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Mass Spectra of Pyrimidines

Part I. *N*-Alkyluracils

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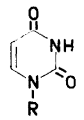
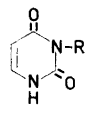
The mass spectrometric fragmentation of simple 1-alkyluracils and 3-alkyluracils has been studied and interpreted. The most abundant ions in the mass spectra of 3-alkyluracils with an alkyl chain length of three or more carbon atoms arise by double hydrogen transfer from the alkyl chain. In the corresponding 1-alkyluracils only one hydrogen atom is transferred. Thus, mass spectrometry provides a rapid and convenient method for distinguishing between the two types of compounds.

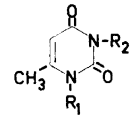
The fragmentation of simple pyrimidines upon electron impact has been previously studied;[1,2] 1,3-dimethyluracil, however, seems to be the only *N*-alkylated uracil of which the mass spectrum is recorded.[1] For the present study alkyluracils substituted at the N-1 or N-3 position were selected. Formerly the structure determination of *N*-alkyluracils was mainly based on the presence or absence of bathochromic shifts in the ultraviolet spectra in basic solution, differences which were first observed in the spectra of 1-methyl- and 3-methyluracil.[3] The diagnostic value of this behaviour for other alkyluracils has, however, not been demonstrated. Owing to the biological importance of uracil derivatives it seemed desirable to determine the scope of the latter method by an independent study of the mass spectra of a series of alkylated uracils.



1: R = CH_3
2: R = CH_3CH_2
3: R = $CH_3CH_2CH_2$
4: R = $(CH_3)_2CH$
5: R = $CH_3CH_2CH_2CH_2$



6: R = CH_3
7: R = CH_3CH_2
8: R = $CH_3CH_2CH_2$
9: R = $(CH_3)_2CH$
10: R = $CH_3CH_2CH_2CH_2$



11: R_1 = $CH_3CH_2CH_2$, R_2 = H
12: R_1 = H, R_2 = $CH_3CH_2CH_2$

Fig. 1. Structures of the compounds investigated.

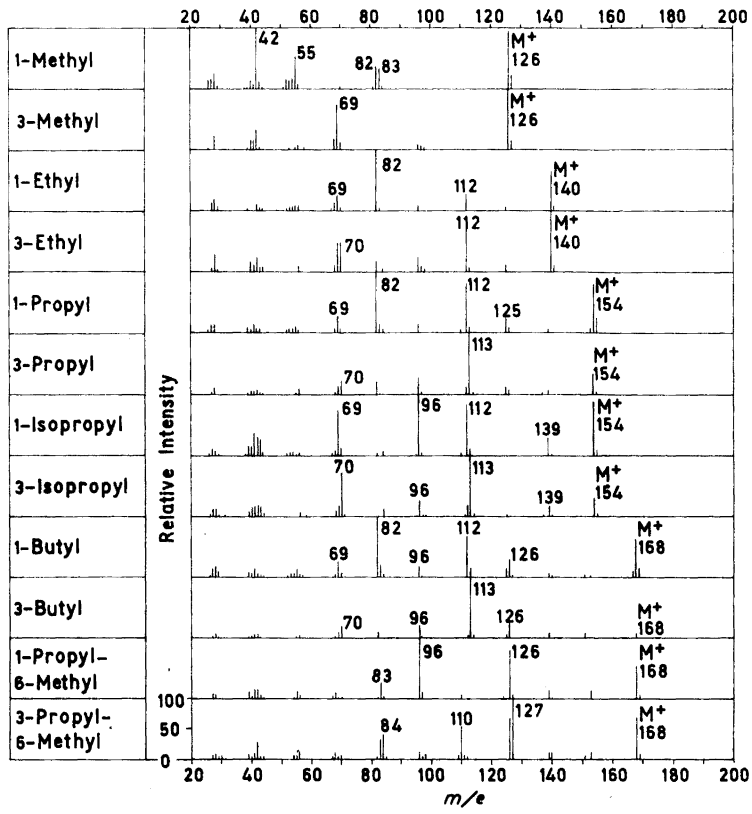


Fig. 2. Mass spectra of uracils.

Convenient synthetic procedures have been described for the preparation of both 1-alkyl-[4] and 3-alkyluracils,[5] but only sporadic attempts have been made to confirm the structure of the reported compounds. The mass spectrometric fragmentation patterns described in this paper, however, unequivocally proves the structures to be as previously assigned.

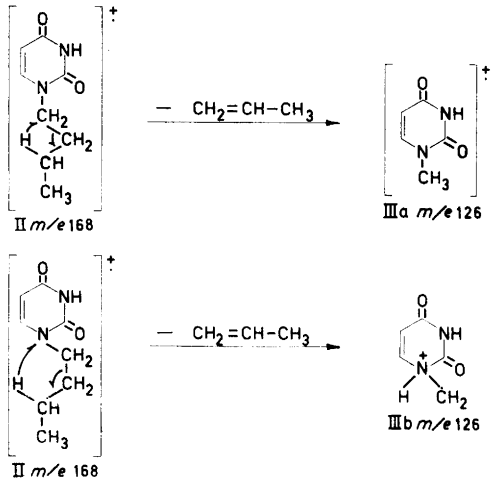
1-Alkyluracils (1—5 *and* 11, *Fig. 1*). The mass spectrometric fragmentation of 1-methyluracil is almost identical to that of 1,3-dimethyluracil.[1] The first step in the fragmentation of the two compounds is the expulsion of HNCO and CH_3NCO, respectively, giving rise to the same ion with mass 83 (I).

$$[CH_3\text{-}N{=}CH\text{-}CH{=}C{=}O]^+$$

I *m/e* 83

The mass spectra of the 1-alkyluracils (*2—5*) are very similar, and the genesis of ions at every commonly occurring mass number need not be described in detail. The spectrum of the 6-methyl derivative (*11*) is almost identical to

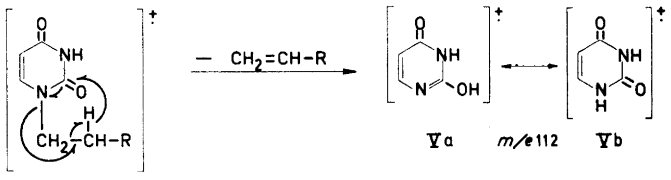
that of *3* except for the additional 14 mass units of the 6-methyl group. The peak at *m/e* 126 found in the spectra of *3* and *5*, is considered analogous to one arising from an ion in the spectra of *N*-propyl- and *N*-butylpyrrolidine, as well as the corresponding *N*-succinimides.[6] For the latter compounds it was shown, by deuterium labelling, that this ion contains the γ-hydrogen and the α-carbon of the alkyl chain. In the present cases, the rearrangement can be depictured by a mechanism involving a four-membered, (II→IIIa), or a five membered, (II→IIIb), transition state. The same ion appears in the spectra of 3-propyl- and 3-butyluracil (*8* and *10*).



II *m/e* 168 IIIa *m/e* 126

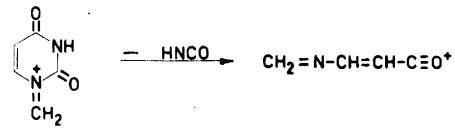
II *m/e* 168 IIIb *m/e* 126

An abundant peak in the spectra of 1-alkyluracils, other than the 1-methyl derivative, appears at *m/e* 112, resulting from loss of the alkyl chain with transfer of one hydrogen atom, most likely through a McLafferty rearrangement (IV→Va or Vb).



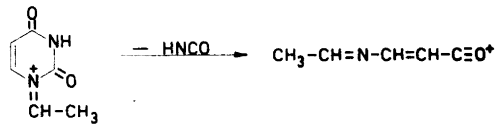
IV Va *m/e* 112 Vb

The base peak in the spectra of all 1-alkyluracils occurs at *m/e* 82, except in that of *4* where the most intense peak is found at *m/e* 96, a relatively abundant ion also in the spectra of the other 1-alkyluracils. This suggests that the origin of the peak at mass 82 is the ion at *m/e* 125 (VI) resulting after α-cleavage of the alkyl chain, giving, by expulsion of HNCO, the ion VII.



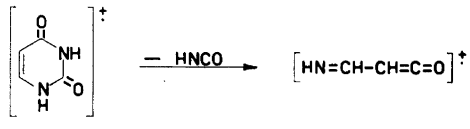
VI *m/e* 125 VII *m/e* 82

In 1-isopropyluracil (*4*), where the probability of the ion at *m/e* 139 (VIII) is greater because of the branched alkyl chain, the base peak at *m/e* 96 is consistent with the same type of ion genesis, *i.e.* expulsion of HNCO to give IX.



VIII *m/e* 139 IX *m/e* 96

The peak at *m/e* 69 is conspicuous in the spectra of all the uracils, including uracil itself.[1] Its origin in the 1-alkyluracils must almost necessarily be the rearrangement ion at *m/e* 112 (Vb) which by expulsion of HNCO gives the ion X.



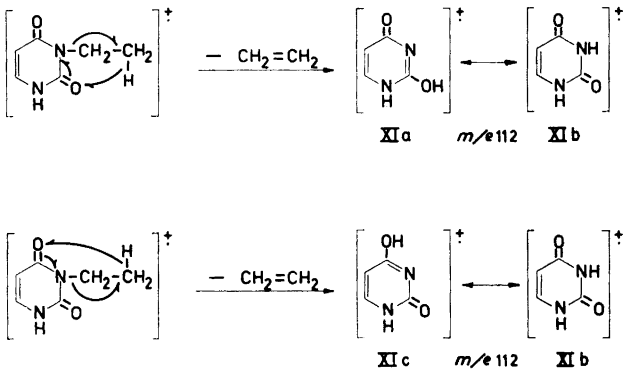
Vb *m/e* 112 X *m/e* 69

The losses of H, HCN, CO, H+CO, and C_2HO from X resulting in ions at *m/e* 68, 42, 41, 40, and 28, respectively, have been described earlier.[1]

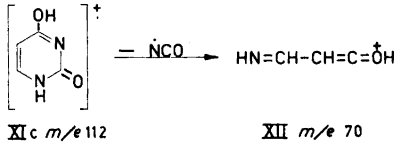
*3-Alkyluracils (*6—10, *and* 12, *Fig. 1).* The mass spectra of 3-methyluracil (*6*) and uracil [1] are very similar, both displaying the same abundant peaks. The loss of CH_3NCO and HNCO, respectively, results in the ion at *m/e* 69 (X) which is also seen in the spectra of 1-alkyluracils, and in all other 3-alkyluracils.

In 3-ethyluracil (*7*) the most abundant ion is the molecular ion. The peak at *m/e* 125 (M—15) results from α-cleavage, and the ion at *m/e* 112 (XIa, b, or c) from a McLafferty rearrangement analogous to the one described for 1-alkyluracils.

No definite distinction can be made between the possible representations XIa, b, and c. That the carbonyl function in the 4-position is involved appears likely in view of the appearance of the abundant ion at *m/e* 70 in all spectra of 3-alkyluracils with the exception of *6*. Conceivably, the origin of this ion could

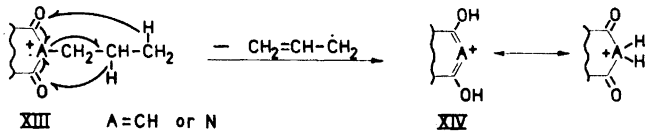


be XIc which on expulsion of NCO affords the ion XII. Alternatively, XII may be formed from the molecular ion by transfer of one hydrogen atom and expulsion of CH_2CH_2NCO.

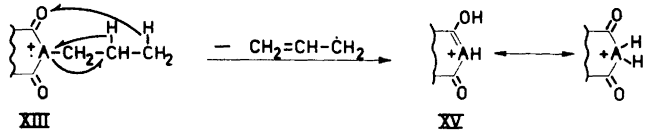


The most striking difference in the spectra of 1-propyluracil (*3*) and 3-propyluracil (*8*) is the absence of the ion at *m/e* 112 and the appearance of the ion at *m/e* 113 in the latter compound.

The ion with mass 113 constitutes the base peak in the spectra of both 3-propyl-, 3-isopropyl- and 3-butyluracil, and must originate from loss of the alkyl chain with transfer of two hydrogen atoms. An analogous rearrangement is reported for *N*-alkylsuccinimides,[6] 5-alkylbarbituric acids,[7] 2-alkyl-1,3-cyclohexadiones,[8] and *N*-alkylphthalimides,[9] whenever the length of the alkyl chain is three carbon atoms or more. It has further been shown by deuterium labelling of the *N*-alkylsuccinimides that the sources of the transferred hydrogens are the *β*- and *γ*-carbon atoms. The examples recorded in the literature suggest that transfer of two hydrogen atoms occur in all molecules with two carbonyl functions adjacent to the atom to which the alkyl chain is attached. Two representations are possible for the origin of the ion of mass 113: (i) one in which the two hydrogen atoms are each transferred to an oxygen atom (XIII→XIV), and (ii) another, where hydrogen from the *γ*-carbon is transferred to the oxygen, and hydrogen from the *β*-carbon to the atom carrying the alkyl chain (XIII→XV). Since, however, this rearrangement is not observed in the 1-alkyluracils, the mechanism of the rearrangement is probably best represented by XIII→XIV. The alternative route XIII→XV should, of course, be possible with only one adjacent carbonyl



XIII A=CH or N XIV



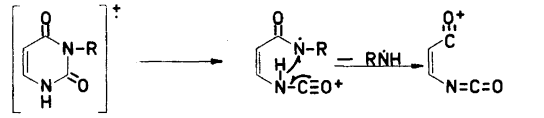
XIII XV

function present. The ion of mass 113, in the spectra of *8*, *9*, and *10*, is thus represented by XVI.

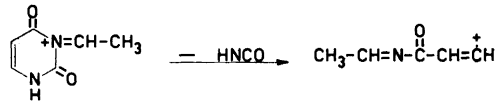
XVI *m/e* 113

An abundant ion in the mass spectra of all 3-alkyluracils occurs at mass 96. High-resolution mass spectrometry * of 3-propyluracil (*8*) indicated that the peak consisted of the ion $C_4H_2NO_2^+$ (85 %) (XVIII) contaminated with the species $C_5H_6NO^+$ (15 %), respresented by XX.

The major fragment XVIII most likely originates from the molecular ion by expulsion of RNH, as illustrated by the sequence XVII→XVIII, whereas the fragment XX probably arises by expulsion of HNCO from the product resulting after β-cleavage of the alkyl chain (XIX).



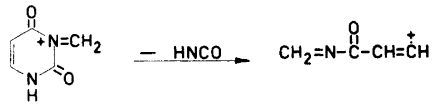
XVII XVIII *m/e* 96



XIX *m/e* 139 XX *m/e* 96

* The author is indebted to Dr. Jørgen Møller, Physical Laboratory II, University of Copenhagen, for the high-resolution mass spectral data.

The spectra of all 3-alkyluracils exhibit the same ion of mass 82 (XXII) of relatively low abundance derived by expulsion of HNCO from the product of α-cleavage of the alkyl chain (XXI).



XXI *m/e* 125 XXII *m/e* 82

The spectrum of 6-methyl-3-propyluracil (*12*) is almost identical with that of 3-propyluracil (*8*) with the notable exception that the ion at *m/e* 126 in *12*, corresponding to the ion at *m/e* 112 in *8*, is of much higher abundance.

Ultra-violet spectroscopy. All 1-alkyluracils exhibited two absorption maxima in EtOH: at 210 nm and 266 nm, respectively. In base (0.1 N NaOH), the maxima were unchanged. In contrast, the maxima in EtOH at 210 nm and 258 nm of 3-alkyluracils were bathochromically displaced in base to 220 nm and 283 nm, respectively. Thus, these results are in agreement with previously reported data for other *N*-alkyluracils.[3,4]

EXPERIMENTAL

The mass spectra were recorded on an LKB 9000 mass spectrometer fitted with an all-glass heated inlet system, maintained at 90—110°. An ionizing potential of 70 eV was used.

All 1-alkyluracils were synthesized by direct alkylation of uracil in DMSO.[4] The 3-alkyluracils were prepared by decarboxylation of the corresponding 3-alkylorotic acids,[5] by the method of Atkinson *et al.*[10] 6-Methyl-1-propyluracil (*11*) and 6-methyl-3-propyluracil (*12*) were synthesized by direct alkylation of 6-methyl-uracil followed by separation of the isomers by recrystallization.[11] The structures assigned to the compounds were found to agree with the mass spectrometric fragmentations.

Table 1. Melting points (uncorr.) of the 1- and 3-alkyluracils studied.

Comp. No.[a]	m.p.	Comp. No.	m.p.
1	233—237° [b]	*7*	174—175° [f]
2	146—147° [c]	*8*	157—158°
3	119—121°	*9*	126—127°
4	132—134°	*10*	151—152° [g]
5	102—103° [d]	*11*	170—172° [h]
6	181—182° [e]	*12*	189—190° [i]

[a] *cf.* Fig. 1; [b] 232—233°;[12] [c] 147°.5;[13] [d] 100—103°;[4] [e] 179°;[12] [f] 173—174°;[14] [g] 152—153°;[15] [h] 170—172°;[11] [i] 184°;[11]

Melting points (uncorrected) are reported in Table 1. The microanalytical data for all compounds agreed within ±0.3 of the calculated values.

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REFERENCES

1. Rice, J. M., Dudek, G. O. and Barber, M. *J. Am. Chem. Soc.* **87** (1965) 4569.
2. Nishiwaki, T. *Tetrahedron* **22** (1966) 3117.
3. Shugar, D. and Fox, J. J. *Biochim. Biophys. Acta* **9** (1952) 199.
4. Baker, B. R. and Schwan, T. J. *J. Med. Chem.* **9** (1966) 73.
5. Whitehead, C. W. *J. Am. Chem. Soc.* **74** (1952) 4267.
6. Duffield, A. M., Budzikiewicz, H. and Djerassi, C. *J. Am. Chem. Soc.* **87** (1965) 2913.
7. Costopanagiotis, A. and Budzikiewicz, H. *Monatsh.* **96** (1965) 1800.
8. Vandewall, M., Schamp, N. and DeWilde, H. *Bull. Soc. Chim. Belges* **76** (1967) 123.
9. Aplin, R. T. and Jones, J. H. *Chem. Commun.* **1967** 261.
10. Atkinson, M. R., Maguire, M. H., Ralph, R. K., Shaw, G. and Warrener, R. N. *J. Chem. Soc.* **1957** 2363.
11. Bückendorff, O. *Ann.* **385** (1911) 314.
12. Brown, D. J., Hoerger, E. and Mason, S. F. *J. Chem. Soc.* **1955** 211.
13. Hilbert, G. E. *J. Am. Chem. Soc.* **59** (1937) 330.
14. Johnson, T. B. and Heyl, F. W. *Am. Chem. J.* **37** (1907) 628.
15. Logemann, W., Caprio, L. and Artini, D. *Farmaco (Pavia) Ed. Sci.* **12** (1957) 586.

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