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♣Derivatization of Keto Fatty Acids. III. Synthesis of Terminal Thiazole and Oxazole Derivatives from α-Bromoketones

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ABSTRACT

The synthesis of alkyl chain substituted thiazole and oxazole derivatives is described. The reaction of 11-bromo-10-oxoundecanoic acid with thiourea and acetamide yielded terminally located thiazole and oxazole derivatives, respectively. A similar treatment with urea produced the unexpected urea-substituted product, together with an unidentified product.

INTRODUCTION

Compounds containing thiazole and oxazole nuclei are known to possess pharmacoactive properties and are used as antibacterial agents (1), fungicides (2), surface and infiltration anaesthesia (3) and tranquilizers (4). Long-chain sulfur and oxygen-containing heterocycles have recently been an area of wide interest. Several thiazolidinones prepared from oxoesters were reported in a previous paper (5). Because fatty derivatives with terminally located heterocyclic functions are comparatively rare or little known, an attempt was made to synthesize these compounds from long-chain α-bromoketones. In this paper we report the use of thiourea, acetamide and urea in the synthesis of long-chain thiazole and oxazole derivatives from the bromoketones.

EXPERIMENTAL PROCEDURES

All melting points are uncorrected. Infrared (IR) spectra were obtained on samples in nujol (6) with a Perkin-Elmer 621 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were run in $CDCl_3$ on a Varian A-60 spectrometer with tetramethylsilane (TMS) as the internal standard. The abbreviations s, d, m, q, br and t denote singlet, doublet, multiplet, quartet, broad and triplet. Mass spectra were measured with AEI MS-902 spectrometer coupled to a DS-55 mass data system at 70 eV. Thin layer chromatographic (TLC) plates were coated with silica gel G, and a mixture of petroleum ether/ether/acetic acid (80:20:1, v/v) was used as developing solvent. The spots were visualized by charring after spraying with a 20% aqueous solution of perchloric acid. Light petroleum refers to a fraction of b.p. 40-60 C.

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MATERIALS AND METHODS

10-Undecenoic acid (I, 1.84 g, 0.01 mol), when stirred with N-bromosuccinimide (NBS, 1.88 g, 0.01 mol) and water (4 mL) (7) for 1 hr yielded 11-bromo-10-hydroxyundecanoic acid (II) m.p. 48-49 C. The exclusive formation of II, is in accordance with Markovnikoff's rule, which on Jones oxidation (8) gave 11-bromo-10-oxoundecanoic acid (III). The Jones reagent was prepared by dissolving chromium trioxide (35 g) in water (100 mL), and added concentrated sulphuric acid (30 mL) by drops. The compound (III) m.p. 90-91 C (positive Beilstein test) was further characterized by elemental and spectral analysis (recorded in Results and Discussion section).

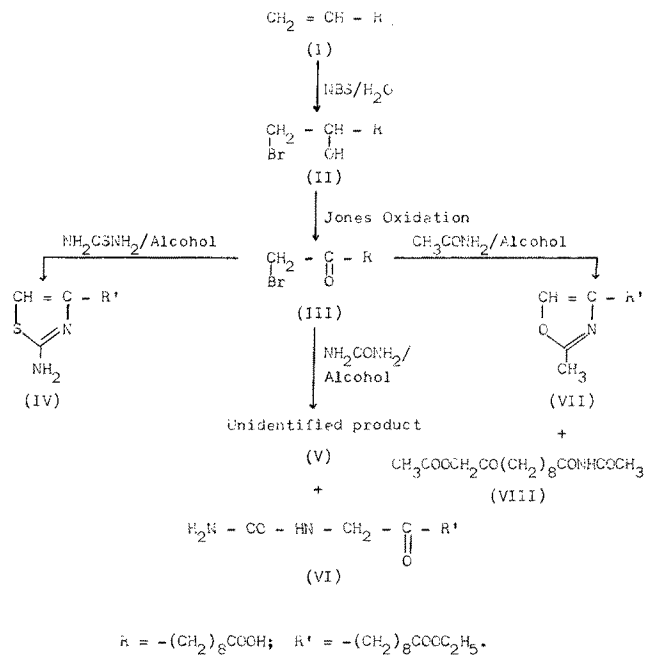
Reaction of Thiourea with III (9)

11-Bromo-10-oxoundecanoic acid (III, 2.0 g, 0.007 mol) was refluxed with thiourea (0.53 g, 0.007 mol) in alcohol (4 mL) for 2 hr. The reaction mixture was allowed to cool at room temperature and poured into ice-water (100 mL). To this solution ammonium hydroxide was added to make it just alkaline. The reaction mixture was extracted with ether, washed with water and dried over anhydrous sodium sulphate. Evaporation of ether gave a solid that on crystallization from alcohol at low temperature, yielded 2-amino-4-(8-carboethoxyoctyl) thiazole, IV (1.42 g, ca. 71%) m.p. 81-82 C (Scheme 1). Analysis: calculated for $C_{14}H_{24}N_2O_2S$: C, 56.25; H, 7.81; N, 10.93. Found: C, 55.81; H, 7.23; N, 10.12% (spectral values are recorded in the discussion part of this paper).

Reaction of Urea with III

A similar treatment as described above, α-bromoketone (III, 2.0 g, 0.007 mol) on refluxing with urea (0.42 g, 0.007 mol) in alcohol (4 mL) for 2 hr yielded a brown viscous oil (1.9 g), which showed 2 distinct spots on TLC plate.

A column of silica gel G (38 g), prepared in petroleum ether, was charged with total crude mixture, and the column was eluted with a mixture of petroleum ether/benzene (95:5, v/v) (fractions of 15 mL were collected). TLC-monitored eluates were combined to give product (V) (Scheme 1) as a yellow viscous oil (0.65 g, ca. 34%, not identified).



SCHEME 1. Reaction scheme.

Subsequent elution with a mixture of petroleum ether/benzene (45:55, v/v) gave ethyl 11-carbamido-10-oxoundecanoate (VI) as a white solid (1.10 g, ca. 58%) m.p. 137-138 C. Analysis: calculated for $C_{14}H_{26}N_2O_4$: C, 58.74; H, 9.09; N, 9.79; found: C, 58.61; H, 9.02; N, 9.63%.

Reaction of Acetamide with III

A similar treatment of α-bromoketone, III (2 g, 0.007 mol) with acetamide (0.41 g, 0.007 mol) in alcohol (4 mL) yielded an oil (1.7 g) that showed 2 distinct spots on TLC and was chromatographed over a column of silica gel G (34 g). Elution with a mixture of benzene/ether (90:10, v/v) afforded 2-methyl-4-(8-carboethoxyoctyl)oxazole (VII) (Scheme 1) (1.0 g, ca. 59%). Analysis: calculated for $C_{15}H_{25}NO_3$: C, 67.16; H, 9.71; N, 5.20; found: C, 67.10; H, 9.68; N, 5.01%.

Subsequent elution with a mixture of benzene/ether (80:20, v/v), followed by crystallization from petroleum ether, gave 11-acetoxy-10-oxoundecacetamide (VIII, 0.61 g, 36%) m.p. 94-95 C. Analysis: calculated for $C_{15}H_{25}NO_5$: C, 60.20; H, 8.36; N, 4.86; found: C, 60.10; H, 8.21; N, 4.68%.

RESULTS AND DISCUSSION

The starting material 11-bromo-10-oxoundecanoic acid (III) was obtained by Jones Oxidation (8) of 11-bromo-10-hydroxyundecanoic acid (II), which was prepared by the reaction of 10-undecenoic acid (I) with NBS and water (7). The exclusive formation of II has also been reported by Champetier and Despas (10) by the addition of hypobromous acid to 10-undecenoic acid (I). The compound (III) responded positively to dinitrophenylhydrazine (DNP) for oxo function, and Beilstein test for presence of halogen in compound.

Compound III, analyzed for $C_{11}H_{19}O_3Br$. Its IR spectrum showed bands at 3410 (COOH), 1730 ($BrCH_2\underline{CO}$), 1710 (COOH) and 720 cm^{-1} (C-Br). The rise in carbonyl frequency (1730 cm^{-1}) was associated with a close approach of the halogen atom (11). The NMR spectrum exhibited peaks at δ 3.75 s (2H, $Br\underline{CH_2}$); 2.55 t (2H, $BrCH_2CO\underline{CH_2}$); 2.2 t (2H, $\underline{CH_2}COOH$) and 1.25 br,s (chain-$\underline{CH_2}$). From these data, III was formulated as 11-bromo-10-oxoundecanoic acid.

The α-bromoketone (III), when refluxed with thiourea in the presence of alcohol for 2 hr gave a TLC homogenous product, IV, which was purified by crystallization. The compound, IV, was analyzed for $C_{14}H_{24}N_2O_2S$. Its IR spectrum revealed absorption bands at 3490, 3290, 3100 (NH_2), 1740 ($\underline{COO}C_2H_5$), 1630 (C=C), 1615 (C=N), 1400 (C-N), 1225 (C-S wag.), 1170, 1030 (C-O), 960 cm^{-1} (*trans* unsaturation) and 710 cm^{-1} (C-S stretch.). The NMR spectrum exhibited signals at δ 5.9 s (1H, $\underline{CH}$=C); 4.88 br,s (2H, $N\underline{H_2}$, disappeared on D_2O shake); 4.0 q (2H, $O\underline{CH_2}CH_3$, J=6Hz); 2.4 t (2H, CH=C-$\underline{CH_2}$); 2.2 t (2H, $\underline{CH_2}COOC_2H_5$); 1.25 br,s (chain-$\underline{CH_2}$). Its mass spectrum (Fig. 1) showed a molecular ion peak at m/e 284 ($C_{14}H_{24}N_2O_2S$) along with (M+1) and (M+2) peaks. The salient peaks are shown in Scheme 2. On the basis of these data, the structure of IV was assigned 2-amino-4-(8-carboethoxyoctyl)thiazole.

The similar treatment of α-bromoketone (III) with urea in alcohol gave 2 products (V and VI). The only major project, VI (m.p. 137-138 C), was characterized as ethyl 11-carbamido-10-oxoundecanoate. It corresponded to the formula $C_{14}H_{26}N_2O_4$. Its IR spectrum revealed bands at

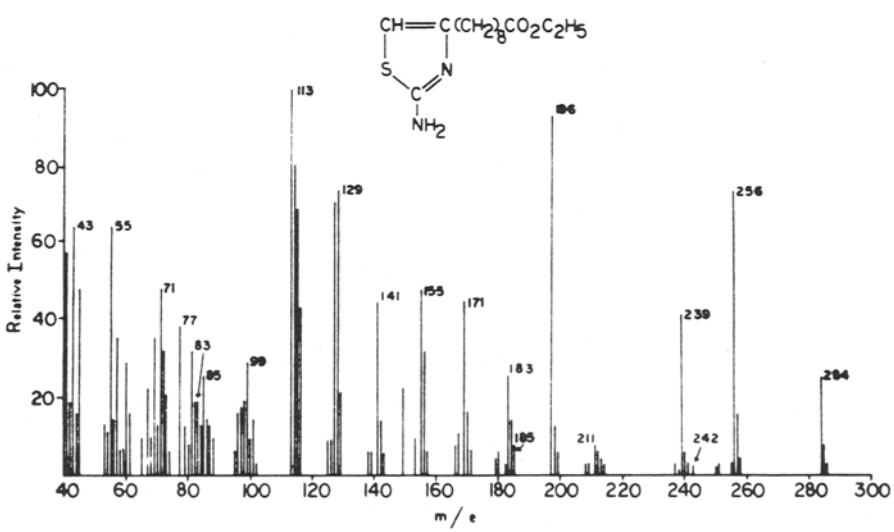
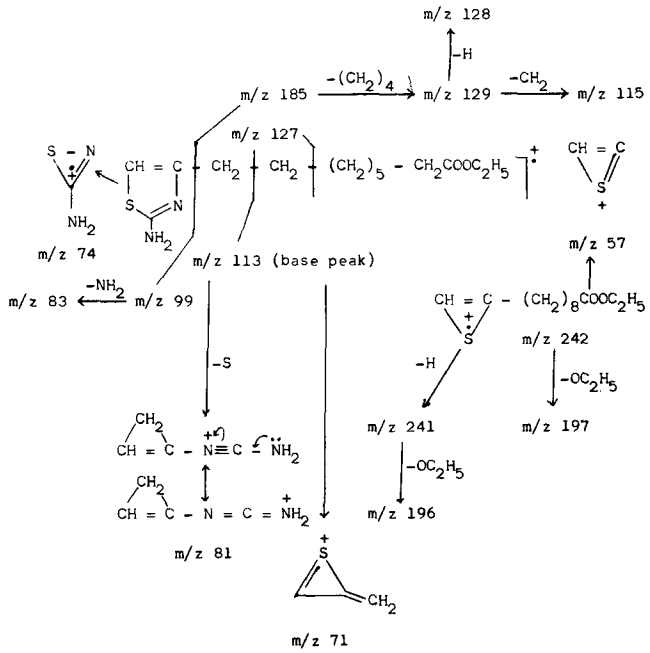


FIG. 1. Mass spectrum of IV.

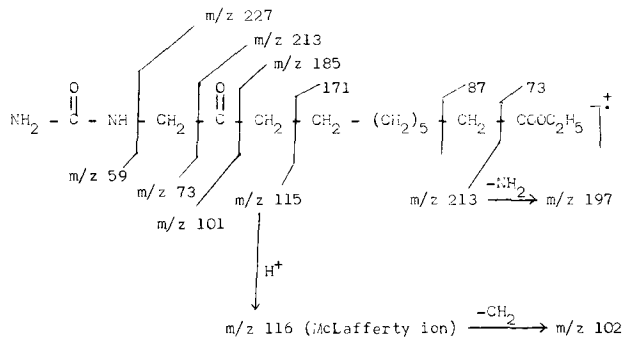


m/e 284 (M^+)(M+1, M+2); 256 (M-C_2H_4); 239 (M-OC_2H_5); 196 (M-$C_4H_8O_2$); 185 (M-$C_3H_3N_2S$); 171 (185-CH_2); 114 (113+H or 115-H).

SCHEME 2. Mass fragmentation pattern of IV.

3370, 3300, 3210 (NHCONH$_2$), 1740 (COOC$_2$H$_5$), 1700 (CO), 1685 (NHCONH$_2$), 1590 (NH$_2$- def.), 1170, 1080 (C-O) and 800 cm^{-1} (NH$_2$ wag.). The structure of VI was confirmed by its mass spectrum (Fig. 2). It showed a molecular ion peak at m/e 286 followed by other salient peaks shown in Scheme 3.

A similar treatment of α-bromoketone (III) with acetamide in alcohol afforded 2 products (VII and VIII). The major compound, VII, was analyzed for $C_{15}H_{25}NO_3$. In IR spectrum, a strong band at 1740 (COOC$_2$H$_5$), 1640 (C=C),



m/e 286 (M^+); 257 (M-C_2H_5); 241 (M-OC_2H_5); 239 (257-H_2O); 238 (239-H); 166 (239-$C_2H_5N_2O$); 88 (McLafferty ion).

SCHEME 3. Mass fragmentation pattern of VI.

1600 (C=N), 1410 (C-N), 1175, 1090, 1025 (C=O) and 940 cm^{-1} (*trans* unsaturation) were observed. The NMR spectrum gave signals at δ 6.2 s (1H, CH=C, relatively downfield, which is probably caused by oxygen); 4.1 q (2H, OCH$_2$CH$_3$, J=6Hz); 2.4 s (3H, -N=C-CH$_3$); 2.2 m (4H, CH=C-CH$_2$(CH$_2$)$_6$-CH$_2$COOC$_2$H$_5$); 1.3 br,s (chain-CH$_2$) and 1.1 t (3H, OCH$_2$CH$_3$, partly merged with chain methylene protons). Its mass spectrum (Fig. 3) showed molecular ion peak at m/e 267 ($C_{15}H_{25}NO_3$) followed by other important peaks shown in Scheme 4.

The rearranged minor product, VIII (m.p. 94-95 C), was analyzed for $C_{15}H_{25}NO_5$. Its IR spectrum gave absorption bands at 1745 (OCOCH$_3$), 1715 (CO), 1685 (CONHCOCH$_3$), 1215 (acetate), 1100, 1060 and 1010 cm^{-1} (C-O). NMR spectrum exhibited peaks at δ 4.55 s (2H, OCH$_2$), 2.4 m (4H, COCH$_2$(CH$_2$)$_6$CH$_2$CO); 2.25 s (3H, NHCOCH$_3$); 2.1 s (3H, OCOCH$_3$, partly merged with methyl protons of NHCOCH$_3$), 1.8 br,s (1H, NH, disappeared on D$_2$O shake), 1.35 br,s (chain-CH$_2$). The mass

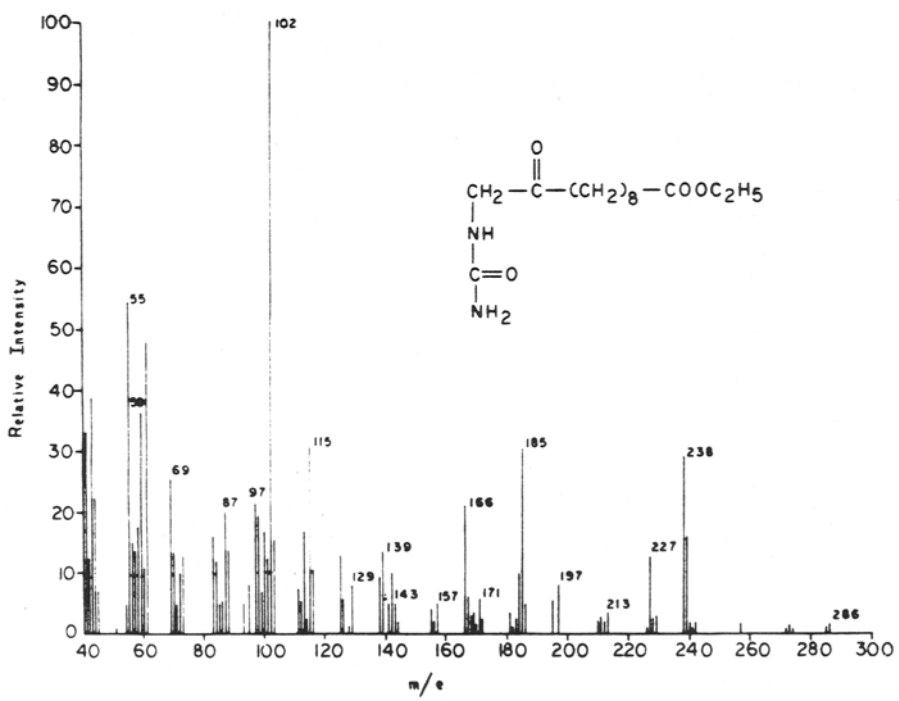


FIG. 2. Mass spectrum of VI.

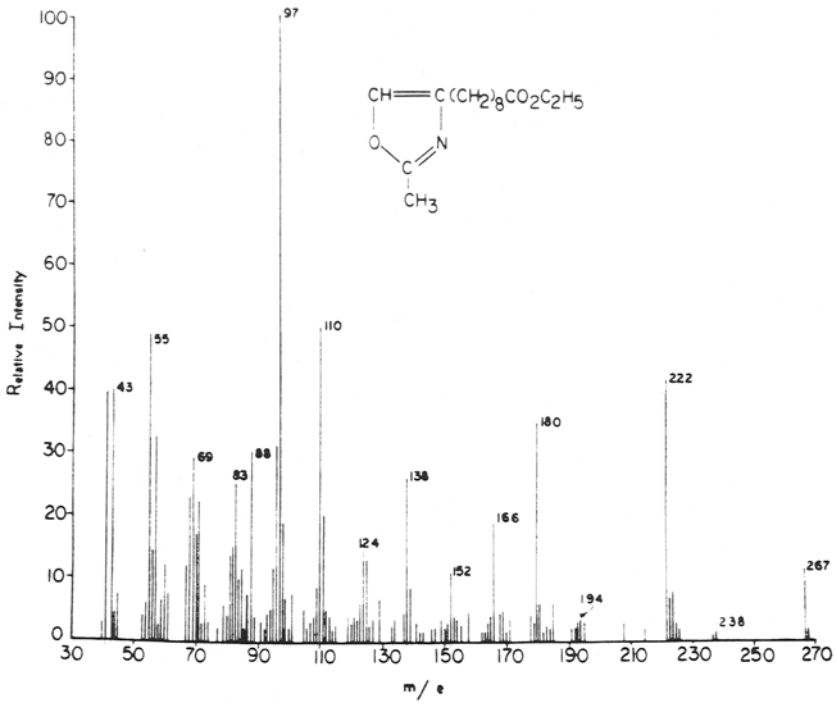
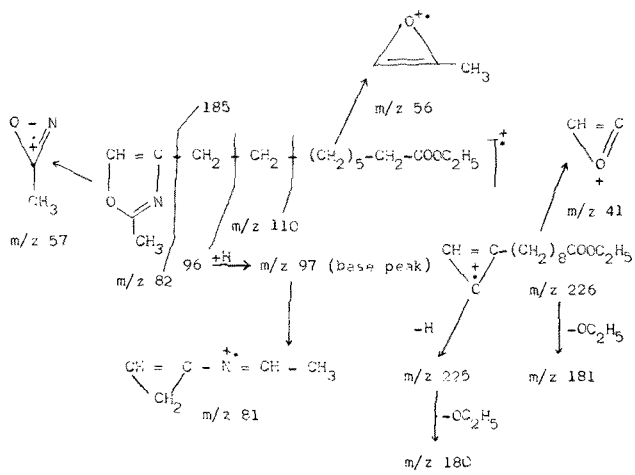


FIG. 3. Mass spectrum of VII.



m/e 267 (M^{+}); 238 ($M-C_2H_5$); 222 ($M-OC_2H_5$), 194 (222-CO); 180 (194-CH_2); 69 (83-CH_2); 68 (83-CH_3); 67 (82-CH_3).

SCHEME 4. Mass fragmentation pattern of VII.

spectrum (Fig. 4) displayed a molecular ion peak at m/e 299 ($C_{15}H_{25}NO_5$). The genesis of structure-revealing fragment ions is shown in Scheme 5. The formation of VIII can be shown through the substitution of bromine of α-bromoketone (III) by acetamide from the oxygen side and the attack of water present in alcohol with the simultaneous evolution of ammonia. The subsequent substitution of hydroxyl function of carboxylic group by acetamide finally gave the product.

Yields of oxazoles are always lower than for corresponding thiazoles, and reaction takes place less easily. This is probably related to the fact that the sulfur has a greater tendency than oxygen to increase its covalency (12).

ACKNOWLEDGMENT

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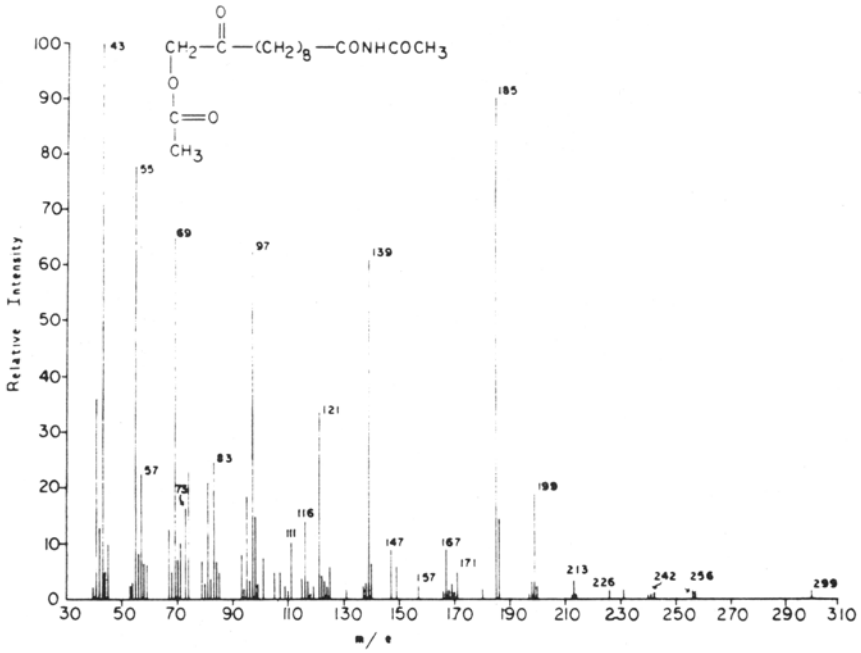
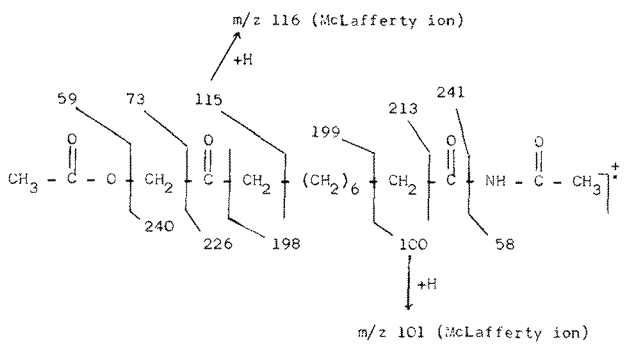


FIG. 4. Mass spectrum of VIII.



m/e 299 ($M^{+\cdot}$); 256 ($M-CH_3CO$); 185 ($199-CH_2$); 157 ($199-(CH_2)_3$); 140 ($198-NHCOCH_3$); 139 ($199-CH_3COOH$); 97 ($157-CH_3COOH$); 73 ($116-CH_3CO$).

SCHEME 5. Mass fragmentation pattern of VIII.

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