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SHORT COMMUNICATIONS

Ethyl 3-Thioxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylate, New Specimen of Derivatives of Partially Hydrogenated Isoquinoline-4-carboxylic Acids

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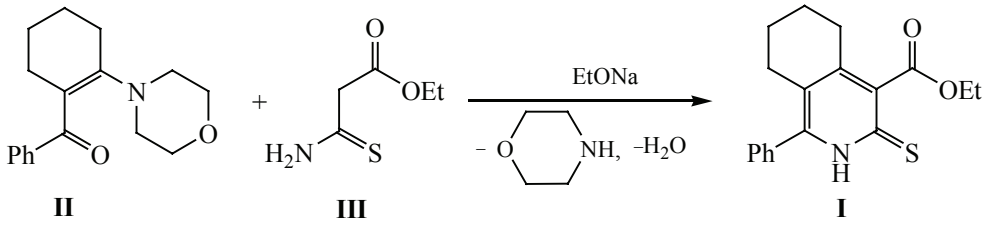
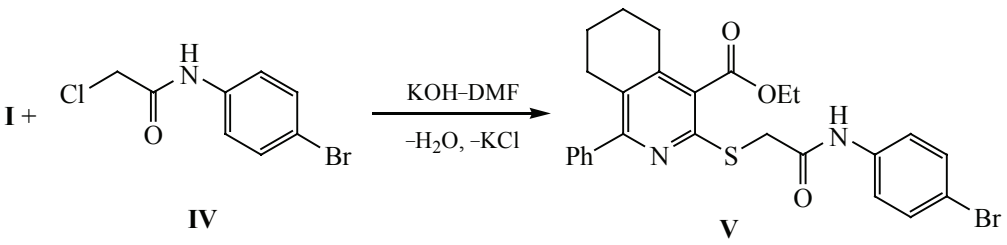
Derivatives of partially hydrogenated 3-thioxoisoquinoline-4-carboxylic acids are a promising type of heterocyclic synthons. For instance, their nitriles easily obtained from 2-acylcyclohexanons and cyanothioacetamide [1] are used as semiproducts in the synthesis of HIV-1 reverse transcriptase [2], antimicrobial preparations [3], substances with the fungicidal [4] and cardiotonic action [5]. We recently synthesized the corresponding amides by condensation of 1-amino-2-acylcycloalkenes with monothiomalonodiamide [6]. The esters of these acids were not described.

We describe here a convenient method of the synthesis of ethyl 3-thioxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylate (**I**) consisting in the reaction of 1-benzoyl-2-(morpholin-4-yl)cyclohexene (**II**) [6] with ethyl 3-amino-3-thioxopropanoate (**III**) in anhydrous ethanol at 20°C in the presence of sodium ethylate.

The alkylation of compound **I** with *N*-(4-bromophenyl)-2-chloroacetamide (**IV**) in DMF in the presence of alkali resulted in the formation of the corresponding thioester ethyl 3-[2-(4-bromophenylamino)-2-oxo-ethylsulfanyl]-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxylate (**V**) in keeping with the general rules of the chemistry of 3-thioxo-2,3,5,6,7,8-hexahydroisoquinolines [7].



II **III** **I**



IV **V**

Ethyl 3-thioxo-1-phenyl-2,3,5,6,7,8-hexahydroisoquinoline-4-carboxylate (I). To a mixture of 2.71 g (10 mmol) of enaminoketone **II** and 1.47 g (10 mmol) of thioamide **III** in 20 ml of anhydrous ethanol was added at 20°C while stirring a solution of sodium ethylate prepared from 0.23 g (10 mmol) of sodium and 10 ml of anhydrous ethanol, the mixture was stirred for 15 min and left standing for 2 days. The reaction mixture was diluted with 10% hydrochloric acid till pH 5, an 2 days later the formed precipitate was filtered off and washed in succession with water (15 ml), ethanol (15 ml), hexane (15 ml), dried, and crystallized from ethanol. Yield 2.03 g (65%), yellow powder, mp 180°C (decomp.). IR spectrum, ν, cm^{-1}: 3431 (NH), 1726 (C=O), 1232 (C=S). ^{1}H NMR spectrum, δ, ppm: 1.32 t (3H, CH_3, *J* 6.2 Hz), 1.51–1.56 m (2H, CH_2), 1.58–1.66 m (2H, CH_2), 2.33–2.38 m (2H, CH_2), 2.45–2.49 m (2H, CH_2), 4.29 q (2H, OCH_2, *J* 6.2 Hz), 7.39–7.56 m (5H, Ph), 13.57 br.s (NH). ^{13}C NMR spectrum, δ, ppm: 14.39, 21.43, 22.01, 25.78, 27.04, 61.24, 121.19, 128.78 (2C), 129.60 (2C), 130.04, 132.73, 136.09, 145.88, 148.74, 166.81, 171.16. Mass spectrum, *m*/*z* (I_{rel}, %): 314 (100) $[M + 1]^+$. Found, %: C 68.86; H 5.94; N 4.35. $C_{18}H_{19}NO_2S$. Calculated, %: C 68.98; H 6.11; N 4.47. *M* 313.422.

Ethyl 3-[2-(4-bromophenylamino)-2-oxoethylsulfanyl]-1-phenyl-5,6,7,8-tetrahydroisoquinoline-4-carboxylate (V). To a solution of 3.13 g (10 mmol) of isoquinolinethione **I** in 15 ml of DMF was added at stirring in succession 5.6 ml (10 mmol) of 10% water solution of KOH and 2.5 g (10 mmol) of chloroacetamide (**IV**), the mixture was stirred for 2 h and left standing for 24 h. The reaction mixture was diluted with the same volume of water, the formed precipitate was filtered off and washed in succession with water (15 ml), ethanol (15 ml), hexane (15 ml), dried, and crystallized from 1-butanol. Yield 3.9 g (74%), colorless crystals, mp 153–155°C. IR spectrum, ν, cm^{-1}: 3339 (NH), 1718 (C=O), 1668 (CONH). ^{1}H NMR spectrum, δ, ppm: 1.34 t (3H, CH_3, *J* 6.2 Hz), 1.52–1.66 m (2H, CH_2), 1.72–1.81 m (2H, CH_2), 2.53–2.61 m (2H, CH_2), 2.72–2.83 m (2H, CH_2), 3.96 (2H, SCH_2), 4.40 q (2H, OCH_2, *J* 6.2 Hz), 7.24 t (2H, Ph, *J* 7.1 Hz), 7.37 t (1H, Ph, *J* 7.1 Hz), 7.43–7.56 m (6H, H_{arom}), 10.30 br.s (NH). ^{13}C NMR spectrum, δ, ppm: 14.43, 21.66, 22.36, 27.03, 27.40, 35.51, 61.98, 115.11, 121.24 (2C), 126.33, 127.73, 128.35 (2C), 128.74, 129.50 (2C), 131.91 (2C), 138.97, 139.62, 145.75, 150.96, 158.50, 166.90, 167.32. Mass spectrum, *m*/*z* (I_{rel}, %): 527.2 (100) $[M + 1]^+$. Found, %: C 59.26; H 4.64; N 5.25. $C_{26}H_{25}BrN_2O_3S$. Calculated, %: C 59.37; H 4.79; N 5.33. *M* 526.044.

IR spectra of compounds obtained were recorded on a spectrophotometer FIR-spectrometer Spectrum One (Perkin Elmer) from pellets with KBr. ^{1}H NMR spectra were registered on a spectrometer Varian Mercury-400 (400.397 MHz) from solutions in DMSO-d_6, internal reference TMS. ^{13}C NMR spectra were taken on a spectrometer Varian VXR-300 (125.74 MHz) in DMSO-d_6, internal reference TMS. GC-MS analysis was carried out on an instrument Crommas GC/MS Hewlett-Packard 5890/5972, column HP-5 MS (70 eV), eluent CH_2Cl_2. Melting points were measured on a Koeffler heating block. The reaction progress was monitored and the purity of compounds obtained was checked by TLC on Silufol UV-254 plates, eluent acetone–hexane, 3:5, development in iodine vapor and under UV irradiation.

REFERENCES

1. Sharanin, Yu.A., Shestopalov, A.M., Promonenkov, V.K., and Rodinovskaya, L.A., *Zh. Org. Khim.,* 1984, vol. 20, p. 1539; Lozinskii, M.O., Chernega, A.N., and Shelyakin, V.V., *Zh. Org. Khim.,* 2002, vol. 38, p. 1718.
2. Elgemeie, G.E.H., Attia, A.M.E., and Fathy, N.M., *Nucleosides and Nucleotides*, 1997, vol. 16, p. 485.
3. Kamal, A.M., Radwan, S.M., and Zaki, R.M., *Eur. J. Med. Chem.,* 2011, vol. 46, p. 567.
4. Hunt, J.C.A., Briggs, E., Clarke, E.D., and Whittingham, W.G., *Bioorg. Med. Chem. Lett.,* 2007, vol. 17, p. 5222.
5. Mito, K., Kadziya, K., Ito, T., Kitano, T., Maruyama, M., and Khirayama, M., Japan Inventor's Certificate 62-4270, 1985; *Ref. Zh. Khim.,* 1988, 8O98P.
6. Dyachenko, I.V. and Vovk, M.V., *Zh. Obshch. Khim*., 2012, vol. 82, p. 256.
7. *Izbrannye metody sinteza i modifikatsii geterotsiklov. Izokhinoliny. Khimiya i biologicheskaya aktivnost'* (Selected Methods of Synthesis and Modification of Heterocycles. Isoquinolines. Chemistry and Biological Activity), Kartsev, V.G., Ed., Moscow: Nauchnoe Partnerstvo, 2008.