Derivatization of Keto Fatty Acids: Part XIII—Synthesis of Methyl Hexahydro-3-Alkyl-6-Thioxo-1,2,4,5-Tetrazine-3-Alkanoates

M.T. Saeed, J. Mustafa[a], A. Rauf[a] and S.M. Osman*

Section of Oils and Fats, Department of Chemistry, Aligarh Muslim University and [a]Applied Sciences Section, University Polytechnic, Faculty of Engineering and Technology, A.M.U., Aligarh 202 002, India

Hexahydrothioxotetrazine fatty derivatives have been prepared by the reaction of thiocarbohydrazide with oxo fatty esters. Methyl 10-oxoundecanoate (I), methyl 9-oxooctadecanoate (II) and methyl 12-oxooctadecanoate (III) on treatment with thiocarbohydrazide furnish methyl hexahydro-3-methyl-6-thioxo-1,2,4,5-tetrazine-3-nonanoate (IV), methyl hexahydro-3-nonyl-6-thioxo-1,2,4,5-tetrazine-3-octanoate (V) and methyl hexahydro-3-hexyl-6-thioxo-1,2,4,5-tetrazine-3-undecanoate (VI), respectively, in fairly good yields. The structural assignments of the hexahydrothioxotetrazine fatty derivatives are based on microanalysis, infrared, nuclear magnetic resonance and mass spectrometry data.

KEY WORDS: Methyl hexahydro-3-alkyl-6-thioxo-1,2,4,5-tetrazine-3-alkanoates, methyl 9-oxooctadecanoate, methyl 10-oxoundecanoate, methyl 12-oxooctadecanoate, thiocarbohydrazine.

Our program directed towards the synthesis of structurally novel (1–4) and pharmaceutically important heterocyclic systems led us to the preparation of the unknown hexahydrothioxotetrazine nucleus containing a fatty ester chain. Compounds similar to these products have been reported to possess bactericidal (5), pesticidal (6), fungicidal (7), insecticidal (8) and anti-inflammatory (9) activities.

MATERIALS AND METHODS

The 10-oxoundecanoic acid (m.p. 58–59°C), 9-oxooctadecanoic acid (m.p. 83°C) and 12-oxooctadecanoic acid (m.p. 82–82.5°C) were prepared as described in our earlier publications (4,10). Methyl esters of these oxo acids were prepared with CH_3OH/H^+.

All melting points were observed on a Kofler apparatus and are uncorrected. Infrared (IR) spectra (in cm^{-1}) were recorded on a Shimadzu 408 spectrophotometer (Kyoto, Japan). Nuclear magnetic resonance (NMR) spectra in $CDCl_3$ were run on a Varian A 60-MHz spectrometer (Palo Alto, CA) with tetramethylsilyl (TMS) as the internal standard (chemical shifts in δ, ppm), and mass spectra were obtained on a JEOL JMS-D 300 mass spectrometer at 70 eV (Jeol Ltd., Japan).

Reaction of oxo fatty esters with thiocarbohydrazide. To an ethanolic solution of methyl 10-oxoundecanoate (I, 1.07 g, 0.005 mol), a solution of thiocarbohydrazide (0.53 g, 0.005 mol) in acetic acid (10 mL) was added over a period of 15 min. After complete addition, the reaction mixture was stirred for 10 min more and worked up with diethyl ether. The etherial solution was washed with water, sodium bicarbonate (5%), again with water, and then dried over anhydrous sodium sulfate. Evaporation of the solvent provided a semi-solid residue which, on crystallization from methanol, furnished IV in 97% yield, m.p. 120°C. Analysis: $C_{13}H_{26}O_2N_4S$: C, 51.69; H, 8.7; N, 18.50 found; C, 51.6; H, 8.66; N, 18.52% required. Spectral data are given later.

A similar reaction of methyl 9-oxooctadecanoate (II, 1.55 g, 0.005 mol) with thiocarbohydrazide (0.53 g, 0.005 mol) afforded V (yield 94%, m.p. 102°C). Analysis: $C_{20}H_{40}O_2N_4S$: C, 60.71; H, 10.30; N, 14.0 found; C, 59.95; H, 10.06; N, 13.98% required. Similarly, the reaction of III with thiocarbohydrazide gave VI (yield 95%, m.p. 100°C). Analysis: $C_{20}H_{40}O_2N_4S$: C, 60.30; H, 10.40; N, 13.92; found; C, 59.95; H, 10.06; N, 13.98% required.

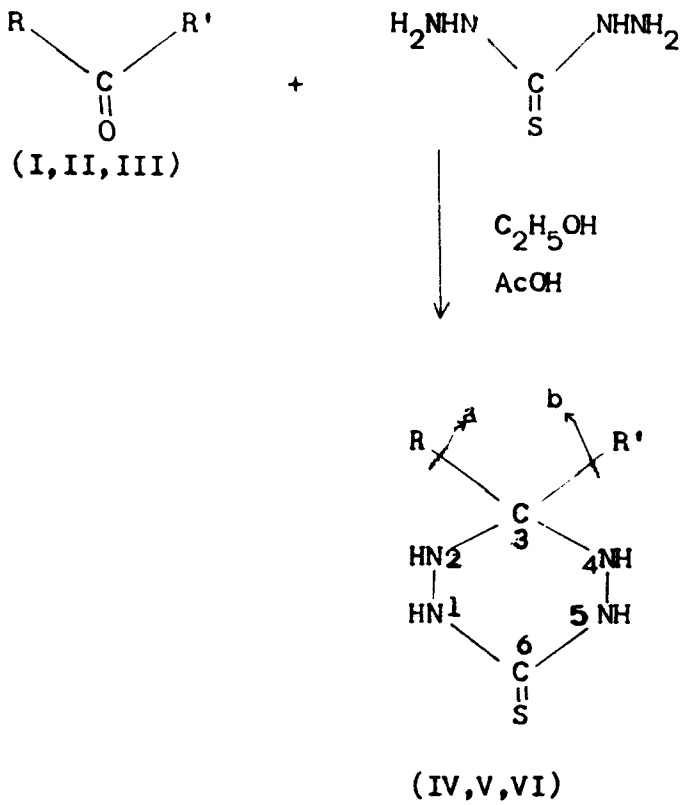
RESULTS AND DISCUSSION

Methyl 10-oxoundecanoate (I), on reaction with an equimolar quantity of thiocarbohydrazide in acetic acid, afforded IV in almost quantitative yield. Its IR spectrum revealed characteristic bands at 3100 (NH), 1740 (ester carbonyl), 1560 (C-N) and 1220, 1170 cm^{-1} (CS-NH, $\begin{matrix}HN\\ HN\end{matrix}\!\!>\!C{=}S$). These values suggest the presence of the hexahydrothioxotetrazine moiety. The NMR spectrum gave a diagnostic broad singlet at 5.15 δ for four protons of ring nitrogens (exchangeable with deuterium) and a singlet at 1.88 δ for terminal CH_3. A broad multiplet at 2.2 δ was assigned to the four protons alpha to ring and ester carbonyl. Other signals present were at 3.65 δ (s, 3H, $COOCH_3$) and 1.25 δ (br s, chain CH_2). On the basis of above data, the compound (IV) was characterized as methyl hexahydro-3-methyl-6-thioxo-1,2,4,5-tetrazine-3-nonanoate. The mass spectrum of IV confirmed the assigned structure by showing a molecular ion peak at *m/z* 302. Two α-cleavage ions at *m/z* 287 (a) and 131 (b) established the position of the hexahydrothioxotetrazine ring (Scheme 1).

Treatment of methyl 9-oxooctadecanoate (II) with thiocarbohydrazide gave V in good yield. Its IR spectrum exhibited bands at 3190 (NH), 1740 (ester CO), and 1560, 1230, 1170 cm^{-1} (CS-NH, $\begin{matrix}HN\\ HN\end{matrix}\!\!>\!C{=}S$). Besides usual fatty acid ester signals, the NMR spectrum gave a broad singlet at 4.65 δ ($4 \times$ N-H, slow D_2O exchangeable) and a broad multiplet at 2.3 δ (6H, CH_2 alpha to ring and ester carbonyl). Mass spectrometry (MS) gave a molecular ion peak at *m/z* 400. Cleavages alpha to the ring provided mass ions at *m/z* 273 (a) and 243 (b) (Scheme 1). These spectral data confirmed the structure of V as methyl hexahydro-3-nonyl-6-thioxo-1,2,4,5-tetrazine-3-octanoate.

Methyl 12-oxooctadecanoate (III) reacted with thiocarbohydrazide and afforded product VI. The IR spectrum displayed bands at 3190 (NH), 1740 (ester carbonyl), and 1565, 1230, 1170 cm^{-1} (CS-NH, $\begin{matrix}HN\\ HN\end{matrix}\!\!>\!C{=}S$). The NMR spectrum exhibited peaks at 4.7 δ (br s, $4 \times$ NH, D_2O exchangeable), 3.65 δ (s, 3H, $COOCH_3$), 2.3 δ (br m, 6H, methylene alpha to ester carbonyl and ring), 1.35 δ (br s,

*To whom correspondence should be addressed.



Compounds	R	R'
I, IV	CH_3	$(CH_2)_8COOCH_3$
II, V	$CH_3(CH_2)_8$	$(CH_2)_7COOCH_3$
III,VI	$CH_3(CH_2)_5$	$(CH_2)_{10}COOCH_3$

SCHEME 1

chain CH_2) and 0.85 δ (t, 3H, CH_3). These data have formulated the compound (VI) as methyl hexahydro-3-hexyl-6-thioxo-1,2,4,5-tetrazine-3-undecanoate. In the MS spectrum, a molecular ion peak was present at *m/z* 400. Mass ions at 315 (a) and 201 (b) are fragments from cleavage alpha to the ring and established the position of the ring at C-12 (Scheme 1).

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