Heterocyclic Studies. Part XXVII.[1] Mass Spectra of 6-(*meta*- and *para*-Substituted-phenyl)-uracil and -thiouracil Derivatives

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Mass spectra of 10 substituted-phenyluracils and 10 substituted-phenyl-2-thiouracils are recorded. Important steps in the fragmentation of the phenyluracils resemble those undergone by uracil itself. Spectra of 2-thio-derivatives show similarities to those of corresponding uracils but some important differences are also revealed.

MASS spectra of uracils, which are of great interest in connection with biologically important nucleosides, nucleotides, and nucleic acids, have been examined in some detail.[2-5] However very little work has been published on mass spectra of thiouracils.[5] Many thiouracils show antithyroid activity[6] and thiouracil, for example, is used clinically.[7] Spectra of such compounds are of interest because they may provide a convenient means of structure determination; comparison of the spectra with those of corresponding uracils is also of interest. This paper describes the fragmentation of ten 6-(*m*- and *p*-substituted-phenyl)-thiouracils and the corresponding uracils.

EXPERIMENTAL

Uracils and thiouracils were prepared by published methods.[8]

Specimens were introduced as solids directly into the ion source of an A.E.I. MS-12 single focusing mass spectrometer. The source was maintained at 200° and spectra recorded at an electron beam energy of 70 eV, trap current 100 μA, and accelerating voltage 8 kV. The spectrum of each *meta*-substituted phenyl-uracil or -thiouracil derivative was very closely similar to its *para*-substituted analogue. Line diagrams illustrate the spectra of the *meta* compounds while those of *para*-derivatives are presented in tabular form.

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[2] J. M. Rice, G. O. Dudek, and M. Barber, *J. Amer. Chem. Soc.*, 1965, **87**, 4569.
[3] T. Nishinaki, *Tetrahedron*, 1966, **22**, 3117; 1967, **23**, 1153; E. Falch, *Acta Chem. Scand.*, 1970, **24**, 137.
[4] J. Ulrich, R. Teoule, R. Massot, and A. Cornu, *Org. Mass Spec.*, 1969, **2**, 1183.
[5] R. W. Reiser, *Org. Mass Spec.*, 1969, **2**, 467.
[6] E. B. Astwood, *J. Pharmacol.*, 1943, **78**, 79; G. W. Anderson, I. F. Halverstadt, W. H. Miller, and R. O. Roblin, jun., *J. Amer. Chem. Soc.*, 1945, **67**, 2197; W. H. Miller, A. M. Dessert, and G. W. Anderson, *ibid.*, 1948, **70**, 500.
[7] E. B. Astwood, *J. Amer. Med. Assoc.*, 1943, **122**, 78; H. P. Hunsworth, *Proc. Roy. Soc. Med.*, 1944, **37**, 693; W. Van Winkle, S. M. Hardy, G. R. Hazel, D. C. Hines, E. A. Sharp, and W. N. Sisk, *J. Amer. Med. Assoc.*, 1946, **130**, 343.
[8] J. Clark and Z. Munawar, *J. Chem. Soc.* (*C*), 1971, 1945.

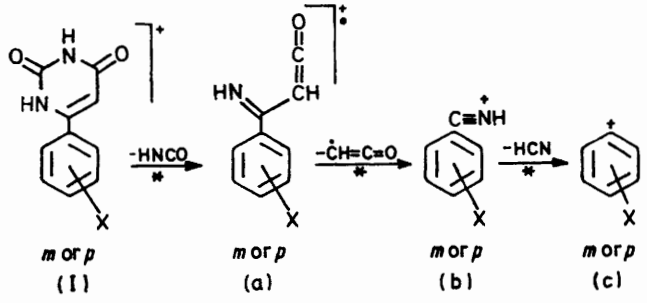
RESULTS

Spectra of uracils published so far do not include any examples with a *C*-phenyl or substituted phenyl group. The spectra of our compounds belonging to this class are therefore briefly compared with these of uracil and alkyluracils.

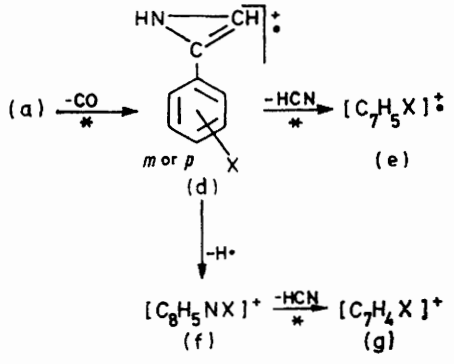
The most important fragmentation path for molecular ions of 6-halogen-substituted-phenyluracils (I; X = F, Cl, or Br) are illustrated in Schemes 1 and 2 and correspond with those of uracil.[2] Breakdown of ions (c) (Scheme 1) varied with the substituent in the aromatic ring. The fluoro-ions (c; X = F) lost HF, the chloro-ions HCl or Cl· and the bromo-ions HBr or ·Br. The corresponding ions (c; X = Me) from the tolyluracils probably isomerise to tropylium ions and the subsequent loss of 26 a.m.u. substantiates this.[9] The methoxy-phenyluracils (I; X = OMe) differed from the other compounds in that ions (b; X = OMe) tended to lose CH_3· or CH_2O from the methoxy-group rather than HCN at that stage.

6-(*Substituted-phenyl*)-2-*thiouracils*.—The spectra of our 6-(substituted-phenyl)-2-thiouracils (II; X = *m*- or *p*-F, -Cl, -Br, -Me, or -OMe) had many features in common with their uracil analogues but they also differed in several important ways.

Loss of HCNS from molecular ions (II), presumably by a retro-Diels–Alder reaction analogous to that in uracils,[2] gave moderately intense $(M - 59)^+$ peaks. Subsequent decomposition of the resulting ions (a) proceeded according to reaction Schemes 1 and 2.



SCHEME 1



SCHEME 2

The thiouracil spectra also exhibited important $(M - 58)^+$ peaks due to loss of ·NCS radicals from the molecular ions. The corresponding losses of ·NCO radicals from the uracils was relatively unimportant, the $(M - 42)^+$ peaks being quite small after deduction of the ^{13}C isotope contributions. A possible route for the formation of $(M - 58)^+$ or $(M - 42)^+$ ions involves prior tautomerism

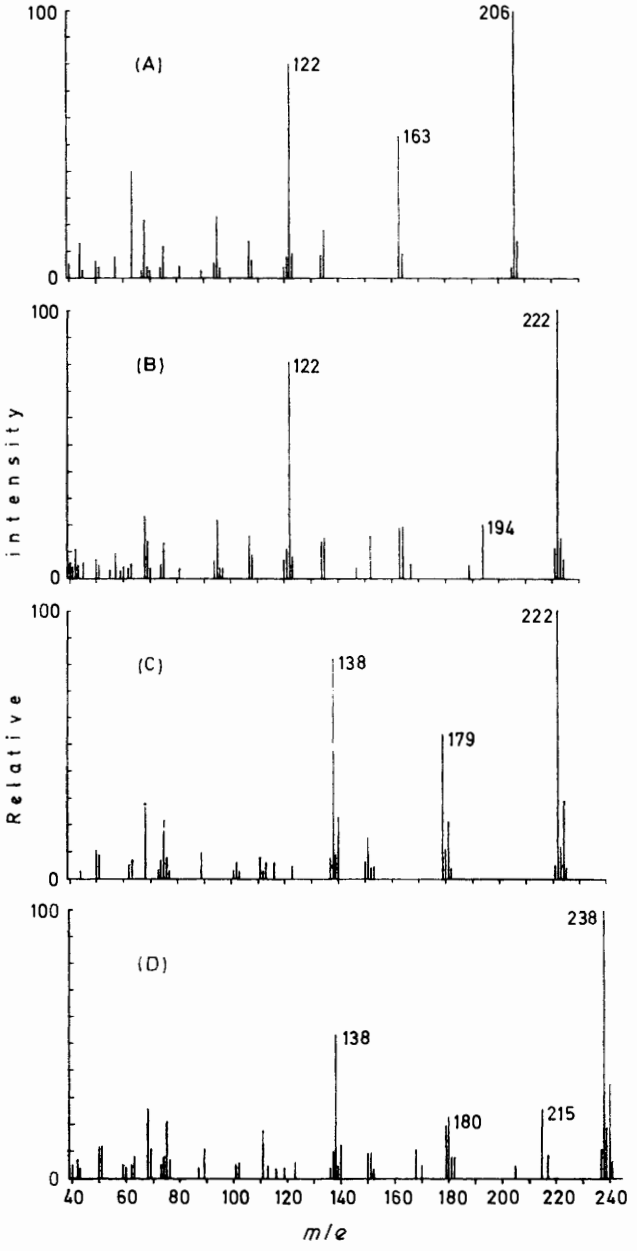


FIGURE 1 Mass spectra of (A) 6-*m*-fluorophenyluracil, (B) 6-*m*-fluorophenyl-2-thiouracil, (C) 6-*m*-chlorophenyluracil, (D) 6-*m*-chlorophenyl-2-thiouracil

of the uracil or thiouracil derivative (III) ⇌ (IV) (Scheme 3). The ions (h) may then break down by loss of a hydrogen atom or keten molecule to give ions (a) or (b) already encountered in Scheme 1. However metastable peaks in several spectra indicate that ions (h) break down at least partly by consecutive losses of a ketenyl radical and HCN molecule (Scheme 3).

Several other fragmentation paths of the thiouracils

[9] H. Budzikiewicz, C. Djerrassi, and D. H. Williams, *Mass Spectrometry of Organic Compounds*, Holden-Day, San Francisco, 1967.

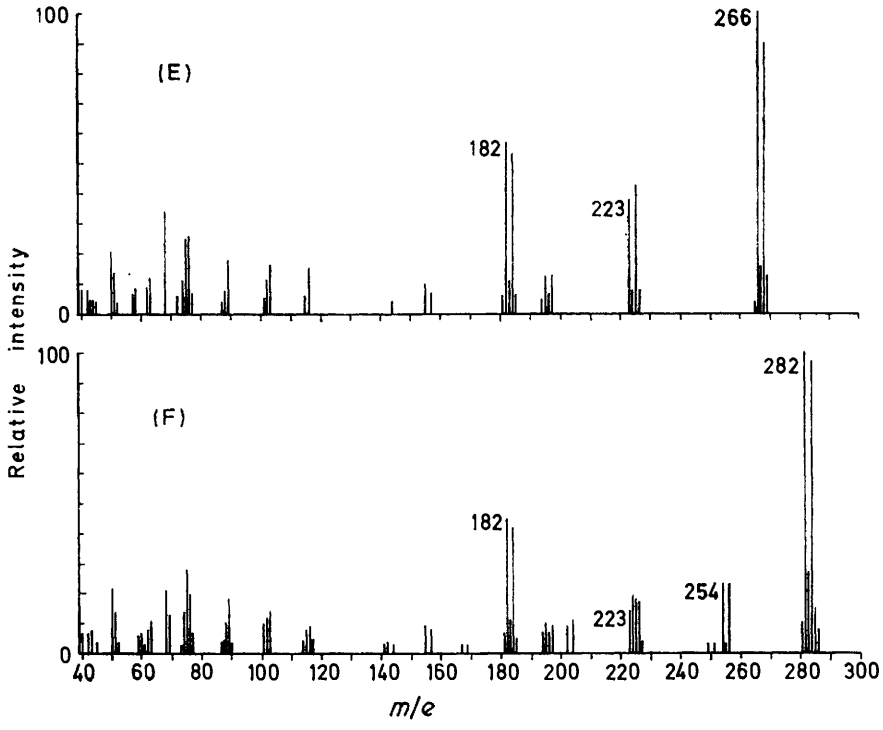
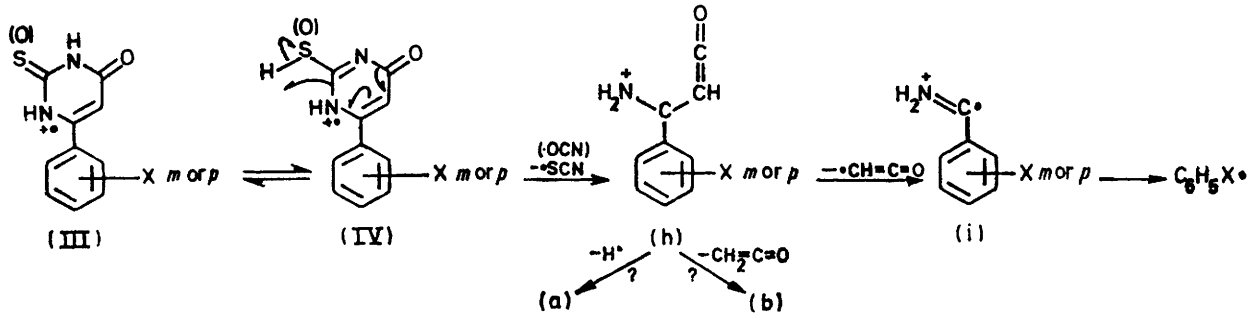


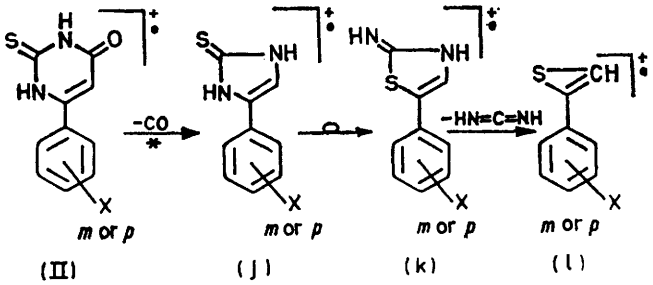
FIGURE 2 Mass spectra of (E) 6-*m*-bromophenyluracil, (F) 6-*m*-bromophenyl-2-thiouracil



SCHEME 3

did not have counterparts in the uracil breakdowns. The molecular ions lost 28 and 42 a.m.u. successively in processes which were confirmed by metastable peaks. The only reasonable loss of 28 is CO (II) ⟶ (j) (Scheme 4) and this was confirmed by an accurate mass measurement of the *m/e* 190 peak of 6-*m*-tolyl-2-thiouracil (II; X = *m*-CH_3) (Mass = 190·0564. Calc. for $C_{10}H_{10}N_2S$ 190·0565). The subsequent loss is CH_2N_2 which must occur *via* a rearrangement process, possibly as suggested in Scheme 4 (j ⟶ k ⟶ l). The ion (j) also lost HCN in an alternative breakdown. Loss of an SH radical from the molecular ion (II) was the start of yet another minor fragmentation pathway. $(M - 1)^+$ ions were also more prominent in the spectra of the thio-compounds.

Comparison of the relative abundancies of ions (a) formed by loss of HNCO or HNCS respectively with those of their decomposition products showed that ions formed by loss of HNCO from uracils were not identical with those formed by loss of HNCS from thiouracils. For example, in the case of *m*-fluoro-derivatives, ions (a) (*m/e* 122) from the uracil (I; X = *m*-F) had relative abundancies of 53



SCHEME 4

and 90% (ratio 1 : 1·7) while the *m/e* 163 and 122 ions from the corresponding thiouracil (II; X = *m*-F) had relative abundancies of 19 and 81% (ratio 1 : 4·3). Similarly ions

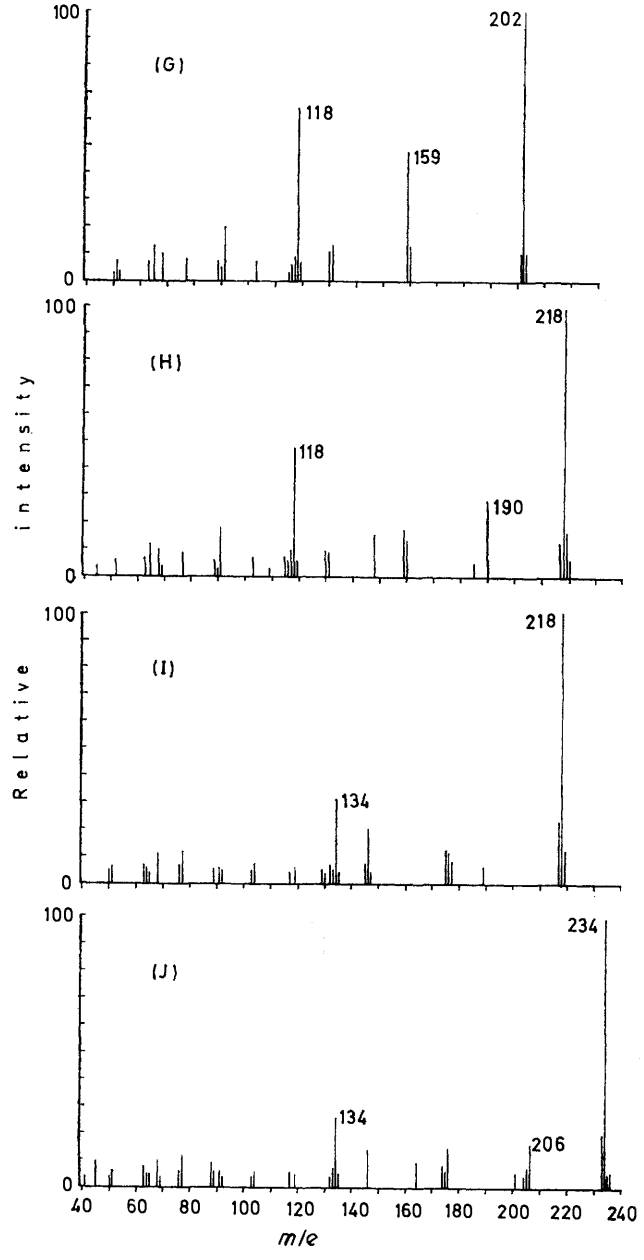


FIGURE 3 Mass spectra of (G) 6-*m*-tolyluracil, (H) 6-*m*-tolyl-2-thiouracil, (I) 6-*m*-methoxyphenyluracil, (J) 6-*m*-methoxyphenyl-2-thiouracil

(a) and (d) (*m/e* 163 and 135 respectively) from the uracil (I; X = *m*-F) had relative abundancies of 53 and 18% (ratio 1 : 0·34) compared with 19 and 15% (ratio 1 : 0·79) from the thiouracil (II; X = *m*-F). It appears that ions

TABLE 1

Mass spectra of 6-(*p*-substituted-phenyl) uracils

6-*p*-Tolyluracil (I; X = *p*-Me)

m/e (I) 203 (12), 202 (100), 201 (10), 160 (11), 159 (42), 131 (12), 130 (9), 119 (9), 118 (59), 117 (7), 116 (5), 115 (4), 103 (5), 91 (16), 90 (4), 89 (4), 87 (4), 77 (8), 68 (7), 65 (12), 63 (6), 51 (7), 45 (6)

*m** 126·7 (202→160), 125·1 (202→159), 107·9 (159→131), 87·7 (159→118), 81·6 (130→103), 70·1 (118→91), 46·4 (91→65)

TABLE 1 (*Continued*)

6-*p*-Methoxyphenyluracil (I; X = *p*-OMe)

m/e (I) 219 (13), 218 (100), 217 (13), 177 (4), 176 (20), 75 (22), 160 (5), 147 (7), 146 (6), 135 (7), 134 (38), 133 (7), 132 (8), 119 (7), 104 (5) 95 (4), 91 (6), 89 (4), 77 (11), 76 (5). 68 (6), 64 (4), 63 (6), 51 (5), 50 (5), 45 (12), 43 (4), 41 (4)

*m** 142·1 (218→176), 140·5 (218→175), 123·5 (175→147), 105·7 (134→119) 85·4 (134→107)

6-*p*-Fluorophenyluracil (I; X = *p*-F)

m/e (I) 207 (11), 206 (89), 205 (5), 164 (10), 163 (38), 135 (21), 134 (9), 123 (10), 122 (100), 121 (9), 120 (4), 108 (7), 107 (13), 96 (3), 95 (20), 94 (6), 89 (4), 81 (3), 75 (10), 74 (3), 69 (3), 68 (11), 67½ (4), 57 (6), 50 (5), 45 (6), 42 (6), 40 (3)

*m** 162·0 (164→163), 129·0 (206→163), 111·8 (163→135), 91·3 (163→122), 86·4 (135→108), 85·4 (134→107), 74·0 (122→95), 59·2 (95→75)

6-*p*-Chlorophenyluracil (I; X = *p*-Cl)

m/e (I) 225 (4), 224 (41), 223 (16), 222 (100), 221 (6), 182 (4), 181 (18), 180 (12), 179 (54), 153 (6), 152 (5), 151 (20), 150 (7), 140 (28), 139 (13), 138 (82), 137 (9), 136 (4), 123 (7), 116 (5), 113 (5), 111 (16), 103 (5), 102 (12), 101 (4), 97 (5), 89 (12), 76 (9), 75½ (8), 75 (23), 74 (8), 73 (5), 68 (23), 63 (8), 62 (6), 57½ (4), 51 (10), 50 (13), 44 (4), 43 (4), 42 (6), 40 (6)

*m** 146·25 (224→181), 144·3 (222→179), 129·3 (181→153), 127·4 (179→151), 108·3 (181→140), 106·4 (179→138), 102·8 (152→125), 100·9 (150→123), 91·2 (140→113), 89·3 (138→111), 50·7 (111→75)

6-*p*-Bromophenyluracil (I; X = *p*-Br)

m/e (I) 269 (14), 268 (100), 267 (20), 266 (99), 265 (5), 226 (9), 225 (41), 224 (10), 223 (36), 197 (14), 196 (8), 195 (16), 194 (6), 185 (7), 184 (62), 183 (14), 182 (64), 181 (7), 169 (3), 167 (3), 157 (9), 155 (9), 144 (4), 116 (14), 115 (7), 103 (19), 102 (15), 101 (7), 98 (9), 97 (10), 90 (3), 89 (21), 88 (8), 87 (5), 77 (6), 76 (25), 75 (25), 74 (12), 68 (24), 63 (13), 62 (9), 61 (4), 58 (8), 57½ (9), 53 (5), 52 (16), 51 (25), 45 (5), 44 (6), 43 (6), 42 (6), 41 (4), 40 (9)

*m** 188·9 (268→225), 186·9 (266→223), 172·5 (225→197), 170·5 (223→195), 150·5 (225→184), 148·5 (223→182), 68·3 (116→89)

TABLE 2

Mass spectra of 6-(*p*-substituted-phenyl)-2-thiouracils

6-*p*-Tolyl-2-thiouracil (II; X = *p*-Me)

m/e (I) 220 (7), 219 (16), 218 (100), 217 (15), 190 (32), 185 (5), 160 (12), 159 (16), 148 (23), 131 (10), 130 (11), 119 (8), 118 (48), 117 (13), 116 (7), 115 (9), 104 (3), 103 (9), 95 (5), 91 (19), 90 (3), 89 (6), 77 (10), 69 (5), 68 (8), 65 (14), 63 (8), 51 (8), 50 (4), 45 (4), 43 (5), 41 (3)

*m** 165·6 (218→190), 107·9 (159→131), 70·1 (118→91), 46·4 (91→65)

6-*p*- Methoxyphenyl-2-thiouracil (II; X = *p*-OMe)

m/e (I) 236 (5), 235 (12), 234 (100), 233 (13), 206 (28), 201 (5), 191 (9), 176 (6), 175 (7), 164 (14), 149 (6), 147 (5), 146 (6), 135 (6), 134 (27), 133 (9), 132 (6), 119 (8), 117 (4), 104 (4), 103 (6), 91 (6), 89 (6), 88 (4), 77 (10), 76 (5), 69 (4), 68 (5), 63 (7), 60 (4), 51 (6), 50 (4), 45 (8), 43 (6), 39 (5)

*m** 181·3 (234→206), 177·1 (206→191), 105·7 (134→119)

6-*p*-Fluorophenyl-2-thiouracil (II; X = *p*-F)

m/e (I) 224 (5), 223 (16), 222 (100), 221 (8), 194 (19), 189 (4), 167 (3), 164 (13), 163 (14), 152 (16), 135 (14), 134 (11), 123 (7), 122 (60). 121 (12), 120 (8), 108 (7), 107 (15), 97 (4), 95 (16), 94 (6), 81 (3), 75 (9), 74 (4), 69 (11), 68 (12), 63 (3), 60 (4), 57 (6), 51 (3), 50 (5), 45 (5), 43 (7). 42 (5), 40 (3)

*m** 169·5 (222→194), 121·1 (222→164), 119·7 (222→163), 119·1 (194→152), 111·8 (163→135), 91·3 (163→122), 89·3 (164→121), 85·4 (134→107), 74·0 (122→95), 59·2 (95→75)

TABLE 2 (*Continued*)

6-*p*-Chlorophenyl-2-thiouracil (II; X = *p*-Cl)

m/e (I)	241 (6), 240 (39), 239 (22), 238 (100), 237 (13), 212 (12), 210 (29), 205 (5), 182 (7), 181 (8), 180 (19), 179 (17), 170 (7), 168 (17), 153 (4), 152 (4), 151 (14), 150 (10), 140 (19), 139 (11), 138 (6), 137 (10), 136 (5), 123 (7), 113 (5), 111 (13), 102 (11), 101 (6), 89 (12), 87 (5), 76 (7), 75 (20), 74 (8), 73 (5), 69 (14), 68 (19), 63 (8), 62 (5), 60 (4), 59 (5), 51 (12), 50 (13), 43 (5), 42 (5), 40 (5)
*m**	187·3 (240→212), 185·3 (238→210), 136·3 (212→170), 134·4 (210→168), 129·3 (181→153), 127·4 (179→151), 108·3 (181→140), 106·4 (179→138), 91·2 (140→113), 89·3 (138→111), 50·7 (111→75)

6-*p*-Bromophenyl-2-thiouracil (II; X = *p*-Br)

m/e (I)	286 (6), 285 (15), 284 (98), 283 (26), 282 (100), 281 (11), 257 (4), 256 (24), 255 (4), 254 (24), 251 (4), 249 (5), 226 (17), 225 (15), 224 (15), 223 (16), 214 (14), 212 (13), 197 (10), 196 (9), 195 (11), 194 (8), 185 (6), 184 (46), 183 (14), 182 (50), 181 (8), 169 (4), 167 (3), 157 (9), 155 (8), 117 (3), 116 (8), 115 (8), 114 (3), 103 (14), 102 (14), 101 (12), 90 (3), 89 (18), 88 (9), 87½ (8), 87 (5), 77 (6), 76 (20), 75 (28), 74 (14), 73 (3), 69 (14), 68 (27), 64 (3), 63 (28), 62 (9), 61 (3), 60 (5), 59 (5), 52 (4), 51 (15), 50 (20), 43 (5), 40 (7)
*m**	230·7 (284→256), 228·8 (282→254), 179·8 (284→226), 177·9 (282→224), 178·3 (284→225), 176·3 (282→223), 150·5 (225→184), 148·5 (223→182), 134·0 (184→157), 132·0 (182→157), 68·3 (116→89)

TABLE 3

Metastable transitions for 6-(*m*-substituted-phenyl)-uracils

6-*m*-Tolyluracil

126·7 (202→160), 125·1 (202→159), 107·9 (159→131), 87·7 (159→118), 81·6 (130→103), 70·1 (118→91), 46·4 (91→65)

6-*m*-Methoxyphenyluracil

142·1 (218→176), 140·5 (218→175), 122·1 (177→147), 105·7 (134→119), 85·4 (134→107)

6-*m*-Fluorophenyluracil

162·0 (164→163), 129·0 (206→163), 111·8 (163→135), 91·3 (163→122), 86·4 (135→108), 85·4 (134→107), 74·0 (122→95), 59·2 (95→75)

6-*m*-Chlorophenyluracil

146·2 (224→181), 144·3 (222→179), 129·3 (181→153), 127·4 (179→151), 108·3 (181→140), 106·4 (179→138), 102·8 (152→125), 100·9 (150→123), 91·2 (140→113), 89·3 (138→111), 50·7 (111→75)

6-*m*-Bromophenyluracil

188·9 (268→225), 186·9 (266→223), 172·5 (225→197), 170·5 (223→195), 150·5 (225→184), 148·5 (223→182), 68·3 (116→89)

TABLE 4

Metastable transitions for 6-(*m*-substituted-phenyl)-2-thiouracils

6-*m*-Tolyl-2-thiouracil

165·6 (218→190), 107·9 (159→131), 70·1 (118→91), 46·4 (91→65)

6-*m*-Methoxyphenyl-2-thiouracil

181·3 (234→206), 150·4 (206→176), 105·7 (134→119), 85·4 (134→107)

6-*m*-Fluorophenyl-2-thiouracil

169·5 (222→194), 121·1 (222→164), 119·7 (222→163), 119·1 (194→152), 111·8 (163→135), 91·3 (163→122), 89·3 (164→121), 85·4 (134→107), 74·0 (122→95), 59·2 (95→75)

6-*m*-Chlorophenyl-2-thiouracil

187·3 (240→212), 185·3 (238→210), 136·3 (212→170), 134·4 (210→168), 129·3 (181→153), 127·4 (179→151), 108·3 (181→140), 106·4 (179→138), 91·2 (140→113), 89·3 (138→111), 50·7 (111→75)

6-*m*-Bromophenyl-2-thiouracil

230·8 (284→256), 228·8 (282→254), 179·8 (284→226), 177·9 282→224), 178·2 (284→225), 176·3 (282→223), 150·5 (225→184), 148·5 (223→182), 134·0 (184→157), 132·0 (182→155), 68·3 (116→89)

(a) formed by loss of HNCS are more energetic than those formed by loss of HNCO and therefore more prone to further fragmentation.

The differences may arise partly from differences in charge distribution in the parent ions and partly from differences in energies of the expelled neutral fragments. Uracils are essentially cyclic urea derivatives and the location of charges on the molecular ions of ureas and thioureas is known to differ.[10]

The fact that molecular ions of the 2-thiouracils (II) lose HNCS but not HNCO provides a method of differentiating between 2- and 4-thiouracils as has already been pointed out.[5]

We thank Mrs. Ruth Maynard for assistance in measuring and tabulating spectra and preparing line diagrams.

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[10] M. A. Baldwin, A. Kirkien-Konasieivicz, A. G. Loudon, A. Maccoll, and B. Saville, *Some Newer Phys. Methods Struct. Chem., Proc. Symp.*, 1966, ed. R. Bonnett, United Trade Press Ltd., London, P. 22 (1967); A. Maccoll in ' Modern Aspects of Mass Spectrometry,' ed. by R. I. Reed, Plenum Press, New York, 1968, p. 143.