Heterocyclic Studies. Part XXXVI.[1] Mass Spectra of 5*H*-Pyrimido-[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-diones

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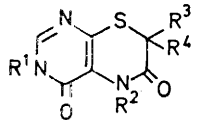
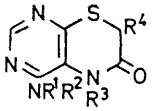
Mass spectra of 5*H*-pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-dione and its mono- and poly-methyl derivatives are described. The fragmentation pathways were elucidated with the aid of deuterium labelling and accurate mass measurements. Spectra of some 5-allyl derivatives are also described.

PYRIMIDOTHIAZINES are of interest as potential pharmaceutical agents; for example some 5-alkyl-pyrimido-[4,5-*b*][1,4]thiazines exhibit pharmacological activity.[2] Although mass spectra of many pyrimidines have been examined in detail [3] and a few thiazines have been dealt with,[4] only one brief account of mass spectra of any pyrimidothiazines has appeared.[5]

We now describe the mass spectra of some 5*H*-pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-diones (1)—(17). By contrast with 4-(substituted amino)-5*H*-pyrimido[4,5-*b*]-[1,4]thiazin-6(7*H*)-ones (18), most of whose fragmentations are directed by the 4-substituent,[5] all the important fragmentations of the present compounds involve the thiazine ring.





(1) $R^1 = R^2 = R^3 = R^4 = H$
(2) $R^1 = R^2 = H$, $R^3 = R^4 = D$
(3) $R^1 = R^3 = R^4 = H$, $R^2 = Me$
(4) $R^1 = R^3 = R^4 = H$, $R^2 = CD_3$
(5) $R^1 = D$, $R^3 = R^4 = H$, $R^2 = Me$
(6) $R^1 = R^2 = Me$, $R^3 = R^4 = H$
(7) $R^1 = Me$, $R^2 = CD_3$, $R^3 = R^4 = H$
(8) $R^1 = R^2 = CD_3$, $R^3 = R^4 = H$
(9) $R^1 = R^2 = H$, $R^3 = R^4 = Me$
(10) $R^1 = H$, $R^2 = R^3 = R^4 = Me$
(11) $R^1 = R^2 = D$, $R^3 = R^4 = Me$
(12) $R^1 = R^2 = CD_3$, $R^3 = R^4 = Me$
(13) $R^1 = R^3 = H$, $R^2 = R^4 = Me$
(14) $R^1 = R^2 = R^4 = Me$, $R^3 = H$
(15) $R^1 = R^3 = R^4 = H$, $R^2 = CH_2 : CH \cdot CH_2$
(16) $R^1 = Me$, $R^3 = R^4 = H$, $R^2 = CH_2 : CH \cdot CH_2$
(17) $R^1 = R^3 = H$, $R^4 = Me$, $R^2 = CH_2 : CH \cdot CH_2$

(18)

5H-*Pyrimido*[4,5-b][1,4]*thiazin*-6(7H)-*one*.—The most abundant fragment ions of the simplest compound (1) [Figure 1(a)], *m/e* 155 (11%), 154 (22), 149 (11), and 123 (35), were shown by exact mass measurements to correspond with losses of CO, CHO, H_2S, and SCO (Scheme 1). The loss of CO (metastable) gives a pyrimidothiazolinium ion (*b*) which loses H· to give the more stable pyrimidothiazolium ion (*c*). That the H atom came mainly from the 7-position was shown by the observation that the 7,7-dideuterio-derivative (2) [Figure 1(c)] gave a corresponding peak at *m/e* 155 [23% (corrected), *M* — CDO], but a smaller peak at *m/e* 156 [13% (corrected), *M* — CHO] showed that some also came from position 5, possibly following partial hydrogen scrambling in the ion (*b*). Loss of SCO (metastable) which must involve a rearrangement, possibly (*a*) ⟶ (*d*), leads to ion (*e*), *m/e* 123 (35%). H_2S loss must also involve one or more rearrangements.

5-*Methyl*-5H-*pyrimido*[4,5-b][1,4]*thiazine*-4,6(3H,7H)-*diones*.—Introduction of a 5-methyl group to give compound (3) led to some changes in fragmentation [Figure 1(b)]. Loss of CO and H· (metastables) still occurred to give ions (*g*), *m/e* 169 (4%), and (*h*), *m/e* 168 (15%), and the H atom must have come almost exclusively from the

[1] Part XXXV, J. Clark and M. S. Morton, *J.C.S. Perkin I*, 1974, 1818.
[2] Abbott Laboratories, B.P. 1,165,260/1969.
[3] J. M. Rice, G. O. Dudek, and M. Barber, *J. Amer. Chem. Soc.*, 1965, **87**, 4569; T. Nishiwaki, *Tetrahedron*, 1966, **22**, 3117; 1967, **23**, 1153.
[4] J. W. Lown and J. C. N. Ma, *Canad. J. Chem.*, 1967, **45**, 939, 953.
[5] J. Clark and I. W. Southon, *J.C.S. Perkin I*, 1974, 1805.

7-position since the 5-trideuteriomethyl compound (4) [Figure 1(e)] and the 3-deuterio-compound (5) [Figure 1(d)] also lost CO + H· rather than CO + D·. There was no appreciable peak due to CSO loss from (*f*) but instead one due to loss of CHSO appeared at *m/e* 136 (12%), accompanied by an appropriate metastable peak loss of CDSO equivalent to (*i*) ⟶ (*k*) (Scheme 2) and consecutive losses of SH· and CO equivalent to (*f*) ⟶ (*j*) ⟶ (*k*).

A peak at *m/e* 154 (37%, $M - C_2H_3O$) in the spectrum of the 5-methyl compound (3) had no equivalent in the spectra of the 5-unsubstituted compounds (1) and (2).

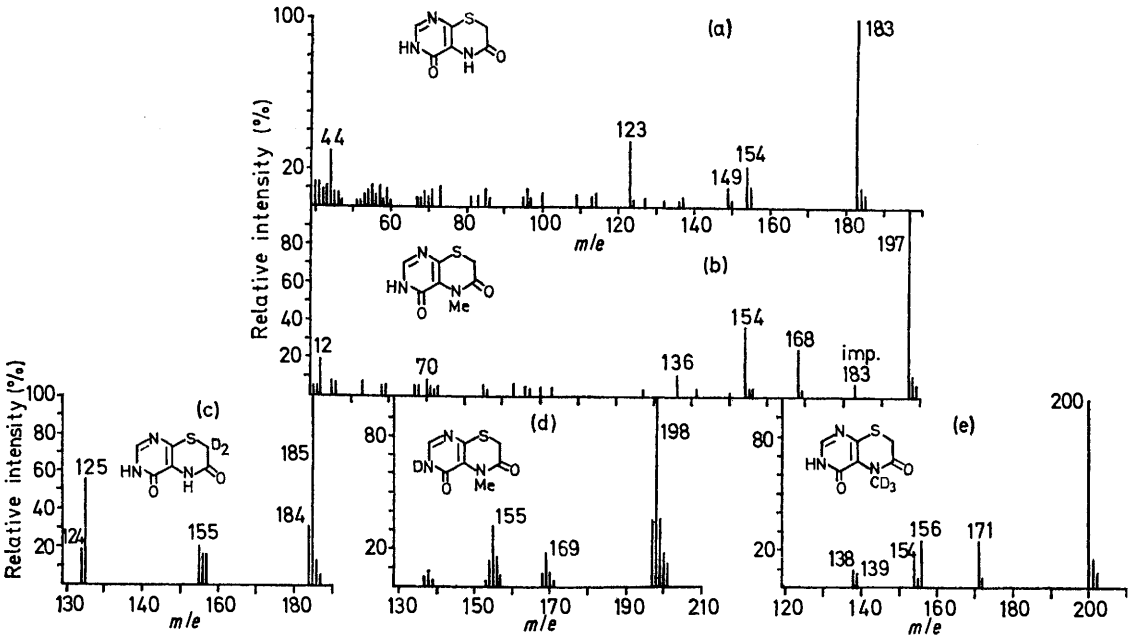
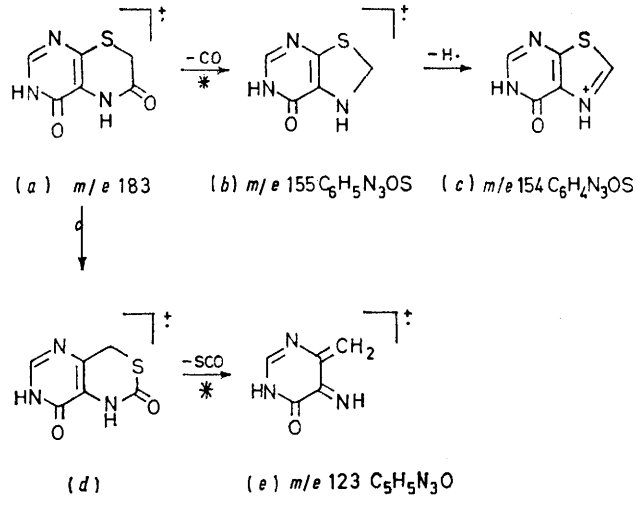


FIGURE 1 Mass spectra of 7-unsubstituted 5*H*-pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-diones. The 7,7-dideuterio-compound [spectrum (c)] contains 24% of 7-monodeuterio-derivative. The 3-deuterio-5-methyl compound [spectrum (d)] contains 26% of undeuteriated derivative

at *m/e* 93·9 (197 ⟶ 136). The hydrogen atom must have come almost equally from the 7-position and the 5-methyl group since the 5-trideuteriomethyl compound



SCHEME 1

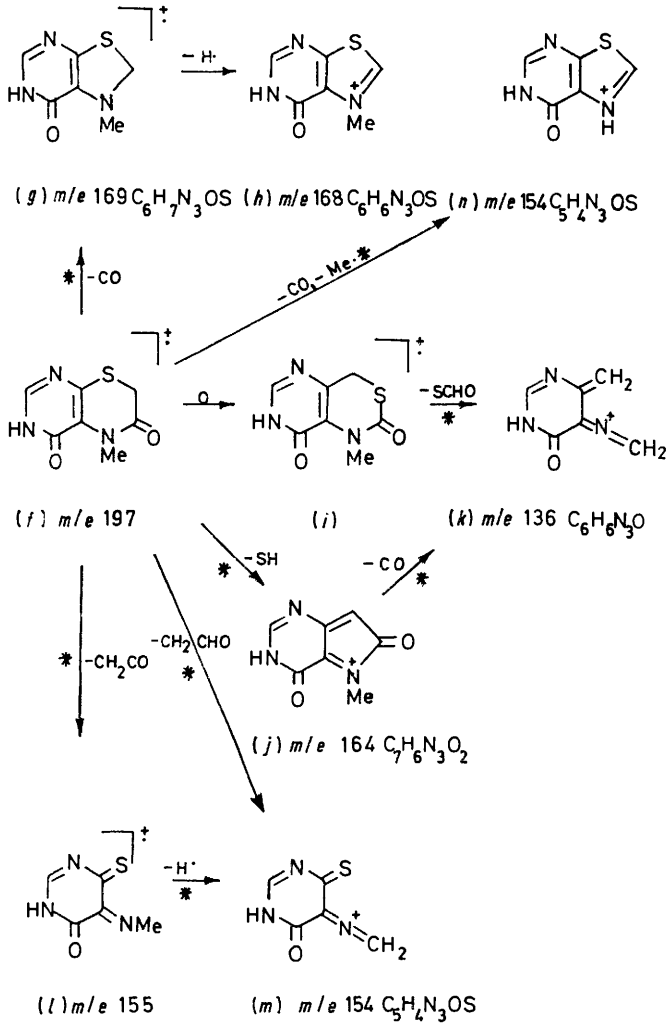
(4) gave peaks at *m/e* 139 (8%, M — CHSO) and 138 (9%, M — CDSO). This suggested that there are two decomposition modes, and these are probably direct

Two likely mechanisms for loss of C_2H_3O are a retro-Diels–Alder loss of keten followed by H· loss giving ions (*l*) and (*m*), and loss of the 6-CO and 5-Me groups to give ion (*n*). Both mechanisms seem to be operative because the 5-trideuteriomethyl compound (4) lost C_2D_3O (CO + CD_3) in one step (metastable) to give ion (*n*), *m/e* 154 (15%), and also C_2H_2DO (CH_2CO + D) in two steps (metastables) to give a peak equivalent to (*m*) at *m/e* 156 (26%). Loss of C_2H_3O had already been noted as a minor process in fragmentation of 4-(substituted amino)-derivatives (18).[5]

The low mass fragment ion, *m/e* 42 ($CH_3C{\equiv}NH^+$), must originate from the 5-methyl group because it occurs at *m/e* 45 ($CD_3C{\equiv}NH^+$) in the spectrum of the 5-trideuteriomethyl compound (4). The lack of involvement of the pyrimidine ring in all these fragmentations was shown by the 3-deuterio-5-methyl compound (5), which retains the deuterium atom in all the important fragment ions [Figure 1(d)], and the 3,5-dimethyl derivative (6), whose spectrum [Figure 2(a)] shows a simple upward shift of 14 mass units of all major fragment ions as compared with those from the 5-methyl compound (3).

The spectrum of the 3-methyl-5-trideuteriomethyl compound (7) [Figure 2(b)] confirms that C_2H_3O loss from the 5-methyl compound occurs by the two mechan-

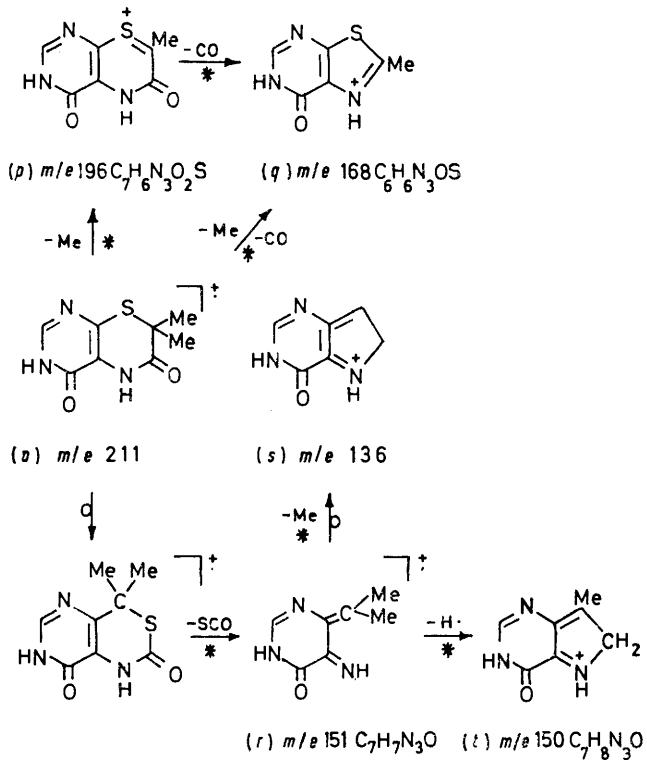
isms shown in Scheme 2: it contains peaks at *m/e* 168 (19%, $M - C_2D_3O$) and 170 (32%, $M - C_2H_2DO$). The



SCHEME 2

3,5-bistrideuteriomethyl derivative (8) retains the 3-CD_3 group in all the major fragment ions as expected [Figure 2(c)].

7-Substituted 5H-Pyrimido[4,5-b][1,4]thiazine-4,6(3H,7H)-diones.—The nature of some important fragmentation pathways was changed by the introduction of one or more 7-substituents. The spectrum of the 7,7-dimethyl derivative (9) [Figure 3(a)] showed an abundant



SCHEME 3

$(M - C_2H_3O)^+$ peak (*q*) at *m/e* 168 (50%). Appropriate metastable peaks suggested that it was formed, *via* ions (*o*) and (*p*), by successive loss of Me· and CO, and also by loss of MeCO in one step (Scheme 3). Loss of SCO gave an ion (*r*), *m/e* 151 (15%), which, in turn, lost H· or CH_3· (metastables) to give ions (*s*), *m/e* 150 (46%), and (*t*), *m/e* 136 (15%). The hydrogen atom came from one of the 7-methyl groups (Scheme 3) and not from the 5-position

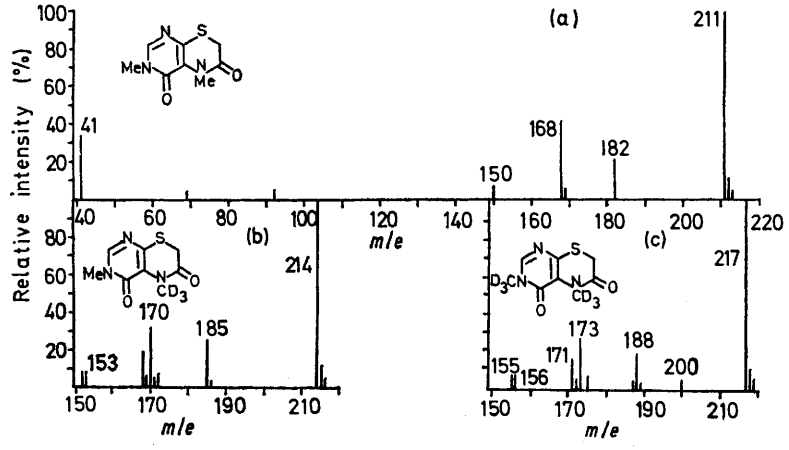


FIGURE 2 Mass spectra of 7-unsubstituted 3,5-dialkyl-5*H*-pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-diones

even though the CHSO loss was greatly reduced in the 5,7,7-trimethyl compound (10) [Figure 3(b)]. This was shown by the spectrum of the 3,5-dideuterio-7,7-dimethyl compound (11) [Figure 4(c)], which retained both deuterium atoms in the major fragment ions.

respectively, to give ions (*l*) and (*m*) in a fashion analogous to that shown in Scheme 2. The 7,7-dimethyl-3,5-bistrideuteriomethyl compound (12) [Figure 3(c)] showed corresponding losses of dimethylketen and dimethylketen plus D· with resulting peaks at *m/e* 175 (11%) and

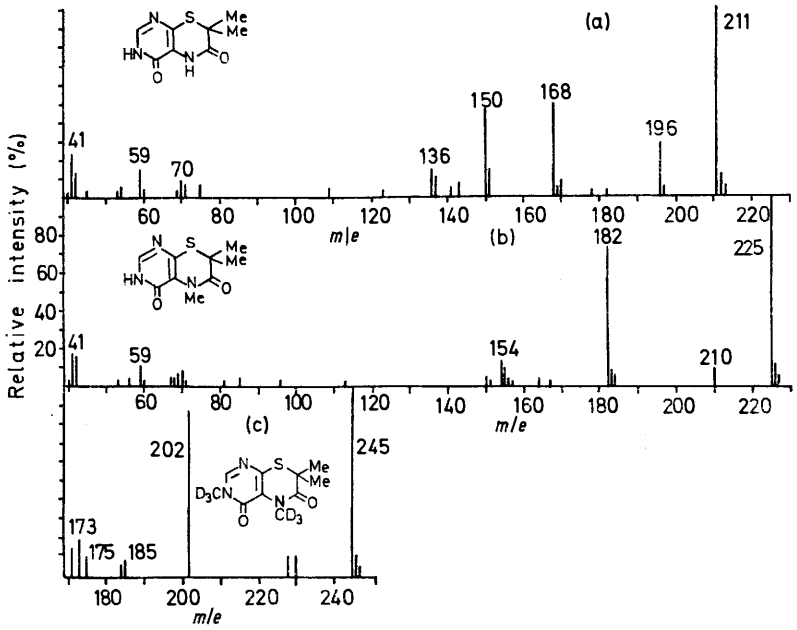


FIGURE 3 Mass spectra of 7,7-dimethyl-5*H*-pyrimido[4,5-*b*][1,4]thiazone-4,6(3*H*,7*H*)-diones

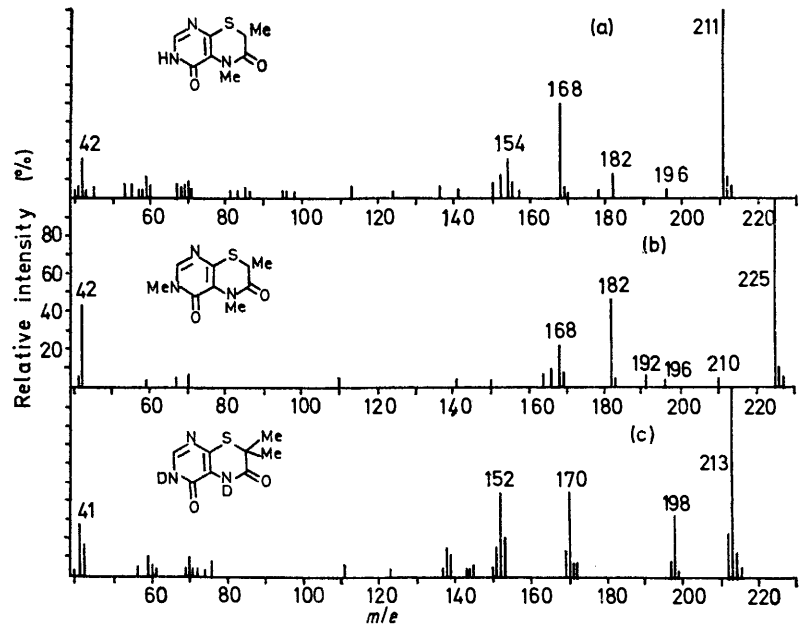


FIGURE 4 Mass spectra of 7-substituted 5*H*-pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-diones. The 3,5-dideuterio-derivative [spectrum (c)] contains 19% of monodeuterio-compounds

Introduction of a 5-methyl group again encouraged a retro-Diels–Alder reaction and peaks at *m/e* 155 (10%) and 154 (15%) in the spectrum of the 5,7,7-trimethyl compound (10) [Figure 3(b)] represent losses of dimethylketen (metastable) and dimethylketen plus H·, 173 (20%). However a peak also appeared at *m/e* 171 (16%) due to loss of $C_4H_5D_2O$ and this indicates that there may be some hydrogen scrambling between the 5- and 7-methyl groups.

The spectrum of the 5,7-dimethyl compound (13)

[Figure 4(a)] resembles that of the corresponding 5,7,7-trimethyl derivative (10) in showing an abundant peak at *m/e* 168 (50%), due to loss of CO + Me·. The similar loss of CO + H· is less important [*m/e* 182 (13%)]. The retro-Diels–Alder reaction gives the expected peaks at *m/e* 155 (8%) and 154 (20%). Introduction of a further methyl group at position 3 (14) [Figure 4(b)] simply moves all the major peaks up by 14 mass units.

5-Allyl-5H-pyrimido[4,5-b][1,4]*thiazine-4,6(3H,7H)-diones.*—Spectra of 5-allyl derivatives were more complex give an ion (*ff*), *m/e* 154 (71%). The latter must involve loss of the 7- but not the 3-substituent because the corresponding loss in the 7-methyl compound (17) is C_5H_7O, giving a peak still at *m/e* 154 (57%), but in the 3-methyl compound (16) the corresponding peak appears at *m/e* 168 (73%).

Most of the fragmentations described in this paper involve a thiazine ring. By contrast fragmentations of very closely related 4-(substituted amino)pyrimidothiazines (18) involved the 4-substituent and the pyrimidine

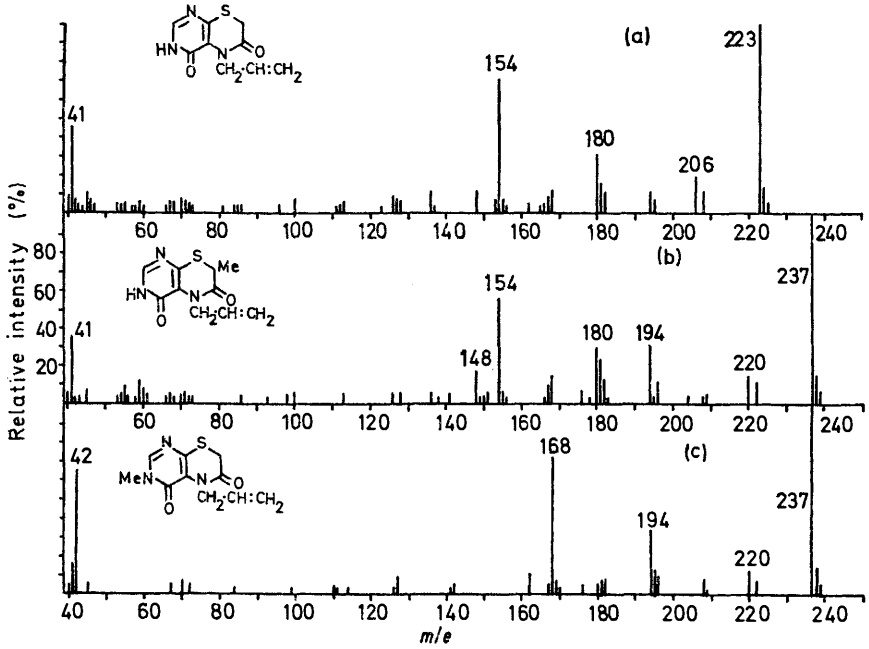


FIGURE 5 Mass spectra of 5-allyl-5*H*-pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-diones

but some fragmentations paralleled those of compounds already discussed. Thus retro-Diels–Alder loss of keten and then loss of H· to give $(M - 42)^{+\cdot}$ and $(M - 43)^{+}$ ions (*v*) and (*w*) were observed in 7-unsubstituted derivatives (15) [Scheme 4 and Figure 5(a)] and (16) [Figure 5(c)]. Corresponding losses of 56 and 57 mass units occurred in the 7-methyl compound (17) [Figure 5(b)]. Loss of 43 mass units occurred in another way. This involved loss of CO and then CH_3· from the allyl group to give ions (*x*) and (*y*). The 7-methyl derivative (17) revealed the two different mechanisms because the retro-Diels–Alder reaction led to a peak at *m/e* 180 (30%) $(M - C_3H_4O - H\cdot)^+$ while the $M - CO - CH_3$· mechanism gave a peak at *m/e* 194 (32%). Loss of CO may also be followed by loss of H· or allyl· to give ions (*z*) and (*aa*).

The molecular ion (*u*) also fragmented by loss of the whole allyl side-chain to give an ion *m/e* 182 (11%) (*bb*) or by loss of CH_3· from the allyl side-chain to give an ion *m/e* 208 (11%) (*cc*). Without ^{13}C labelling it is not possible to say which carbon atom of the allyl group is lost.

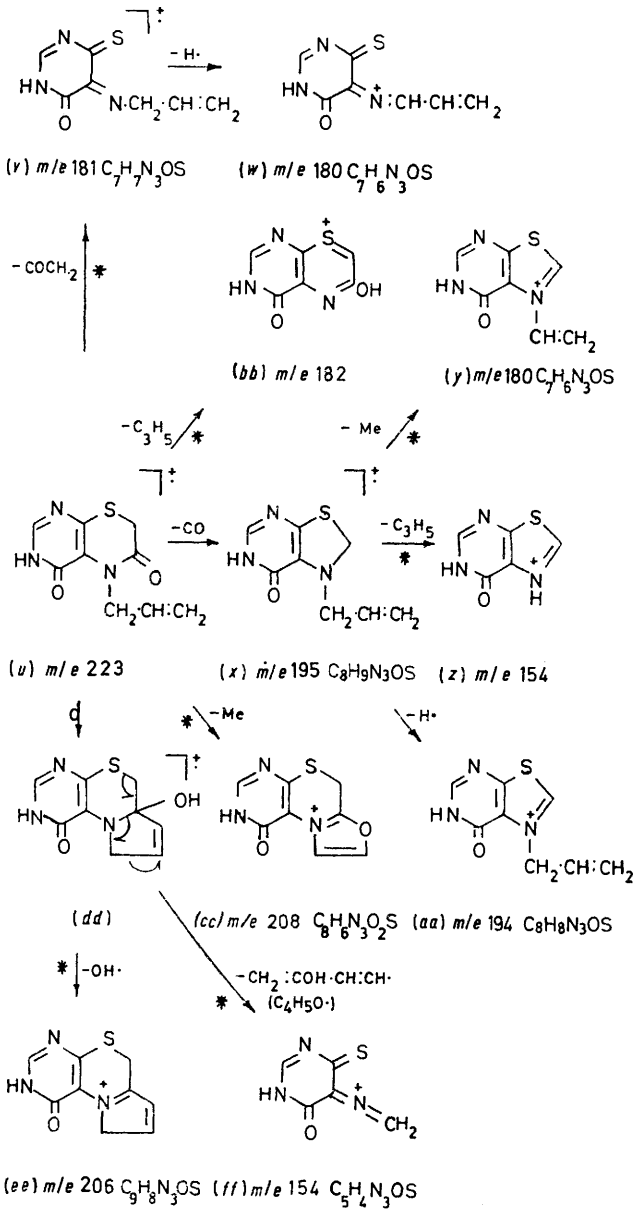
Several fragmentations may be rationalised by postulating a rearrangement ion (*dd*) which can lose ·OH to give an ion (*ee*), *m/e* 206 (19%), or $CH_2{:}COH{\cdot}CH{:}CH\cdot$ to ring to a very large extent.[5] This suggests major differences in the location of the charge on ions derived from the present compounds as compared with those from the amino-compounds.

EXPERIMENTAL

Non-deuterium-containing compounds were prepared as described previously.[6,7] [*N*-^{2}H]-Derivatives were prepared by evaporating the corresponding unlabelled compounds to dryness with deuterium oxide two or three times.

5-Trideuteriomethyl-5H-pyrimido[4,5-b][1,4]*thiazine-4,6-(3H,7H)-dione.*—4-Methoxy-5*H*-pyrimido[4,5-*b*][1,4]*thiazin-6(7H)-one* (0·24 g) was dissolved in 0·5N-sodium hydroxide (2·8 ml) and cooled to 0°. Cooled trideuteriomethyl iodide (0·085 ml) was added, the mixture was shaken vigorously for 24 h, and 4-methoxy-5-trideuteriomethyl-5*H*-pyrimido-[4,5-*b*][1,4]thiazin-6(7*H*)-one (0·13 g), m.p. 140—142°, was filtered off. The solid was heated under reflux with 2N-hydrochloric acid (1·3 ml) for 2 h; the mixture was then cooled and filtered to yield the *dione*, m.p. 230—232° (Found: C, 41·8; N, 20·2. $C_7D_3H_4N_3O_2S$ requires C, 42·0; N, 21·0%).

[6] J. Clark and I. W. Southon, *J.C.S. Perkin I*, 1974, 1814.
[7] T. S. Safonova and M. P. Nemeryuk, *Khim. geterotsikl. Soedinenii*, 1966, **5**, 714.



SCHEME 4

3-*Methyl*-5-*trideuteriomethyl*-5H-*pyrimido*[4,5-b][1,4]*thiazine*-4,6(3H,7H)-*dione*.—The foregoing dione (0·05 g), methyl iodide (0·0037 g), and 0·1N-sodium hydroxide (0·26 ml) were sealed in an ampoule and shaken for 24 h. The product was extracted with chloroform and the extract was dried and evaporated to dryness (*cf.* ref. 6 for preparation of undeuteriated analogue).

3,5-*Bistrideuteriomethyl*-5H-*pyrimido*[4,5-b][1,4]*thiazine*-4,6(3H,7H)-*dione*.— 5*H*-Pyrimido[4,5-*b*][1,4]thiazine-4,6-(3*H*,7*H*)-dione [6] (0·2 g) was dissolved in N-sodium hydroxide (2·1 ml) and cooled to 0°. Cooled trideuteriomethyl iodide (0·13 ml) was added and the mixture shaken vigorously for 24 h. The *bistrideuteriomethyl compound* (0·06 g), m.p. 238—240°, was then filtered off (Found: C, 43·7; N, 18·9. $C_8D_6H_3N_3O_2S$ requires C, 44·25; N, 19·35%).

7,7-*Dimethyl*-3,5-*bistrideuteriomethyl*-5H-*pyrimido*[4,5-b]-[1,4]*thiazine*-4,6(3H,7H)-*dione*.— 7,7-Dimethyl-5*H*-pyrimido[4,5-*b*][1,4]thiazine-4,6(3*H*,7*H*)-dione [6] (0·0058 g), trideuteriomethyl iodide (0·0034 g), and 0·2N-sodium hydroxide (0·25 ml) were sealed in an ampoule and shaken for 24 h. The product was extracted with chloroform and the extract was dried and evaporated to dryness.

7,7-*Dideuterio*-5H-*pyrimido*[4,5-b][1,4]*thiazine*-4,6(3H,-7H)-*dione*.—A solution of chloroacetic acid (0·176 g) in N-sodium deuterioxide (4·1 ml) was set aside for 24 h, then 5-amino-6-methoxypyrimidine-4(3*H*)-thione (0·26 g) was added. The mixture was heated under reflux for 2 h, cooled, and acidified with N-hydrochloric acid. The precipitate was collected, heated under reflux with N-hydrochloric acid (1·84 ml) for 2 h, and cooled. The compound (0·037 g) which separated was shown by mass spectrometry to contain both 7-mono- (24%) and 7,7-di- (76%) deuterio-derivatives.

Mass spectra were measured on an A.E.I. MS-902S instrument with source temperature *ca.* 160° and ionising voltage 70 eV. Compounds were introduced on a direct insertion probe. Only ions of relative abundance $\geqslant 3\%$ are shown in line diagrams. Accurate mass measurements were carried out at a resolving power of *ca.* 10,000. Where a formula is given for an ion, in a Scheme, it is based on a mass measurement which agrees with the calculated mass within 10 p.p.m.

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