-8-carbonitriles [4], however, synthesis of the corresponding 3-substituted 4,7-dihydrothiazolo[3,2-*a*]pyridine-8-carbonitriles proved difficult. Along with the expected intramolecular cyclization of the functional group of the 2-alkylthiosubstituent with the nucleophilic nitrogen of the 1,4-dihydropyridine ring, leading to their formation, a Thorpe cyclization readily occurred concurrently between the activated methylene group of the 2-alkylthio substituent and the cyano groups in position 3 to give a hydrogenated thieno[2,3-*b*]pyridine [5].



To overcome this problem we set about the synthesis of methyl 2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxylate as a substrate in which the very reactive cyano group would be replaced by the less reactive, but more lipophilic methoxycarbonyl group.

Condensation of benzalacetophenone with methyl thiocarbamoylacetate in the presence of piperidine with subsequent brief boiling with dilute HCl gave initially methyl 4,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxylate (I). Subsequent treatment of (I) with ethyl 4-chloroacetoacetate in the presence of an equimolar amount of triethylamine at 60-70°C for 30 min lead via the intermediate formation of the 1,4-dihydropyridine (II) to methyl 5,7-diphenyl-3-ethoxycarbonylmethyl-4,7-dihydrothiazolo[3,2-*a*]pyridine-8-carboxylate (III).

Methyl 4,6-diphenyl-2-thioxo-1,2,3,4-tetrahydropyridine-3-carboxylate (I, $C_{19}H_{17}NO_2S$). Yield 59%. M.p. 142-143°C. IR Spectrum: 1732 (C), 3276 cm^{-1} (NH). ^1H NMR spectrum ($CDCl_3$): 3.68 (3H, s, $COOCH_3$), 4.06 (1H, d, $^3J_{34}$ = 8 Hz, 3-H), 4.24 (1H, dd, 4-H), 5.76 (1H, d, $^3J_{45}$ = 4 Hz, 5-H), 7.22 and 7.42 (10H, s and s, 4- and 6-C_6H_5), 9.08 ppm (1H, br s, NH).

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Methyl 5,7-diphenyl-3-ethoxycarbonylmethyl-4,7-dihydrothiazolo[3,2-*a*]pyridine-8-carboxylate (III, $C_{25}H_{23}NO_4S$). Yield 46%. M.p. 194-196°C. IR spectrum: 1663, 1732 cm^{-1} (C). ^1H NMR spectrum ($CDCl_3$): 1.08 (3H, t, CH_2CH_3), 2.80 (2H, q, ^2J = 17 Hz, 3-CH_2COO), 3.68 (3H, s, $COOCH_3$), 3.96 (2H, q, $\underline{CH_2}CH_3$), 4.80 (1H, d, J = 7Hz, 7-H), 5.32 (1H, d, J = 7 Hz, 6-H), 6.12 (1H, s, 2-H), 7.1-7.4 (10H, m, 4- and 6-C_6H_5).

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