## Potentiation of Cell Growth Inhibition by Furanosides

**Keyphrases** ☐ Furanosides—self-potentiation, cell growth inhibition ☐ Cells, microbial, tumor, growth inhibition—furanoside combinations

*Sir:*

Potentiation of the inhibition of the growth of microbial or tumor cell systems has been achieved in a number of instances by the combined use of two antagonists (or occasionally three) (1) which have presumably functioned by sequential (2, 3) or concurrent (4) blockade of a few specific enzymes. We have postulated another possibility of achieving potentiation, by selection of compounds which should have a slight but significant capacity to inhibit each of a selected spectrum of enzymes. Such "selective spectrum inhibition" should give rise, *via* "self-potentiation," to an observable capacity to inhibit the growth of cells, and, moreover, should be widely capable of potentiating the inhibitory action of other compounds which inhibit particular enzymes of the same spectrum.

From the observation that a common feature of the natural substrates of the spectrum of enzymes involved in nucleic acid synthesis is a furanose moiety, we have anticipated that certain of the methyl aldofuranosides might be capable of the foregoing postulated "self potentiation," and thus contribute to sequential or concurrent blockade of a number of such enzymes. In preliminary experiments, we have found that methyl β-D-xylofuranoside, methyl β-D-arabinofuranoside, methyl α-L-threoside, and methyl β-D-threoside each inhibit by 50% the growth of *Streptococcus faecalis* 8043, at approximately $5 \times 10^{-3}$ *M* concentration levels. When these compounds are tested in pairs, interference effects are observed. Of these, the first three have an apparent capacity to potentiate tenfold or more the capacity to inhibit cell growth, in *Streptococcus faecalis*, of several inhibitors—such as 6MPR, FUdR, and MUdR—whose major sites of action are believed to involve enzymes of nucleic acid pathways. Details of these studies will be given in a forthcoming report.

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## The $(M-43)^+$ Ion in the Mass Spectra of Some Medicinal Barbiturates

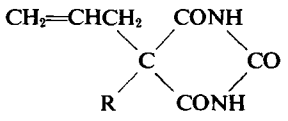
**Keyphrases** ☐ Barbiturates—mass spectra ☐ Ion, $(M-43)^+$, composition—identification ☐ Mass spectroscopy—structure

*Sir:*

The high sensitivity of mass spectrometers makes mass spectrometry an important tool in forensic analysis. In order that this method's potential in the identification of small quantities of unknown drugs or metabolites may be fully realized, it is essential that proposed fragmentation modes should not be speculative but should be substantiated by accurate mass determinations or by means of studies using labeled compounds. Otherwise, erroneous structures may be ascribed to fragment ions and a meaningful comparison of the spectrum of a compound of unknown structure with that of a known structure would not be possible.

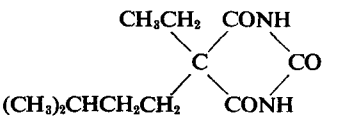
Grützmacher and Arnold (1) examined the mass spectra of numerous medicinal barbiturates and illustrated the value of mass spectrometry in the identification of these compounds. It is our opinion, however, that these authors have wrongly identified some ions in these spectra. An inconsistency with our own work in this field has already been reported (2). We now wish to report that the $(M-43)^+$ ion, present in some of the barbiturate spectra, does not have the composition ascribed to it.

A comparison of the published (1, 2) spectra of secobarbital (I*a*) and talbutal (5-allyl-5-*sec*-butylbarbituric acid) (I*b*) revealed that they were almost identical. Neither spectrum shows an abundant molecular ion

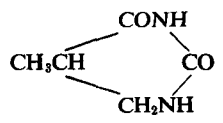


I

I*a*, R = $CH_3CH_2CH_2CH(CH_3)$—
*b*, R = $CH_3CH_2CH(CH_3)$—
*c*, R = $(CH_3)_2CHCH_2$—
*d*, R = $CH_2$=$CHCH_2$—
*e*, R = $(CH_3)_2CH$—



II



III

but both show an ion of *m/e* 195 of significant abundance (~26% relative abundance). Grützmacher and Arnold (1) identified this ion in the mass spectrum of I*b* as $(M-C_2H_5)^+$, but in the spectrum of I*a* they concluded that it was an $(M-HNCO)^+$ ion. This latter conclusion seemed unlikely to us; an $(M-C_3H_7)^+$ ion seemed more likely. The mass spectra of amobarbital (II),

**Table I**—Mass Spectral Data of Medicinal Barbiturates

| | Relative Abundance of $(M-43)^+$ Ion | | Accurate Masses | | | Identity of $(M-43)^+$ Ion | |
|---|---|---|---|---|---|---|---|
| | Present Study | Literature[a] Value | Measured | Calcd. $M-C_3H_7$ | Calcd. M-HNCO | Literature[a] | Present Study |
| Secobarbital (*Ia*) | 26.0 | 26.0 | 195.0764 | 195.0770 | 195.1259 | $C_{11}H_{17}NO_2$ | $C_9H_{11}N_2O_3$ |
| Allylbarbituric acid (*Ic*) | 19.0 | 16.5 | 181.0612 | 181.0613 | 181.1103 | $C_{10}H_{15}NO_2$ | $C_8H_9N_2O_3$ |
| Diallylbarbituric acid (*Id*) | 23.2 | 19.7 | 165.0299 | 165.0300 | 165.0790 | $C_9H_{11}NO_2$ | $C_7H_5N_2O_3$ |
| Aprobarbital (*Ie*) | 100 | 100 | 167.0456 | 167.0457 | 167.0947 | $C_7H_7N_2O_3$ | $C_7H_7N_2O_3$ |
| Amobarbital (II) | 6.3 | 6.0 | 183.0771 | 183.0770 | 183.1260 | $C_{10}H_{17}NO_2$ | $C_8H_{11}N_2O_3$ |

[a] Grützmacher and Arnold (1).

allylbarbituric acid (*Ic*) and diallylbarbituric acid (*Id*) were also reported by the same authors to possess significant $(M-HNCO)^+$ ions, whereas in the spectrum of aprobarbital (5-allyl-5-isopropylbarbituric acid) (*Ie*), the $(M-43)^+$ ion was identified as an $(M-C_3H_7)^+$ ion. To resolve these inconsistencies, the mass spectra of amobarbital, allylbarbituric acid, secobarbital, diallylbarbituric acid, and aprobarbital were recorded[1] and an accurate mass of the $(M-43)^+$ ion in each spectrum was determined. The results are summarized in Table I. In all five spectra, the $(M-43)^+$ ion was shown to be the $(M-C_3H_7)^+$ ion.

An ion of this composition in the spectrum of diallylbarbituric acid might seem unlikely. Its formation must involve a rearrangement under electron impact. Rearrangements involving allyl groups in other environments are known (3). The possibility that the sample of diallylbarbituric acid[2] was impure was discounted. Its melting point and gas-chromatographic behavior were in agreement with literature values (4, 5); it analyzed correctly for $C_{10}H_{12}N_2O_3$ and its mass spectrum showed no spurious ions.

It is concluded that 5,5-disubstituted barbiturates do not readily eliminate an HNCO molecule from the molecular ion. This conclusion is in agreement with a mass spectral study carried out on thymine and dihydrothymine (III), which revealed that the ejection of HNCO was a process which occurred readily in the former but not in the latter (6).

[1] All mass spectra were obtained using an A.E.I. M.S.9 mass spectrometer with a direct insertion probe. The source temperature was 155–160°, and the ionizing energy was kept at 70 eV. These conditions were comparable to those employed by Grützmacher and Arnold (*cf.* relative abundancies of $(M-43)^+$ ion in Table I). Accurate mass measurements were carried out by the peak matching method.

[2] The sample was kindly supplied by Ciba Co. Ltd., Montreal, Canada.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