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SYNTHESIS AND HETEROCYCLIZATION OF β-N-(METHACRYLOYLTHIOCARBAMOYL)-ISONICOTINOHYDRAZIDE

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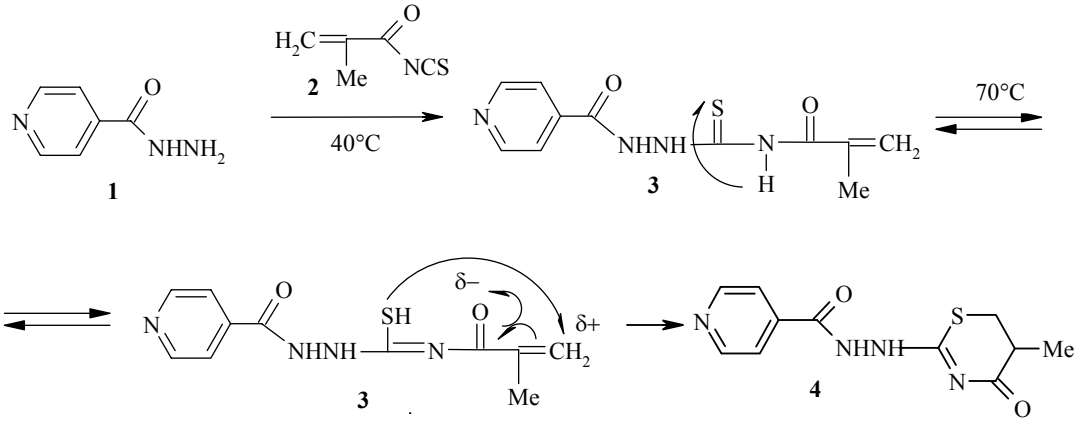
Despite the large range of medicinals used in clinical tuberculosis, the hydrazide of isonicotinic acid has taken the foremost place in the treatment of different forms of tuberculosis. Many different derivatives have been synthesized with a wide variation of antituberculosis activity and toxicity [1-3]. Modifications of known antituberculosis preparations continue to be timely, because this is one of the basic means for obtaining basically new medicinals [4].

With this objective, with the known isothiocyanate method, we have obtained the thiosemicarbazide derivative **3** by the reaction of isonicotinohydrazide (**1**) with methacryloyl isothiocyanate (**2**), prepared *in situ*, by heating methacryloyl chloride with KSCN in acetone.



Compound **3** was formed at 30-40°C in 2-propanol or ethanol. On increasing the reaction time to 16 h and increasing the temperature of the reaction mixture to 70°C, the product of its intramolecular heterocyclization – β-N-(5-methyl-4-oxo-5,6-dihydro-4H-1,3-thiazin-2-yl)isonicotinohydrazide (**4**), formed by a scheme for the formation of 1,3-thazine derivatives which has not previously been described in the literature.

Cyclization of compound **3** into 5,6-dihydro-1,3-thiaxin-4-one **4** probably occurs by intramolecular nucleophilic attack of the sulfur atom in the thione form on the electron deficient carbon atom at the C=C unsaturated bond. The formation of the 5,6-dihydro-1,3-thiazin-4-one **4** is indicated by the absence of the signal

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of the terminal methylene group =CH_2 protons, which appears as two doublets at 5.73 and 6.02 ppm, and the singlet of the amide proton N–H at 12.15 ppm (which is necessary for cyclization of the thionethiol rearrangement), in the ^{1}H NMR spectrum of compound **3.** In addition, splitting of the signals of the CH_3 protons in the ^{1}H NMR spectrum of compound **4** into a doublet, indicating their interaction with the methyne proton CH of the thiazine ring, the signals of the methyne and methylene protons appear as a multiplet and a doublet of doublets, also are in complete agreement with the formation of compound **4** as described in the scheme of cyclization given above.

The IR spectra of KBr tablets were recorded with an AVATAR-329 spectrometer and the ^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Bruker DRX-500 (500 MHz) spectrometer.

β-N-(Methacrolylthiocarbamoyl)isonicotinohydrazide (3). To a suspension of isonicotinylhydrazide (6.58g, 0.05 mol) in 2-propanol (30 ml) an acetone solution of methacryoyl isothiocyanate (made by boiling methacroyl chloride (5.33 g, 0.051 mol) for 2 h with KSCN (4.95 g, 0.051 mol) was added dropwise. The mixture was stirred for 3 h at 40°C, cooled, and the crystalline precipitate was filtered off to give a slightly yellowish crystalline substance (6.96 g, 53%); mp 172-173°C (4:1 2-propanol–DMF). IR spectrum, ν, cm^{-1}: 3232 (NH), 1681 (C=O), 1629 (C=C), 1561, 1482 (NC=S), 1312, 1185 (C–N). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.95 (3H, s, CH_3); 5.73 (1H, d, *J* = 1.5, C=H_a); 6.02 (1H, d, *J* = 1.5, C=H_b); 7.80 (2H, d, *J* = 6.0, β-Py); 8.79 (2H, d, *J* = 6.0, α-Py); 11.29 (1H, s, H–NHN–C=O); 11.37 (1H, s, H–NHNC=O); 12.15 (1H, s, C(O)H–N–C=S). Found, %: C 50.31; H 4.79; N 21.44. $C_{11}H_{12}N_4O_2S$. Calculated, %: C 49.99; H 4.58; N 21.20.

β-N-(5-Methyl-4-oxo-5,6-dihydro-4H-1,3-thiazin-2-yl)isonicotinohydrazide (4). A suspension of compound **3** (1.32 g, 5 mmol) in 2-propanol (20 ml) was stirred for 16 h at 70°C and diluted with water after cooling. The precipitate was filtered off to give compound **4** (0.85 g, 65%); mp 179-180°C (2-propanol). IR spectrum, ν, cm^{-1}: 2971 (NH), 1706 (–C=O), 1646 (–C=O_{amide}), 1576 (C=N), 1300 (C–N). ^{1}H NMR spectrum δ, ppm (*J*, Hz): 1.21 (3H, d, *J* = 6.9, CHCH_3); 2.81 (1H, m, CHCH_3); 3.02, 3.16 (2H, ddd, *J* = 10.1, *J* =4.1, S–CH_aH_b); 7.74 (2H, d, *J* = 6.0, β-Py); 8.74 (2H, d, *J* = 6.0. α-Py); 10.92 (1H, s, HNH–NC=O); 11.20 (1H, s, H–NHN–C=O). Found, %: C 50.17; H 4.71; N 21.39. $C_{11}H_{12}N_4O_2S$. Calculated, %: C 49.99; H 4.58; N 21.20.

REFERENCES

1. E. A. Bezzubets, N. A. Ostapkevich, and E. K. Dyachenko, *Khim.-farm. Zh.,* **14***,* No. 12, 56 (1980).
2. S. D. Fedoryak, P. V. Prisyazhnyuk, and I. I. Sidorchuk, *Khim.-farm. Zh.,* **16***,* No. 1, 48 (1982).
3. V. M. Komarov, A. A. Tsurkan, and I. V. Smirnov, *III Russian National Congress "Man and Medicine", Abs. Papers,* Moscow (1996), p. 28.
4. R. G. Glushkov and M. D. Mashkovskii, *Khim.-farm. Zh.,* **24**, No. 7, 4 (1990).