Novel Derivatives of Methyl Hexahydro-3-Methyl-6-Thioxo-1,2,4,5-Tetrazine-3-Nonanoate

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Methyl hexahydro-3-methyl-6-thioxo-1,2,4,5-tetrazine-3-nonanoate (I) on treatment with reagents such as chloroacetic acid, 1,2-dibromoethane and 2-mercaptoethanol under different reaction conditions afforded methyl 3,4,6,7-tetrahydro-3-methyl-6-oxo-2H-thiazolo[3,2-b]-1,2,4,5-tetrazine-3-nonanoate (II), methyl 3,4,6,7-tetrahydro-3-methyl-2H-thiazolo[3,2-b]-1,2,4,5-tetrazine-3-nonanoate (III) and methyl 8-methyl-1-oxa-4-thia-6,7,9,10-tetraazaspiro-[4.5]-decane-8-nonanoate (IV) in good yields. The structures of compounds II–IV were established by elemental analysis, infrared (IR), nuclear magnetic resonance (NMR), and mass spectral data.

KEY WORDS: Chloroacetic acid, 1,2-dibromoethane, 2-mercaptoethanol, methyl hexahydro-3-methyl-6-thioxo-1,2,4,5-tetrazine-3-nonanoate, methyl 8-methyl-1-oxa-4-thia-6,7,9,10-tetraazaspiro[4.5]-decane-8-nonanoate, methyl 3,4,6,7-tetrahydro-3-methyl-6-oxo-2H-thiazolo[3,2-b]-1,2,4,5-tetrazine-3-nonanoate, methyl 3,4,6,7-tetrahydro-3-methyl-2H-thiazolo[3,2-b]-1,2,4,5-tetrazine-3-nonanoate.

Synthesis of thiazoles and oxathiolanes has attracted attention due to their various biological activities. Thiazoles and their derivatives have shown cancer proliferation and metathesis (1), DNA-binding (2) and antithyroidal activity (3). The oxathiolanes and their derivatives are useful as pesticides (4) and in neoplastic therapy (5). Spirooxathiolane derivatives are diagnostic agents in the central nervous or cholinergic system (6). Earlier, we reported the preparation of fatty acid analogues containing such heterocycles (7–10). Scanning the literature revealed to us that thiazole or oxathiolane rings fused with other heterocyclic systems are not well known in fatty acid chemistry. This fact and the above-mentioned health-related and industrial importance led to this report of the synthesis of several thiazole and oxathiolane derivatives of methyl 10-oxoundecanoate.

EXPERIMENTAL PROCEDURES

Melting points were observed on a Kofler apparatus (Reichert-Jung, Wien, Austria) and are uncorrected. Infrared spectra were recorded as thin films or as nujol mulls on a Pye Unicam SP-3-100 spectrophotometer (Pye Unicam, Cambridge, U.K.), calibrated against polystyrene. Nuclear magnetic resonance (NMR) spectra ($CDCl_3$ for II; CCl_4 for III and IV) were recorded at 60 MHz in a Varian A-60 spectrometer (Varian Associates, Palo Alto, CA). Chemical shifts were observed in ppm with tetramethylsilane as the internal standard. Mass spectra were recorded with a JEOL JMS D 300 instrument (JEOL Ltd., Tokyo, Japan). Compounds were injected by hypodermic needle through a serum cap. Column chromatography was carried out with silica gel (60–120 mesh) at 25–30 gram per gram of material to be purified.

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To an ethanolic solution of methyl 10-oxoundecanoate (11) (0.005 mol), a solution of thiocarbohydrazide (0.005 mol) in acetic acid was added over a period of 15 min. After addition, the reaction mixture was further stirred for 10 min at room temperature and then worked up with diethylether. The ethereal solution was washed with water, sodium bicarbonate (5%) and again with water and dried over anhydrous sodium sulfate. Evaporation of solvent provided a semi-solid residue, which on crystallization from methanol gave I as a white powder in 97% yield, m.p. 120°C (Fig. 1).

Reaction of **I** *with chloroacetic acid.* A mixture of I (2 g, 6 mmol), chloroacetic acid (0.576 g, 6 mmol) and fused sodium acetate (0.5 g, 6 mmol) was dissolved in anhydrous ethanol (70 mL). The mixture was heated under reflux for 3 hr, and then allowed to stand overnight at room temperature. The solid thus obtained was recovered by filtration and was washed with water, dried and crystallized from ethanol to give white needles of II in 80% yield, m.p. 72°C (Fig. 1). Analysis—Found: C, 52.69; H, 7.65; N, 16.36; $C_{15}H_{26}O_3N_4S$ requires: C, 52.62; H, 7.69; N, 16.39%. Spectral data are given in the Discussion section.

Reaction of **I** *with 1,2-dibromoethane.* A mixture of I (2 g, 6 mmol) and 1,2-dibromoethane (1.2 g, 6 mmol) in ethanolic potassium hydroxide (5%, 20 mL) was heated under reflux for 3 hr. The reaction was monitored by thin-layer chromatography (TLC) (petroleum ether:diethyl ether, 90:10, v/v). When the reaction was complete, the reaction mixture was concentrated, cooled in an ice bath and neutralized with diluted acetic acid. It was worked up with diethyl ether, and a crude oily residue (III) was obtained after evaporation of the solvent (Fig. 1). The crude oil was chromatographed on a silica gel column (petroleum ether:diethyl ether, 5:2, v/v) to get a colorless oily product (yield, 73%). Several attempts to crystallize the product failed. Analysis—Found: C, 54.93; H, 8.54; N, 17.05; $C_{15}H_{28}O_2N_4S$ requires: C, 54.87; H, 8.61; N, 17.09%.

Reaction of **I** *with 2-mercaptoethanol.* A solution of I (2 g, 6 mmol) in acetic acid (25 mL), 2-mercaptoethanol (0.4 g, 6 mmol) and BF_3-etherate (5 mL) was stirred at room temperature for 50 min. At the end of the reaction, acetic acid and etherate were removed *in vacuo.* The residue was extracted with diethyl ether, washed with 5% aqueous solution of sodium bicarbonate, and dried over anhydrous Na_2SO_4. After evaporation of the solvent, an oily residue was obtained, which was chromatographed (petroleum ether:diethyl ether, 92:8, v/v) on a silica gel column to afford a colorless oily product (IV) in 60% yield (Fig. 1). The product failed to crystallize. Analysis—Found: C, 52.5; H, 8.72; N, 16.16; $C_{15}H_{30}O_3N_4S$ requires: C, 52.01; H, 8.78; N, 16.19%.

RESULTS AND DISCUSSION

On treatment with an equimolar amount of chloroacetic acid in anhydrous ethanol and sodium acetate, methyl hexahydro-3-methyl-6-thioxo-1,2,4,5-tetrazine-3-nonanoate

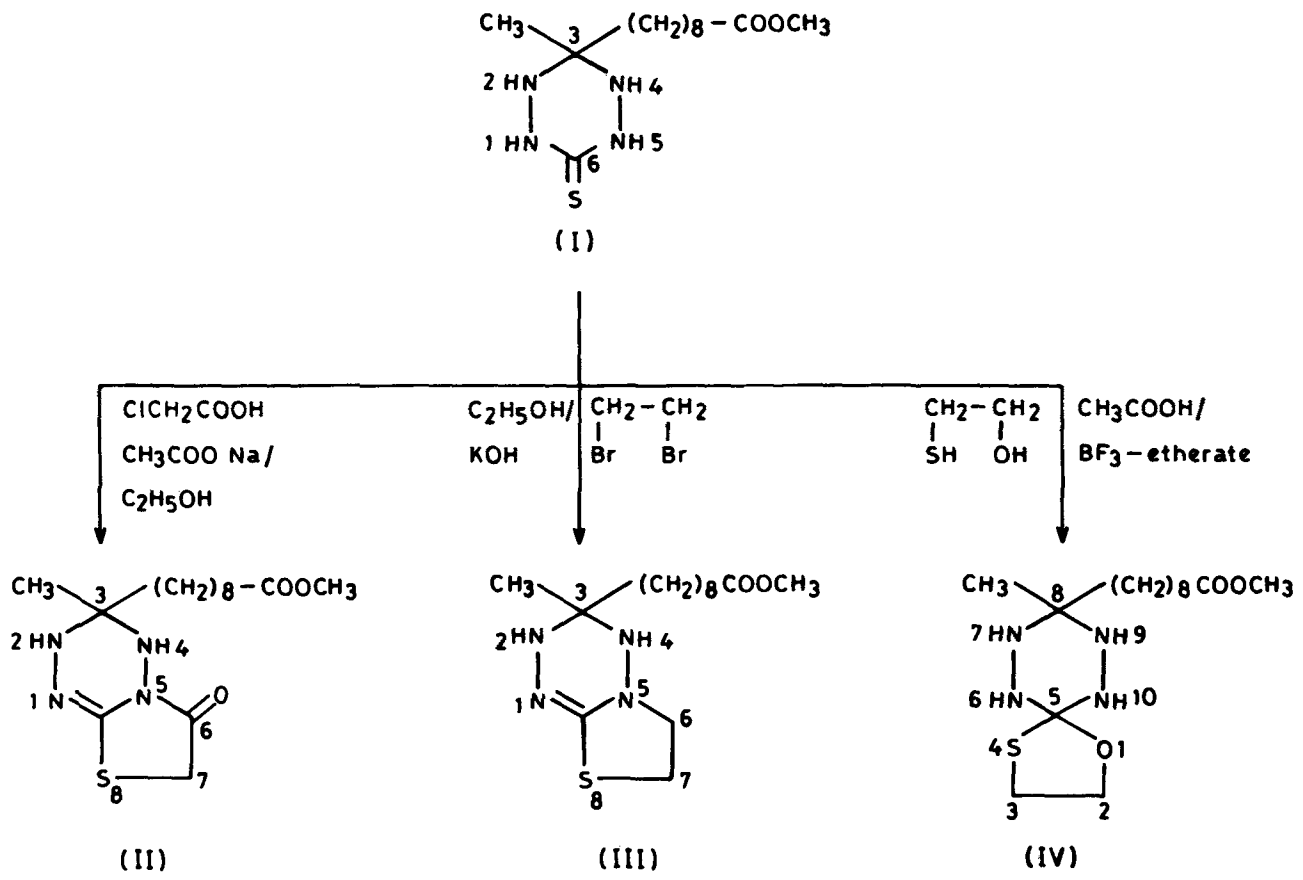

FIG. 1. Reactions of methyl hexahydro-3-methyl-6-thioxo-1,2,4,5-tetrazine-3-nonanoate (I) with chloroacetic acid, 1,2-dibromoethane and 2-mercaptoethanol.

(I) furnished II in high yield. Compound II showed characteristic infrared (IR) absorption bands at 3250 (NH), 1735 (ester CO), 1635 (C=N), 1675 (NCO), 1550 (C-N) cm^{-1}, and 1440 cm^{-1} (CH_2-S). The NMR spectrum showed signals at δ 3.75 *s*(2H, S-C$\underline{H}_2$CO), 3.69 *s*(2H, N$\underline{H}$, slow D_2O exchange), 3.64 *s*(3H, COOC$\underline{H}_3$), 2-2.3 *br m*(4H, C$\underline{H}_2$ α-to ring and ester carbonyl), 1.9 *s*(3H, C$\underline{H}_3$), and 1.3 *br s*(12H, chain C$\underline{H}_2$). The mass spectrum of this compound showed a molecular ion peak at *m/z* 342. Ions at *m/z* 327 and 171, from cleavage α to C_{10}, established the position of the tetrazine ring (Fig. 2). Other significant ions at *m/z* 300, 228, 214 and 130 established the presence of a fused ring system on the fatty ester chain (Fig. 2). Thus, the product (II) is methyl 3,4,6,7-tetrahydro-3-methyl-6-oxo-2$\underline{H}$-thiazolo[3,2-b]-1,2,4,5-tetrazine-3-nonanoate.

A solution of I in ethanolic potassium hydroxide, when refluxed with 1,2-dibromoethane, afforded an oily product (III) in good yield. The product did not respond to the Beilstein test for the presence of bromine. Its IR spectrum displayed bands at 3350 (NH), 1735 (COOCH_3), 1630 (C=N), 1560 (C-N), and 1435 cm^{-1} (CH_2-S). In addition to the usual signals from the fatty acid ester moiety, the NMR spectrum of III showed absorptions at δ 5.3 *br m*(2H, N$\underline{H}$, slow D_2O exchange), 3.8 *t*(2H, >N-C$\underline{H}_2$), and 3.7 *t*(2H, S-C$\underline{H}_2$). Mass spectrometry (MS) showed a molecular ion peak at *m/z* 328. Two α-cleavage ions were at *m/z* 313 and 157, which confirmed the position of the hetero-cyclic system on the fatty ester chain (Fig. 2). These data agree with the formulation of III as methyl 3,4,6,7-tetrahydro-3-methyl-2$\underline{H}$-thiazolo[3,2-b]-1,2,4,5-tetrazine-3-nonanoate.

A solution of I in acetic acid, when reacted with 2-mercaptoethanol and BF_3-etherate at room temperature, gave an oily product, which on fractionation on a silica gel column afforded product IV in good yield. The IR spectrum showed characteristic bands at 3300 (NH), 1740 (ester carbonyl), 1550 (C-N), 1450 (S-CH_2, deformation), 1230 (S-CH_2, wagging) and 1090 (oxathiolane ring). The NMR spectrum showed three structure-revealing signals at δ 6.8 *br m*(4H, N$\underline{H}$, slow D_2O exchange), δ 4.0 *br m*(2H, -O-C$\underline{H}_2$-) and 2.9 *br m*(2H, -C$\underline{H}_2$-S-). On the basis of above data, compound IV was identified as methyl 8-methyl-1-oxa-4-thia-6,7,9,10-tetraazaspiro[4.5]-decane-8-nonanoate. The MS of IV gave a molecular ion at *m/z* 346 and two diagnostic ions at *m/z* 331 and 175, resulting from fragmentation α to the ring at C_{10} (Fig. 2). Scanning of the literature has revealed that the ring system of compound IV is new.

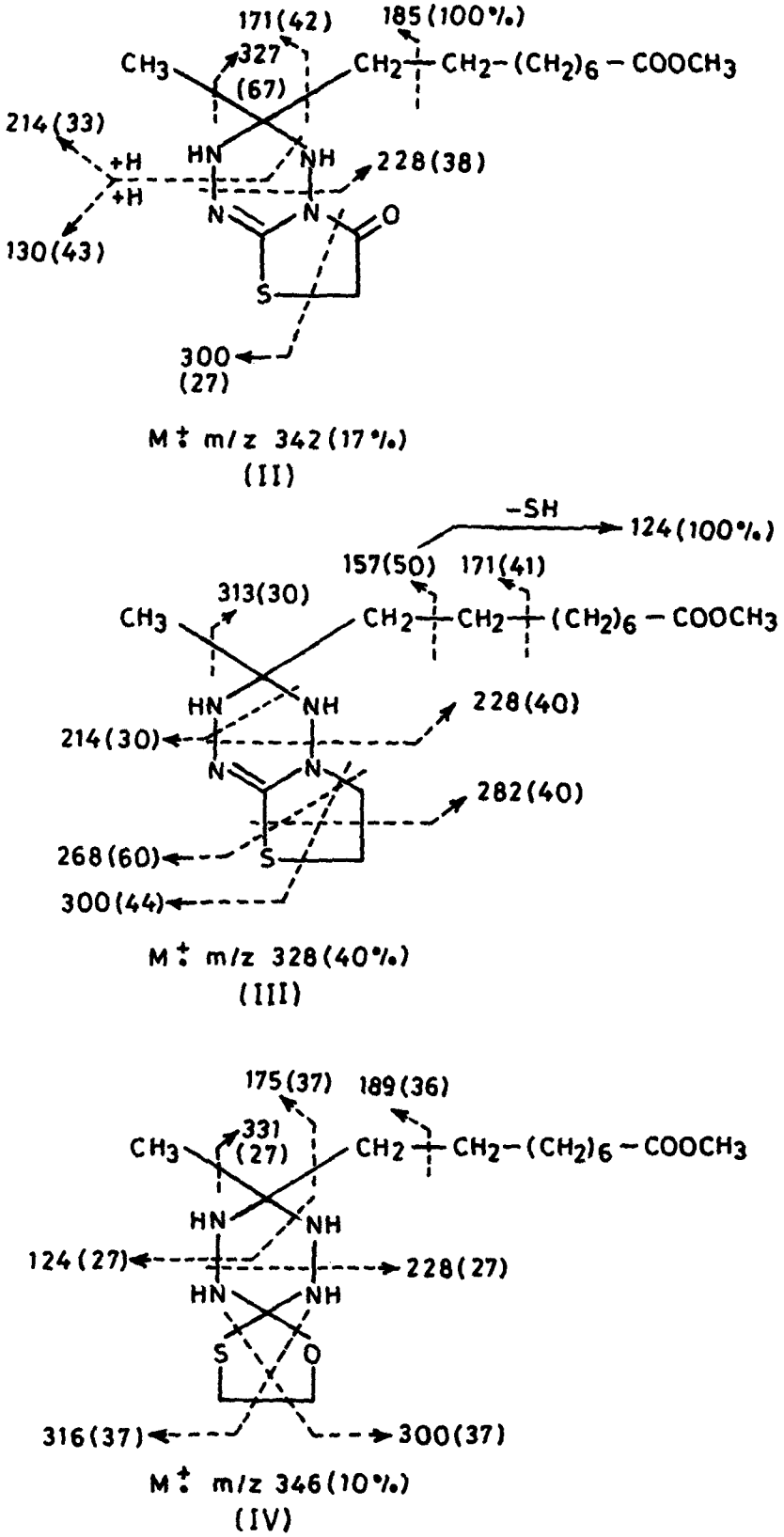

FIG. 2. MS fragmentation patterns of methyl 3,4,6,7-tetrahydro-3-methyl-6-oxo-2H-thiazolo[3,2-b]-1,2,4,5-tetrazine-3-nonanoate (II), methyl 3,4,6,7-tetrahydro-3-methyl-2H-thiazolo[3,2-b]-1,2,4,5-tetrazine-3-nonanoate (III) and methyl 8-methyl-1-oxa-4-thia-6,7,9,10-tetraazaspiro[4.5]-decane-8-nonanoate (IV).

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