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LETTERS TO THE EDITOR

New Method of Synthesis of 5-Acyl-1,3-thiazines

V. N. Yuskovets, A. V. Moskvin, and B. A. Ivin

St. Petersburg State Chemical and Pharmaceutical Academy, St. Petersburg, Russia

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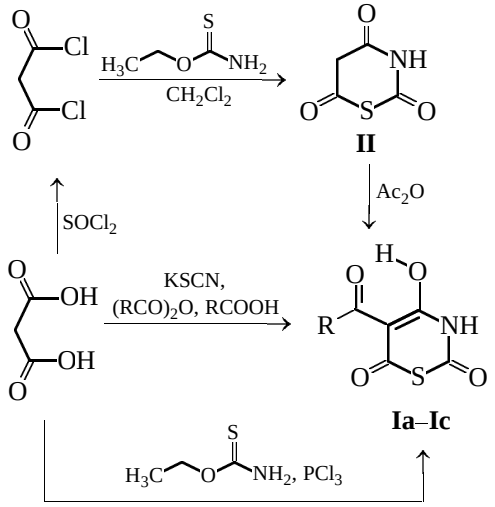
Over the past few years hydroxy(oxo)-1,3-thiazines have attracted increasing attention owing to the discovery of their versatile practically useful properties, specifically antimicrobial, antiviral, and antitumor activity [1–3]. At the same time, synthetic approaches to this group of compounds have insufficiently been developed. Searching for new methods of synthesis of 1,3-thiazines, we decided to make use of the thiocyanate ion as a three-atomic building block for the thiazine ring.

It was found that the reaction of malonic acid with potassium thiocyanate and acetic anhydride in acetic acid provides 45–50% of 5-acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6(3*H*)-dione (**Ia**), mp 198–200°C. Earlier Ziegler and Steiner [4] obtained compound **Ia** by heating a mixture of dithiocarbamide, malonic acid, and PCl_3, but the reported melting point of the product was 184°C. We reproduced this synthesis to obtain a compound melting at 198–200°C. Moreover, both samples of trioxothiazine **Ia** were identical to a compound formed by acetylation of 2*H*-1,3-thiazine-2,4,6(3*H*,6*H*)-trione **II** [5]. These samples had identical NMR and IR spectra, and their mixed samples gave no melting point depression.

The reactions with propionic and butyric anhydrides in solutions of corresponding acids under the above conditions gave 5-propionyl- and 5-butyryl-4-hydroxy-2*H*-1,3-thiazine-2,6(3*H*)-diones (**Ib** and **Ic**, respectively) but in much lower yields compared with 5-acetyl derivative **Ia**. Successful reactions were also observed in DMF and acetonitrile, but the yields of compounds **I** were much lower.

The mass spectra of compounds **I** were typical of hydroxy(oxo)thiazines [6], containing molecular $[M]^{+\cdot}$ and expected fragment ions $[M - COS]^{+\cdot}$, $[M - COS - CO]^{+\cdot}$, $[M - COS - RCO]^{+}$, $[M - COS - RCO - NH]^{+}$ and differing from each other by the fragmentation pathways of the alkyl radicals.

The most characteristic feature of the ^1H NMR spectra of compounds **I** in $CDCl_3$ is the presence of



R = CH_3 (**a**), C_2H_5 (**b**), C_3H_7 (**c**).

an extremely downfield OH proton signal (δ 17.67–18.08 ppm) involved in intramolecular hydrogen bonding. This signal is absent from the spectra of DMSO-d_6 solutions containing traces of water. Furthermore, the spectra of compounds **I** all display NH (δ 8.4–9.0 ppm) and acyl alkyl (δ 1.0–3.2 ppm) proton signals. The ^{13}C NMR spectra of solutions of thiazines **I** in DMSO-d_6 show $C^5C(=O)R$ carbon signals (δ_C 198–202 and 8–40 ppm) which are absent from the spectra of 1,3-thiazine-2,4,6-trione, as well as thiazine ring signals at expected positions [δ_C 179.5–180.3, 173.4–173.6, 163.2–163.3, and 100.4–101.2 (C^5) ppm]. Therewith, the C^5 and C^2, C^4, C^6 signals are shifted downfield by ~10 and ~6 ppm, respectively, compared to respective signals of non-acylated trioxothiazine **II**.

The IR spectra of 5-acylthiazines **Ia**–**Ic** are quite close to those of 2,4,6-trioxothiazine **II** [5] and 2-substituted 4-hydroxy-6-oxo-1,3-thiazines [6] but differ from them by the presence of bands near 1710 cm^{-1}, characteristic of stretching vibrations of ketone carbonyl, broad bands due to stretching and

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bending vibrations of hydrogen-bonded NH and OH groups, as well as alkyl C–H bands.

5-Acetyl-4-hydroxy-2*H*-1,3-thiazine-2,6(3*H*)-dione (Ia). *a*. Acetic anhydride, 45 ml, was added to a solution of 21 g of malonic acid in 100 ml of acetic acid. After 15-min stirring at 20–25°C, potassium thioacynate, 19 g, was added in one portion. The mixture was stirred for 1 h, allowed to stand at ~20°C for 48 h, and then diluted with 300 ml of water. The precipitate that formed was filtered off, washed with water (2.100 ml), and dried in air to obtain 25 g (46%) of thiazine **Ia**, mp 198–200°C (from benzene) (published data: mp 184°C [4]), R_f 0.44. IR spectrum, ν, cm^{-1}: 3500 br (OH), 3150, 3050 (NH), 2850–2950 (CH), 1710 (H_3CC=O), 1660, 1655 ($C^{2(6)}$=O). UV spectrum (alcohol or dioxane), λ_{max}, nm: 260. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.69 s (3H, CH_3), 8.43 br.s (1H, NH), 17.67 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 26.8 (CH_3), 101.2 (C^5), 163.2, 173.4, 180.3 (C^2, C^4, C^6), 198.4 (H_3CC=O). Mass spectrum, *m/z* (I_{rel}, %): 187 (28) $[M]^{+\cdot}$, 127 (28) $[M - COS]^{+\cdot}$, 99 (30) $[M - COS - CO]^{+\cdot}$, 84 (22) $[M - COS - CH_3CO]^+$, 69 (25) $[M - COS(CH_3)CO - NH]^+$, 43 (100) $[CH_3CO]^+$. Found, %: C 38.3; H 2.72; N 7.51; S 17.11. $C_6H_5NO_4S$. Calculated, %: C 38.5; H 2.69; N 7.48; S 17.13.

b. A mixture of 1.05 g of dithiocarbamide and 2.2 g of malonic acid in 3 ml of PCl_3 was heated from 2 h at 70°C. Volatile components were removed in a vacuum (~20 mm), the residue was treated with water, and the precipitate was filtered off and recrystallized from water to obtain 0.35 g (19%) of compound **Ia**, mp 198–200°C, R_f 0.44. The NMR, IR, and UV spectra are identical to those of the sample obtained by procedure *a*.

c. A mixture of 5 mmol of thiazine **II** and 15 ml of acetic anhydride was heated for 35–40 min at 90–95°C and then poured while hot onto ice and ground, The precipitate was filtered off, washed with water, and dried. Yield 22%, mp 198–200°C, R_f 0.44. The NMR, IR, and UV spectra are identical to those of the samples obtained by procedures *a* and *b*.

4-Hydroxy-5-propionyl-2*H*-1,3-thiazine-2,6(3*H*)-dione (Ib) was prepared similarly to thiazine **Ia** by procedure *a* from malonic acid and propionic anhydride in propionic acid at the same reagent molar ratio. Yield 30%, mp 139–140°C (benzene–hexane), R_f 0.47. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.22 t (3H, CH_3), 3.09–3.14 q (2H, CH_2), 8.56 br.s (1H, NH), 18.08 s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 8.6 (CH_3), 32.3 (CH_2), 100.4 (C^5), 163.3, 173.2, 179.5 (C^2, C^4, C^6), 202.3 (H_5C_2C=O). Mass spectrum, *m/z* (I_{rel}, %): 201 (67) $[M]^{+\cdot}$, 141 (31) $[M - COS]^{+\cdot}$, 124 (22), 113 (64) $[M - COS - CO]^{+\cdot}$, 102 (11), 85 (14), 69 (80), 57 (100) $[CH_3CH_2CO]^+$, 56 (33) $[M - COS - CO - CH_3CH_2CO]^+$, 44 (42). Found, %: C 41.77; H 3.55; N 6.97; S 15.91. $C_7H_7NO_4S$. Calculated, %: C 41.79; H 3.51; N 6.96; S 15.93.

5-Butyryl-4-hydroxy-2*H*-1,3-thiazine-2,6(3*H*)-dione (Ic) was prepared similarly to thiazine **Ia** by procedure *a* from malonic acid and butyric anhydride in butyric acid at the same reagent molar ratio. Yield 20%, mp 128–129°C (benzene–hexane), R_f 0.51. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.02 t (3H, CH_3), 1.71 m (2H, CH_2), 3.04 t (2H, CH_2), 8.97 br.s (1H, NH), 17.95 br.s (1H, OH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 13.5 (CH_3), 17.9 (CH_2), 40.2 (CH_2), 100.5 (C^5), 163.2, 173.6, 179.8 (C^2, C^4, C^6), 201.4 (H_7C_3C=O). Mass spectrum, *m/z* (I_{rel}, %): 215 (74) $[M]^{+\cdot}$, 155 (14) $[M - COS]^{+\cdot}$, 138 (57), 127 (60) $[M - COS - CO]$, 99 (24) $[M - COS - CO–CO]^{+\cdot}$, 97 (14), 84 (38), 71 (81) $[CH_3CH_2CH_2CO]^+$, 70 (28), 69 (69), 55 (45), 43 (100) [HNCO]. Found, %: C 44.68; H 4.19; N 6.49; S 14.93. $C_8H_9NO_4S$. Calculated, %: C 44.65; H 4.21; N 6.51; S 14.90.

The mass spectra were obtained on an MX-1321 instrument, ionizing energy 70 eV. The ^{1}H and ^{13}C NMR spectra were measured on a Bruker AM-500 spectrometer (500 and 125 MHz, respectively). The IR spectra were taken on a Specord IR-75 instrument. Reaction progress and purity of products were controlled by TLC on Sorbfil plates (eluent toluene–dioxane–ethanol, 2 : 2 : 1).

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