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# SOME REACTIONS AND MASS SPECTRA OF 2-ACYLTHIOPHENES

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Abstract—The acetylation of 2-isovalerylthiophene has been studied. Condensation of 2-acetylthiopene with ethyl acetate afforded 2-thenoylacetone, which reacted with acrylate ester (Michael condensation). Ureidomethylene-2-thenoylacetone was prepared and cyclized to the 5-thenoylpyrimidine. Mass spectra of 2-monoacyl-, 2,5-diacyl-, and 2-benzoylthiophenes were determined and their fragmentation patterns are discussed. α-Cleavage to the carbonyl group is the dominant feature affording the most prominent ion in most cases. The spectrum of 2-benzoylthiophene suggests that loss of mass units 28 with the phenyl migration from the molecular ion is a likely occurrence.

THE (M-28) ion associated with loss of carbon monoxide from the molecular ion has been reported for the mass spectra of benzophenone,[1] 2-benzoylfuran,[2] and 2-benzoylthiazole.[3] It is the purpose of the present study to see if such a behaviour induced by electron bombardment also prevails for 2-acyl- and 2-aroylthiophenes. Another object is to establish the fragmentation patterns of acylthiophenes, since the only reported mass spectrum of acylthiophene is that of 3-acetyl-4-hydroxythiophene.[4] For this purpose several unknown 2-acyl- and 2-aroylthiophenes were prepared, which are additionally recorded in this paper.

*Syntheses.* Although various reagents have been employed for the acylation of thiophene,[5–7] acylation of 2-acylthiophene[8] has met little success. Condensation of 2-acetylthiophene (I) with isovaleric chloride or isovaleric acid using zinc chloride or phosphorus pentoxide failed whereas the reaction of 2-isovalerylthiophene (II) with acetic acid in the presence of phosphorus pentoxide afforded diacylthiophene in poor yield. The NMR spectrum of this compound in deuterochloroform shows a singlet at 2·30 τ alone in the aromatic region, which is compatible only with 2-acetyl-5-isovalerylthiophene (III) and excludes the other possible alternative, 2,4-diacylthiophene.

Condensation of 2-acetylthiophene (I) with ethyl acetate in the presence of sodium afforded 2-thenoylacetone (IV), from which two compounds were obtained. An

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[1] J. Eland and C. Danby, *J. Chem. Soc.* 5935 (1965).

[2] R. Grigg, M. Sargent, D. H. Williams and J. Knight, *Tetrahedron* 21, 3441 (1965).

[3] G. Clarke, R. Grigg and D. H. Williams, *J. Chem. Soc. Phys. Org.* 339 (1966).

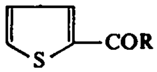
[4] R. Grigg, H. Jacobsen, S.-O. Lawesson, M. Sargent, G. Schloll and D. H. Williams, *J. Chem. Soc. Phys. Org.* 331 (1966).

[5] H. Hartough and K. Kosak, *J. Am. Chem. Soc.* 69, 3098 (1947).

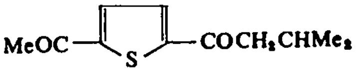
[6] H. Hartough and K. Kosak, *J. Am. Chem. Soc.* 69, 1012 (1947).

[7] M. Sy and B. deMalleray, *Bull. Soc. Chim. Fr* 1276 (1963).

[8] For review of acylthiophenes see H. Hartough, *Thiophene and its derivatives* p. 321. Interscience, New York (1952) and S. Gronowitz, *Advances in heterocyclic chemistry* (Edited by A. Katritzky) p. 1. Academic Press, New York (1963).


I R=Me

II R=$CH_2CHMe_2$


III

attempted Michael condensation[9] with methyl acrylate in the presence of sodium ethoxide gave a compound analysed as $C_{11}H_{14}O_3S$ which was also the reaction product of ethyl acrylate with IV in the presence of sodium ethoxide. An integrated NMR spectrum of this compound in carbon tetrachloride revealed a triplet (3H) at 8·75 $\tau$ ($J = 7$ c/s), a triplet (2H) at 8·03 $\tau$ ($J = 6$ c/s), a quintet (2H) at 7·65 $\tau$ ($J = 6$ c/s), a triplet (2H) at 7·05 $\tau$ ($J = 6$ c/s), and a quartet (2H) at 5·92 $\tau$ ($J = 7$ c/s) in the aliphatic region. This defines the presence of a $CO(CH_2)_3COOEt$ group. In the aromatic region three quartets were visible at 2·96 $\tau$ ($J = 4·8$ c/s and $J = 4·2$ c/s), 2·43 $\tau$ ($J = 4·8$ c/s and $J = 1·5$ c/s), and 2·33 $\tau$ ($J = 4·2$ c/s and $J = 1·5$ c/s) and are assignable to the C-4, 5, and 3-protons of the thiophene ring, respectively, on the basis of coupling constants.[10] These observations coupled with the mass spectrum (*vide infra*) permits the formulation of this compound as ethyl $\gamma$-2-thenoylbutyrate (V).


I IV V

The transformation of compound IV into 5,2'-thenoylpryimidine was carried out in order to examine the possible occurrence of the (M-28) ion in its mass spectrum and add further examples to the catalogue of the electron impact induced fragmentation patterns of the pyrimidine ring.[11,12] Ureidomethylene-2-thenoylacetone (VI), which was obtained by the reaction of IV with urea and ethyl orthoformate, was cyclized with sodium methoxide[13] and gave a compound analysed as $C_{10}H_8N_2O_2S$ with VII-a or VII-b as possible structures. Although lower volatility precluded the mass spectrometry of this compound and hence could not reveal the spectral characteristics (*vide supra*), VII-b is more likely for the subsequent reason. The NMR spectrum of this compound in hexadeuterated DMSO had a Me singlet at 7·57 $\tau$ which showed a remarkable downfield shift (6·98 $\tau$) in trifluoroacetic acid. Such a large downfield shift of the Me signal on going from neutral to acidic solvent, which is caused by the formation of an ammonium ion, is compatible with the structure VII-b, and in fact it has been observed[14] that the resonance peak of the C-4 (or 6) Me of the pyrimidine ring shows a small shift (—0·2 ppm) in acetic acid and a much larger shift (—0·3 to —0·5 ppm) in trifluoroacetic acid from the resonance position in deuterochloroform. However, the Me signal of acetophenone has been reported

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[9] E. Bergman, D. Ginsburg and R. Pappo, *Org. Reactions* **10**, 179 (1959).

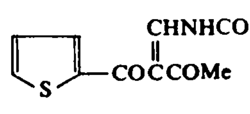
[10] R. White, *Physical methods in heterocyclic chemistry* (Edited by A. Katritzky) Vol. 2; p. 103. Academic Press, New York (1964).

[11] J. Rice, G. Dudek and M. Barber, *J. Am. Chem. Soc.* **87**, 4569 (1965).

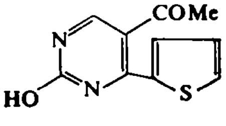
[12] T. Nishiwaki, *Tetrahedron* **22**, 3117 (1966) and his subsequent papers.

[13] C. Whitehead, *J. Am. Chem. Soc.* **75**, 671 (1953).

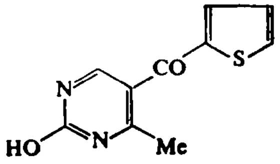
[14] T. Nishiwaki, *Tetrahedron* **23**, 1153 (1967).



VI



VII-a



VII-b

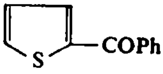
TABLE 1. THE THIOPHENE RING PROTONS OF THE COMPOUND VII-b (τ VALUES)*

| | C-3 | C-4 | C-5 |
|---|---|---|---|
| $d_6$-$Me_2SO$ | 2·11 (q, $J_{34}$ = 4·2)<br>$J_{35}$ = 1·5 | 2·67 (q, $J_{45}$ = 5·4)<br>$J_{34}$ = 4·2 | 1·88 (q, $J_{45}$ = 5·4)<br>$J_{35}$ = 1·5 |
| $CF_3COOH$ | 2·17 broad | 2·66 broad | 1·89 (q, $J_{45}$ = 5·4)<br>$J_{35}$ = 1·5 |

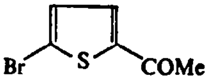
* Spin-spin coupling is indicated in parentheses by the multiplicity (q; quartet) followed by the coupling constant in c/s.

to move downfield (0·14 ppm) to a slight extent on going from deuterochloroform to trifluoroacetic acid.[15] The C-6 (or 4) proton appeared at 1·44 τ in hexadeuterated DMSO in agreement with the reported value[16] which shifted to 0·99 τ in trifluoroacetic acid. No significant change was produced in the line positions of the thiophene ring hydrogens as is indicated in Table 1. This result shows the general applicability of the Whitehead's procedure[13] to the preparation of 5-acetyl and 5-aroylpyrimidines.

*Mass spectra.* The mass spectra of compounds I, II, III, IV, V, VIII and IX



VIII



IX

were determined. Inspection of the spectra of I, II, and VIII reveals, as expected, an analogy with the fragmentation pattern in the spectrum of, for example, acetophenone.[17] α-Cleavage to the carbonyl group is the dominant feature in each of the spectra affording an *m/e* 111 (a) as the base peak. Its counterpart (b) is far less abundant (5–33%) and, as expected, the longer alkyl group decreases the intensity of the ion (b). This behaviour is still maintained in the spectra of the δ-ketoester V and the bromoketone IX in which the *m/e* 111 for V or *m/e* 189 (and its isotopic *m/e*

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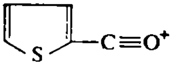
[15] J. Ma and E. Warnhoff, *Canad. J. Chem.* 43, 1849 (1965).

[16] S. Gronowitz, B. Norman, B. Gestblom, B. Mathiasson and R. Hoffman, *Arkiv Kemi* 22, 65 (1964).

[17] R. Budzikiewicz, C. Djerassi and D. H. Williams, Interpretation of mass spectra of organic compounds, chapter 9. Holden-Day, San Francisco (1964).

191) for IX is the base peak whereas the ion (b) was absent for V or of limited abundance for IX. The process can be supported by the presence of an appropriate metastable ion in each of the spectra. The behaviour of the $\beta$-diketone IV is not exceptional in this respect exhibiting the *m/e* 111 species as the most prominent.



(a)

$RC\equiv O^+$

(b)

TABLE 2. MASS SPECTRA OF 2-ACYLTHIOPHENES

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| I | *m/e* | 15 | 18 | 27 | 28 | 29 | 31 | 39 | 43 | 45 | 57 | 58 | 59 |
| | RI (%) | 4 | 3 | 4 | 4 | 6 | 14 | 26 | 16 | 14 | 7 | 4 | 7 |
| | *m/e* | 69 | 75 | 81 | 82 | 83 | 84 | 111 | 112 | 113 | 126 | 127 | |
| | RI (%) | 3 | 4 | 3 | 3 | 12 | 4 | 100 | 6 | 4 | 50 | 4 | |
| | *m/e* | 128 | | | | | | | | | | | |
| | RI (%) | 3 | | | | | | | | | | | |
| II | *m/e* | 18 | 27 | 28 | 29 | 38 | 39 | 41 | 43 | 45 | 53 | 57 | 58 |
| | RI (%) | 6 | 15 | 4 | 12 | 5 | 74 | 24 | 10 | 16 | 8 | 16 | 6 |
| | *m/e* | 60 | 69 | 82 | 83 | 84 | 85 | 97 | 111 | 112 | 113 | 126 | |
| | RI (%) | 9 | 12 | 5 | 25 | 18 | 4 | 9 | 100 | 21 | 16 | 43 | |
| | *m/e* | 127 | 128 | 153 | 168 | 169 | 170 | | | | | | |
| | RI (%) | 10 | 8 | 21 | 68 | 8 | 4 | | | | | | |
| VIII | *m/e* | 38 | 39 | 45 | 51 | 52 | 53 | 54 | 57 | 58 | 63 | 69 | 74 |
| | RI (%) | 1 | 13 | 2 | 5 | 13 | 1 | 1 | 2 | 1 | 1 | 1 | 2 |
| | *m/e* | 75 | 76 | 77 | 78 | 79 | 80 | 82 | 83 | 89 | 105 | 106 | 111 |
| | RI (%) | 2 | 2 | 29 | 2 | 1 | 5 | 2 | 7 | 1 | 31 | 3 | 100 |
| | *m/e* | 112 | 113 | 115 | 160 | 171 | 187 | 188 | 189 | 190 | | | |
| | RI (%) | 6 | 5 | 3 | 8 | 5 | 9 | 73 | 9 | 4 | | | |
| IX | *m/e* | 15 | 37 | 38 | 39 | 41 | 43 | 44 | 45 | 49 | 50 | 53 | 57 |
| | RI (%) | 2 | 4 | 7 | 4 | 3 | 21 | 2 | 6 | 2 | 2 | 3 | 7 |
| | *m/e* | 58 | 69 | 81 | 82 | 83 | 84 | 96 | 117 | 119 | 161 | 162 | |
| | RI (%) | 1 | 4 | 9 | 23 | 5 | 2 | 1 | 7 | 7 | 9 | 2 | |
| | *m/e* | 163 | 164 | 189 | 190 | 191 | 192 | 193 | 204 | 205 | 206 | | |
| | RI (%) | 9 | 2 | 99 | 6 | 100 | 6 | 4 | 43 | 3 | 44 | | |
| | *m/e* | 207 | 208 | | | | | | | | | | |
| | RI (%) | 3 | 3 | | | | | | | | | | |

The 2,5-diacylthiophene III displays a slightly different feature from this generalization. Although $\alpha$-cleavage can furnish (c) and (d), their abundances are supressed in favour of an *m/e* 168 species (e), which is the base peak and is produced by the $\beta$-scission with concomitant migration of a $\gamma$-hydrogen (the McLafferty rearrangement[18,19]). It should be noted that elimination of ketene from III could also furnish the molecular ion of II isobaric with (e), but if such a process should operate to an appreciable extent, the spectrum of III would exhibit a rearranged *m/e* 126 species as is observed in the spectrum of II. However, this was not the case (Fig. 1).

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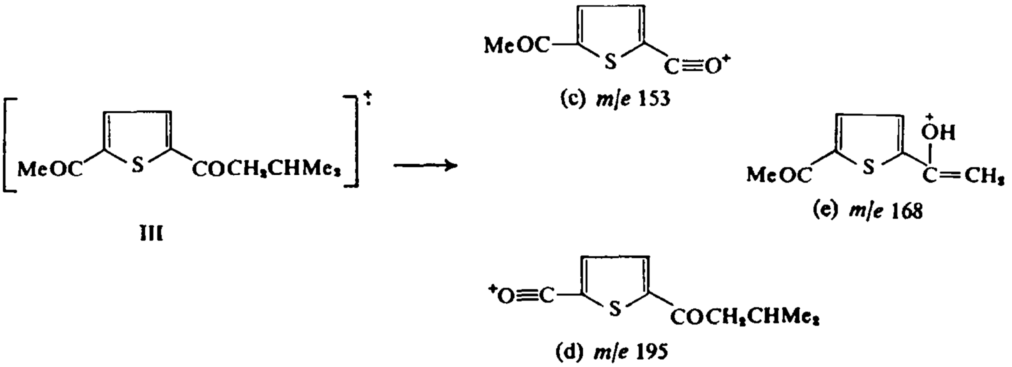
[18] F. McLafferty, *Mass Spectrometry of Organic Ions* p. 336. Academic Press, New York (1963).

[19] H. Budzikiewicz, C. Fenselau and C. Djerassi, *Tetrahedron* **22**, 1391 (1966).



Loss of mass units 15 from (e) leads to (c) as is supported by the presence of a metastable ion at *m/e* 139 (calc. $153^2/168 = 139{\cdot}3$) in the spectrum of III.

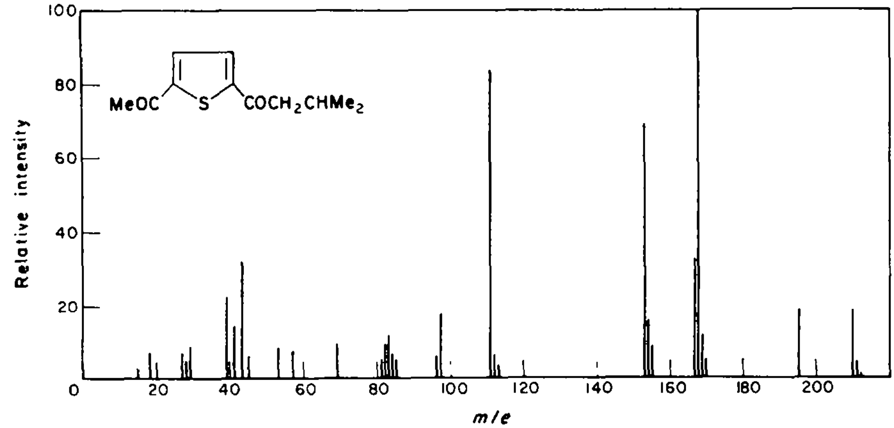


FIG. 1. Mass spectrum of 2-acetyl-5-isovalerylthiophene.

Contrary to γ-ketoester[20] the hydrogen rearrangement to the keto carbonyl should prevail for δ-ketoester. In support of the structure V for the reaction product of the β-diketone IV with acrylate ester an *m/e* 126 ion is observed in its mass spectrum, which, coupled with the presence of *m/e* 139 and *m/e* 153 ions, shows the presence of a system.

Another type of the olefin elimination with a hydrogen rearrangement is likely to operate. An *m/e* 112 for II and an *m/e* 154 for III are more abundant than expected from the $^{13}C$ isotopic peak of their immediate predecessor. One of possible explanations is the migration of a hydrogen to sulphur with concurrent elimination of olefin resulting in the formation of a radical ion (f).[21]

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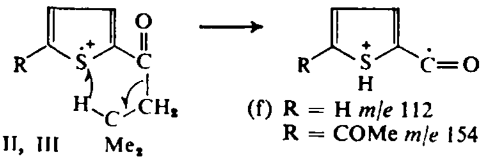
[20] S.-O. Lawesson, J. Madsen, G. Schroll, J. Bowie, R. Grigg and D. H. Williams, *Acta Chim. Scand.* **20**, 1129 (1966).

[21] Recently similar mechanism was suggested for the fragmentation of acylfuran under electron impact. K. Heyns, R. Stute and H. Scharmann, *Tetrahedron* **22**, 2223 (1966).



The *m/e* 111 species (a) is again observed with high intensity in the spectrum of the 2,5-diacylthiophene III, which must be formed by a hydrogen rearrangement in (c) or (d). The ion (c) is a more likely precursor for the *m/e* 111 species because of a metastable ion observed at *m/e* 80·5 (calc. $111^2/153 = 80{\cdot}5$). An added argument in favour of such a rearrangement is that an *m/e* 84 ion was observed (the molecular ion of thiophene itself) in the spectra of I, II and IV, or a bromine-containing ion at *m/e* 162 and 164 in the spectrum of IX. It is speculated that loss of ketene or alkylketene with concurrent migration of a hydrogen to the thiophene ring via a 4-membered cyclic intermediate may operate in the formation of the *m/e* 84 species, but for II the participation of a larger ring size intermediate should not be excluded.

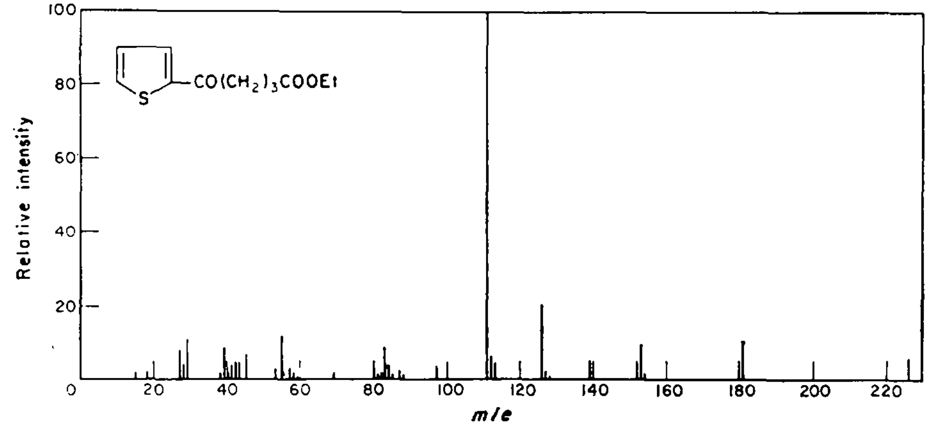


Fig. 2. Mass spectrum of ethyl γ-2-thenoylbutyrate.

According to Djerassi *et al.*,[22] occurrence of the thioformyl ion (*m/e* 45) $CH{\equiv}S^+$ suggests that at least one of the C-2 or C-5 carbon atoms of the thiophene ring is bonded to a hydrogen. The very existence of the *m/e* 45 species, though small in intensity, and a cyclopropenium cation (*m/e* 39)* in the spectra of the 2,5-disubstituted thiophenes III and IX can be accommodated if such a hydrogen rearrangement is invoked and hence additionally supports the foregoing proposal. A substituted cyclopropenium cation (*m/e* 117 and *m/e* 119) was observed for the bromoketone IX which gives rise to an *m/e* 38 species by elimination of a bromine atom.

Loss of mass units 28 from the molecular ion was appreciable for 2-benzoylthiophene VIII (8% of the base peak) but did not occur for 2-acetylthiophene I and other 2-acylthiophenes examined. Analogy with the mass spectral behaviour of benzophenone,[1] 2-benzoylfuran,[2] and 2-benzoylthiazole[3] may permit the speculation

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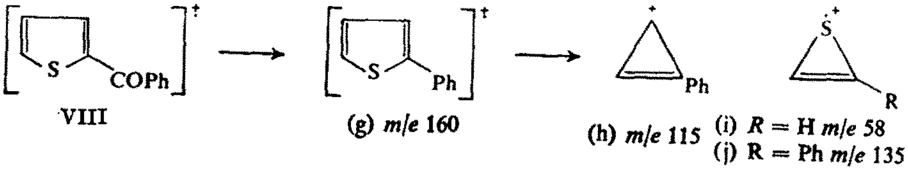
[22] Chapter 11 of Ref. 17.

that the lost entity is carbon monoxide.[23] This suggests that a Ph group has a greater migratory aptitude than Me. A metastable ion was present at m/e 136 (calc. $160^2/188 = 136{\cdot}2$) for this process. The (M-28) ion (g) thus produced closely follows the the fragmentation of thiophene itself,[17] and gives rise to a phenylcyclopropenium cation (h) and thiacyclopropenium cation (i).* However, the phenylthiacyclopropenium cation (j) was completely absent, which may associate with the facile loss of phenylacetylene as a neutral entity.


VIII

(g) m/e 160

(h) m/e 115

(i) R = H m/e 58

(j) R = Ph m/e 135

The spectrum of the diketone IV exhibits an abundant m/e 126 (k) (enol form of I). This will be produced by loss of ketene from the enol form of the diketone or from the diketo form through the McLafferty rearrangement in keeping with the behaviour of, for example, acetyl acetone.[24] An m/e 135 species may be at least in part produced in one step with loss of Me and water from the molecular ion because of the presence of a metastable at m/e 108 (calc. $135^2/168 = 108{\cdot}4$). In the spectrum of IV an m/e 69 species is very prominent contrary to other spectra examined where this species

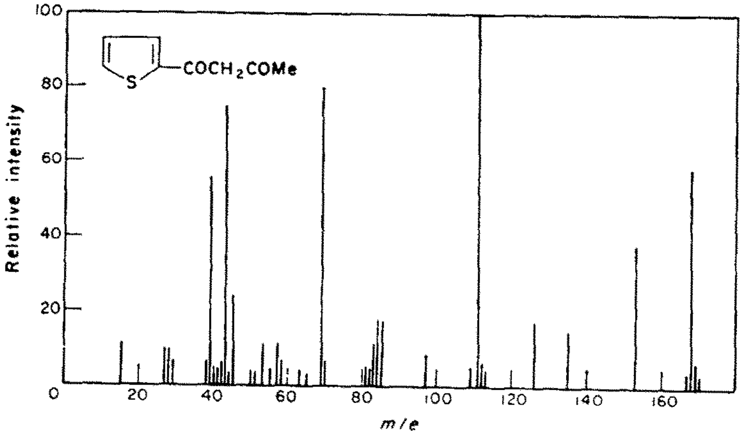
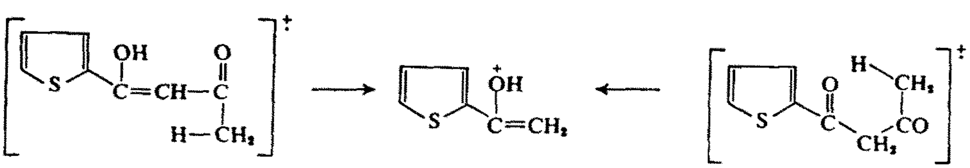


Fig. 3. Mass spectrum of 2-thenoylacetone.



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* For the detailed reasoning behind the formation of the cyclopropenium and thiacyclopropenium cations from thiophene see Ref. 22.

[23] After the submission of this paper similar observation on 2-benzoylthiophene has been reported. J. Bowie, S.-O. Lawesson, P. Jakobsen and G. Schroll, *Chem. Commun.* 539 (1966).

[24] J. Bowie, D. H. Williams, S.-O. Lawesson and G. Schroll, *J. Org. Chem.* **31**, 1384 (1966).

is small to negligible in intensity, but its identity and the mode of formation remains uncertain as yet.

## EXPERIMENTAL

The mass spectra were taken with a Hitachi RMU 6D mass spectrometer fitted with an all glass inlet system at an ionization energy of 80 eV and an ionizing current of 80 $\mu$A. Inlet system and ion source were maintained at about 200°. NMR spectra were taken with a Nihon-Denshi type JNM-3H-60 NMR spectrometer at 60 Mc with TMS as an internal standard. NaOMe was a commercial product. M.ps were taken on a hot stage but were uncorrected.

2-*Acetyl-5-isovalerylthiophene* (III). A mixture of isovalerylthiophene (8·4 g), HOAc (3·0 g), $P_2O_5$ (7·1 g), and benzene (50 ml) was stirred for 4·5 hr under reflux. The benzene soln was decanted, and the residue was dissolved in water and extracted with ether. The benzene soln was combined with the extracts, dried ($Na_2SO_4$), and distilled. Unreacted starting ketone (3·5 g) (b.p. 74–80°/0·8 mm) was recovered and the fraction boiling over 100°/0·8 mm was collected which solidified and recrystallized for several times from ligroin as colourless needles (1·1 g), m.p. 108–109°. (Found: C, 62·90; H, 6·64; S, 15·56. $C_{11}H_{14}O_2S$ requires: C, 62·83; H, 6·71; S, 15·25%.)

2-*Thenoylacetone* (IV). A mixture of I (12·6 g), AcOEt (26·4 g), and powdered Na (3·0 g) was stirred in anhyd ether (100 ml) for 2 hr under reflux, during which time Na dissolved and the reddish brown Na-salts precipitated. They were filtered, washed with ether, and dissolved in water (300 ml). The resulting aqueous soln was washed with ether, acidified with HOAc, and the organic layer was extracted with ether, dried ($Na_2SO_4$), and distilled to afford the compound, b.p. 90–91°/0·4 mm, 9·8 g. It had m.p. 31–32°. (Found: C, 57·18; H, 5·06. $C_8H_8O_2S$ requires: C, 57·12; H, 4·79%.)

*Ethyl γ-2-thenoylbutyrate* (V). To the soln of IV (5·04 g) in NaOEt (Na, 0·4 g and EtOH, 30 ml) was added methyl acrylate (4·00 g) and the mixture was left over for 48 hr at room temp. The solvent was removed, the residue was dissolved in water, acidified with HOAc, and extracted with ether. The ethereal soln, after being dried ($Na_2SO_4$), was distilled at 133–136°/0·4 mm to give the compound (3·4 g), $n_D^{20}$ 1·5239. (Found: C, 58·24; H, 6·59; S, 14·32. $C_{11}H_{14}O_3S$ requires: C, 58·38; H, 6·24; S, 14·17%.)

*Ureidomethylene-2-thenoylacetone* (VI). The compound IV (9·25 g) and ure(a 3·0 g) were heated in ethyl orthoformate (8·9 g) under reflux for 2 hr. After being cooled the solid was collected (8·1 g) and recrystallized twice from nitromethane as light yellow needles, m.p. 203–204° (dec). (Found: C, 50·13; H, 4·30; N, 11·67; S, 13·04. $C_{10}H_{10}O_2N_2S$ requires: C, 50·41; H, 4·23; N, 11·76; S, 13·46%.)

2-*Hydroxy-4-methyl-5-2′-thenoylpyrimidine* (VII-b). To VI (1·35 g) in anhyd MeOH (20 ml) was added NaOMe (0·31 g). The mixture spontaneously turned yellow with slight exothermal reaction and solid began to precipitate. After being left overnight at room temp the solvent was removed by distillation, the residual reddish oil was dissolved in water (30 ml), the resulting clear soln was acidified with HCl, and the ppts (1·12 g) were recrystallized from water and then from MeOH as colourless needles, m.p. 264–267° (dec). (Found: C, 54·20; H, 3·54; N, 12·52; S, 14·53. $C_{10}H_8N_2O_2S$ requires: C, 54·53; H, 3·66; N, 12·72; S, 14·56%.)