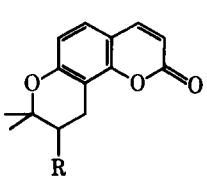
Coumarins VIII

Mass Spectra of Lomatin and Some of Its Derivatives

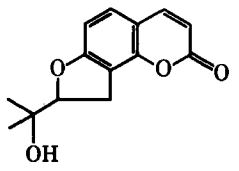
By M. SHIPCHANDLER and T. O. SOINE

The fragmentation behavior of lomatin and certain of its derivatives has been studied. Two distinct fragmentation pathways have been observed, one leading to aromatization of the chroman ring and the other leading to its fission. These findings are in complete agreement with the observations of other workers. Probable fragmentation mechanisms have been proposed.

THE AUTHORS' PAST INTEREST in naturally occurring coumarins had led them to the isolation and structural characterization of several new coumarins (1–5). Among these, lomatin (I) was subsequently obtained as the angelate ester (II) by Shanbhag *et al.* (6), Seshadri *et al.* (7), as well as by this laboratory (3, 5). Additionally, lomatin senecioate (III) was shown to be of natural occurrence (5) and given the



	R
I	—OH
II	—Angeloxy
III	—Senecioyloxy
V	—Acetoxy
VI	=O



IV

provisional name of *nuttallin*. The present authors have previously studied the mass spectral characteristics of columbianetin (IV) and certain of its esters (8) as well as of certain glycosidic derivatives (9). Because of the close relationship of I to IV it seemed desirable to examine the mass spectral characteristics of I and its naturally occurring congeners (II and III) as well as certain other closely related derivatives. The mass spectrum of II has been reported by Seshadri *et al.* (7) but, nevertheless, it has been reexamined in the present work along with the other esters and studied in greater detail. The observations reported herein are concerned with the fragmentation patterns of lomatin (I), lomatin acetate (V), lomatin angelate (II), lomatin senecioate (III), and the ketone (VI) derived from I.

There is a difference of opinion among different groups of workers regarding the structure of the ion arising from 2-pyrones by loss of CO from the lactone carbonyl upon electron impact. It has commonly been assumed to have a furan-type structure although Pirkle (10) and Pirkle and Dines (11) have adduced evidence to show that this is not true. Dean *et al.* (12) support Pirkle's view as do Pike and McLafferty (13) and Bursey and Dusold (14). However, Green and Brown (15) consider the matter to be an open question and Nakata and Tatematsu (16) suggest that the fragmentation occurs, at least in part, through an intermediate with a C—O bond (*i.e.*, a furan-like system). For the sake of simplicity, a practice which is not unprecedented in this field, the present authors prefer to employ a benzofuran structure for the ion arising by loss of CO from the coumarin lactone. This representation, it may be pointed out, is consistent with that of many other workers (17–25).

Metastable ion peaks have been helpful in supporting many of the fragmentation pathways presented in this study and will be represented by a heavily lined arrow. Fragmentation pathways not substantiated by metastable ions but, nevertheless, feasible on mechanistic grounds or because of past precedent, are suggested and represented with ordinary arrows.

The fragmentation characteristics of a number of oxygen-containing heterocyclic compounds have been studied by Willhalm *et al.* (26) and their findings indicate that there is a strong tendency for stable aromatic ions (*e.g.*, benzopyrilium ion in the case of chromenes) to be formed without heterocyclic ring fission. Such fission is observed in the corresponding reduced compounds (*e.g.*, chromans) where such aromatization is not feasible. The appearance of the benzopyrilium ion is a very characteristic feature in the mass spectra of chromenes, arising by expulsion of a methyl radical from the molecu-

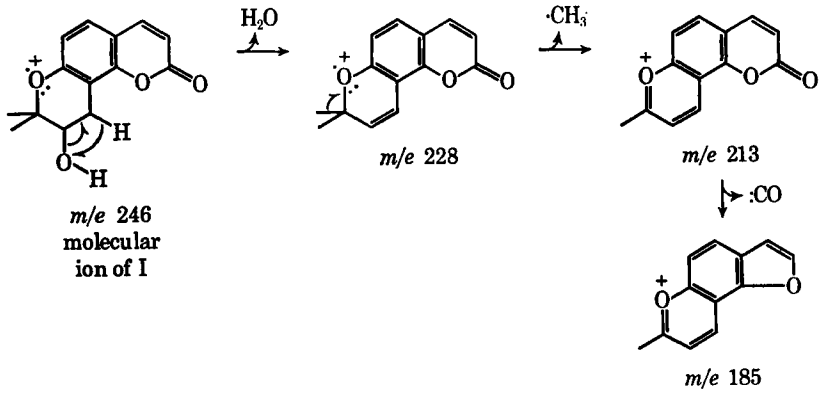
Received July 24, 1968, from the Department of Medicinal Chemistry, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455

Accepted for publication August 27, 1968.

This work was supported by grant HE 07101 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md.

Send communications concerning this paper to Dr. T. O. Soine.

Assistance in the interpretation of the spectra by Dr. Thomas Watson, Pharmacy Department, University of Sydney, Sydney, Australia, is gratefully acknowledged.



Scheme I

lar ion (27). Its highly stable aromatic character minimizes further fragmentation and, therefore, this ion appears as a prominent peak (17). In compounds containing chroman systems with an oxygenated substituent, the benzopyrilium ion is generated in two steps as noted by Willhalm *et al.* (26) and confirmed in the present study. The first step involves a loss of ROH to generate a chromene system and this is followed by expulsion of a methyl radical. Thus, in the mass spectrum of I (see Fig. 1) the molecular ion loses HOH to give an ion of *m/e* 228 which then expels the methyl radical to provide the benzopyrilium ion at *m/e* 213 (see Scheme I). A loss of CO as in the case of seselin (17) is observed and gives a small peak at *m/e* 185. In the mass spectrum of deuterated lomatin (see Fig. 2) the peaks at *m/e* 228 and 213 remain undisplaced. The pathway M → 228 → 213 → 185 is also operative in the case of columbianetin and its derivatives (8, 9). The benzopyrilium ion appears in their mass spectra even though this class of compounds lacks a chroman ring and a mechanism leading to ring expansion has been proposed (8). The pathway M → 228 → 213 → 185 is of minor consequence in the case of I, however, although it is the principal route in the case of the *esters* of I (se below).

The principal route of fragmentation in the case of I is the fission of the chroman ring with a loss of two ring carbons and is in agreement with the observations of Willhalm *et al.* (26). The ring fission, in the present study, occurs with one as well as two hydrogen transfers and generates the ions of *m/e* 175 and 176 (base peak), respectively. As mentioned earlier, such ring fission is characteristic of chroman and 2,2-dimethylchroman and occurs with or without hydrogen transfer in the former and with hydrogen transfer in the latter (26). The mechanism of the ring fission can be rationalized as shown in Scheme II and is partially supported by the fact that the base peak at *m/e* 176 is displaced to *m/e* 177 in the mass spectrum of the deuterated sample (see Fig. 2) indicating that one of the transferred hydrogens arises principally from the hydroxy group. Loss of a hydrogen from the ion of *m/e* 176 would provide the ion of *m/e* 175 which could also arise from the molecular ion directly by a fission with a single hydrogen transfer. The ion of *m/e* 175 very likely rearranges to the corresponding tropylium ion which can lose three molecules of CO in a stepwise manner, a process characteristic of coumarins (27). As a result, the ions of *m/e* 147,

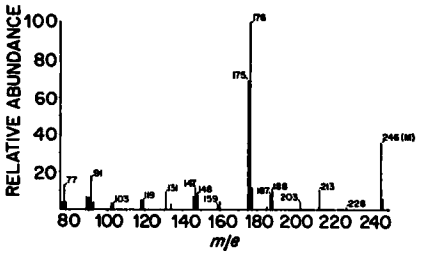


Fig. 1—Mass spectrum of I. Peaks of abundance ratio less than 3% have been omitted in all spectra unless a reference has been made to them in the text.

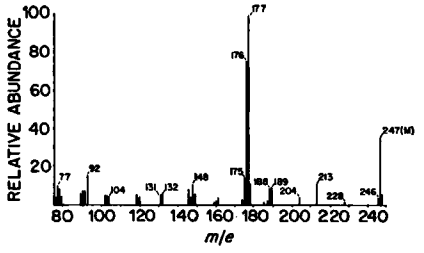
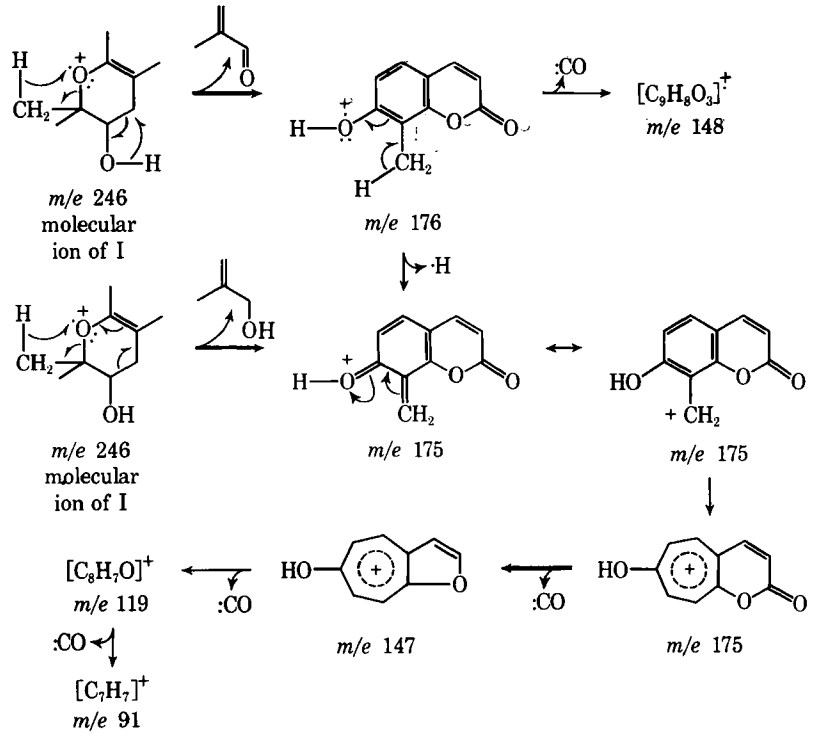


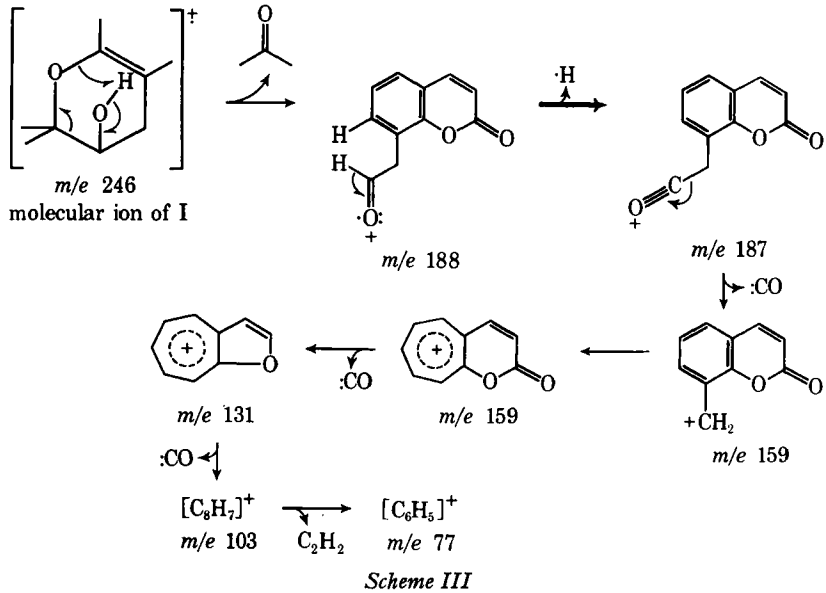
Fig. 2—Mass spectrum of deuterated I.



Scheme II

119, and 91 are produced. The ion of *m/e* 148 can be envisioned as arising from the ion of *m/e* 176 by loss of CO. A very broad metastable ion peak may be due to either the transformation M → 175 (124.5 theory) or to 175 → 147 (123.5 theory) or both. However, the peak at *m/e* 125.9 is distinguishable and corresponds to the transformation M → 176 (125.9 theory).

Another minor pathway observed is a loss of acetone from the molecular ion giving an ion of *m/e* 188 which loses a hydrogen giving rise to an ion of *m/e* 187 (see Scheme III), the latter being



Scheme III

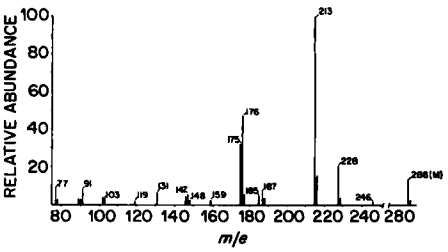


Fig. 3—Mass spectrum of V.

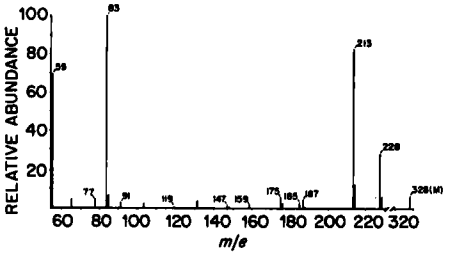
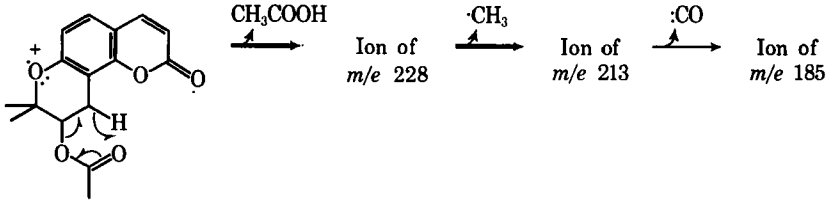


Fig. 4—Mass spectrum of II.

supported by the appearance of the corresponding metastable ion peak. In the deuterated sample, the peaks at *m/e* 188 as well as 187 are displaced to one higher unit, indicating that the transferred hydrogen originates from the hydroxy group. The isomeric IV also shows a loss of acetone followed by a loss of hydrogen (8). However, in this case the pathway is the main fragmentation route giving the base peak at *m/e* 187. Once again, in the present study, a stepwise loss of three molecules of CO is observed giving rise to ions of *m/e* 159, 131, and 103. Finally, the ion of *m/e* 103 can lose a molecule of acetylene to account for the ion of *m/e* 77. The pathway 131 → 103 → 77 is very similar, and probably analogous, to that of IV where it is supported by visualized as resulting from the loss of ketone by the molecular ion (see Scheme V) and it would be expected that this ion would then fragment further just as in the case of lomatin provided that the fragmentation generated ion is similar to that arising by direct electron impact. Therefore, it is expected that almost all of the peaks found in the spectrum of the parent compound would also be found in the spectrum in the present case. Moreover, the ions of *m/e* 176 and 175 could also arise directly from the molecular ion of the acetate as shown in Scheme V.

The mass spectrum of lomatin angelate[1] (II) (see Fig. 4) was reported by Seshadri *et al.* (6) and comparison with the present spectrum shows



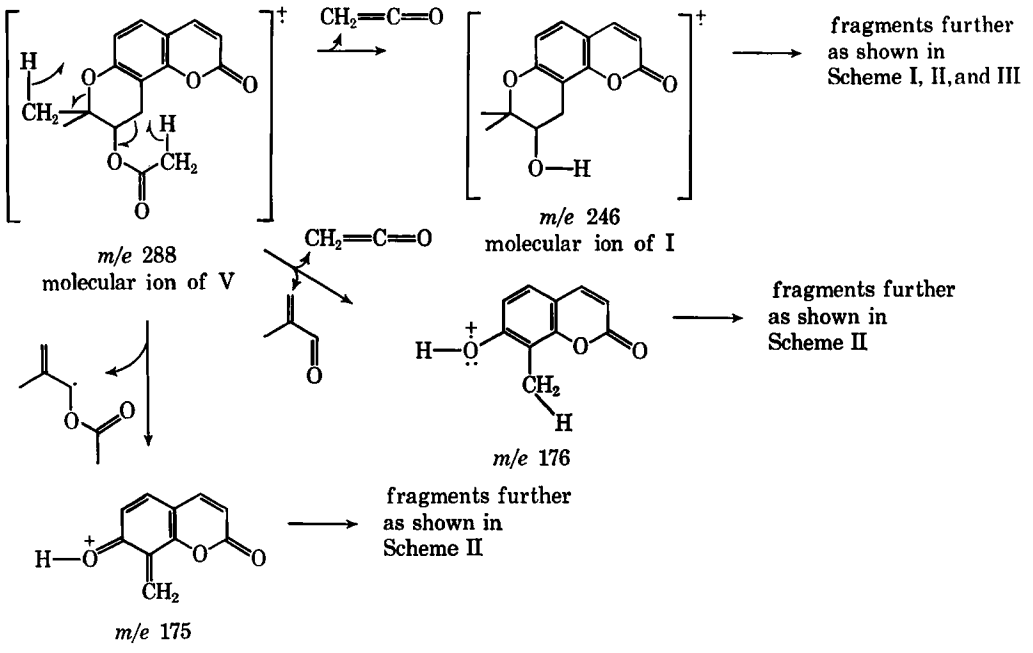
Scheme IV

the corresponding metastable ions. Finally, the proposed structures for the ions of *m/e* 175, 159, 147, and 131 are in accordance with the corresponding ions found in the mass spectra of osthol and dihydroosthol (17, 27).

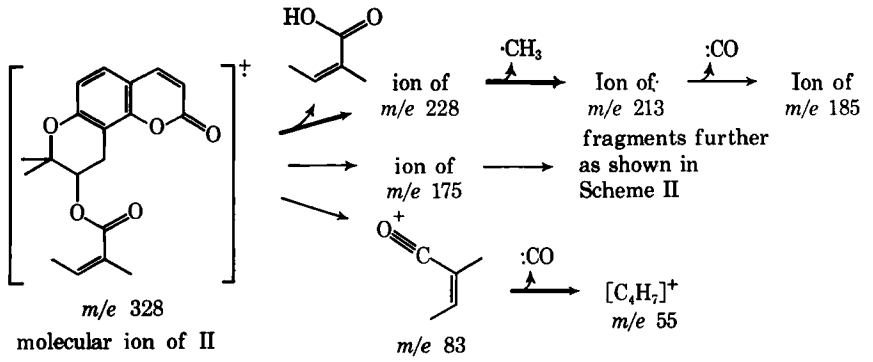
The mass spectrum of lomatin acetate (V) (see Fig. 3) shows a predictable mode of fragmentation as described in Scheme IV. Loss of a molecule of acetic acid by the molecular ion provides the ion of *m/e* 228 which expels a methyl radical to give the stable benzopyrilium ion as the base peak at *m/e* 213 (doubly charged ion at *m/e* 106.5). This ion then loses a molecule of CO to produce the ion of *m/e* 185 (doubly charged ion at *m/e* 92.5). This pathway is analogous to those observed in the case of esters of IV (8) and seselin (17). The M-42 ion can be marked similarity with the principal differences being in peak heights, a behavior not uncommon for identical compounds examined under differing instrumental conditions. The fragmentation pathways have been outlined in Scheme VI and are in agreement with those of the previous workers. In addition, corresponding metastable peaks have been found for the transformations M → 228, 228 → 213, and 83 → 55. Fission of the heterocyclic ring with one hydrogen transfer is observed, giving the ion of *m/e* 175.

The mass spectrum of lomatin senecioate (III) (see Fig. 5) resembles that of the isomeric angelate ester and, presumably, all of the fragmentation pathways for II also hold true for III.

[1] Lomatin angelate was named selinidin by Leshadri *et al.* (7) and jatamansin by Shanbhag *et al.* (6).

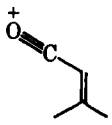


Scheme V



Scheme VI

The ion of *m/e* 228 arises by loss of senecioic acid from the molecular ion and the ion appearing at *m/e* 83 (base peak) probably has the isomeric structure VII.



m/e 83

VII

The proposed fragmentation pathways for the ketone (VI) have been outlined in Scheme VII. The molecular ion appears as an intense peak in this spectrum (see Fig. 6) and most of the peaks arise from either a loss of CO or an expulsion of methyl radical from the molecular ion and then from the subsequent fragments. For example, the molecular ion shows a loss of CO, giving an ion of *m/e* 216 which expels a methyl radical to give the ion of *m/e* 201 (base peak). The alternate route, *i.e.*, initial expulsion of a methyl radical followed by a loss of CO, is also operative. The ion of *m/e* 201 shows a loss of CO to give the

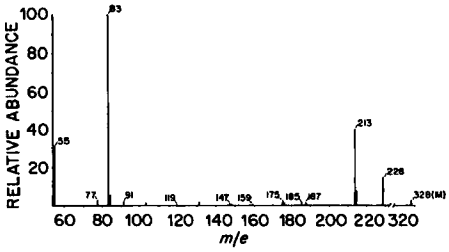
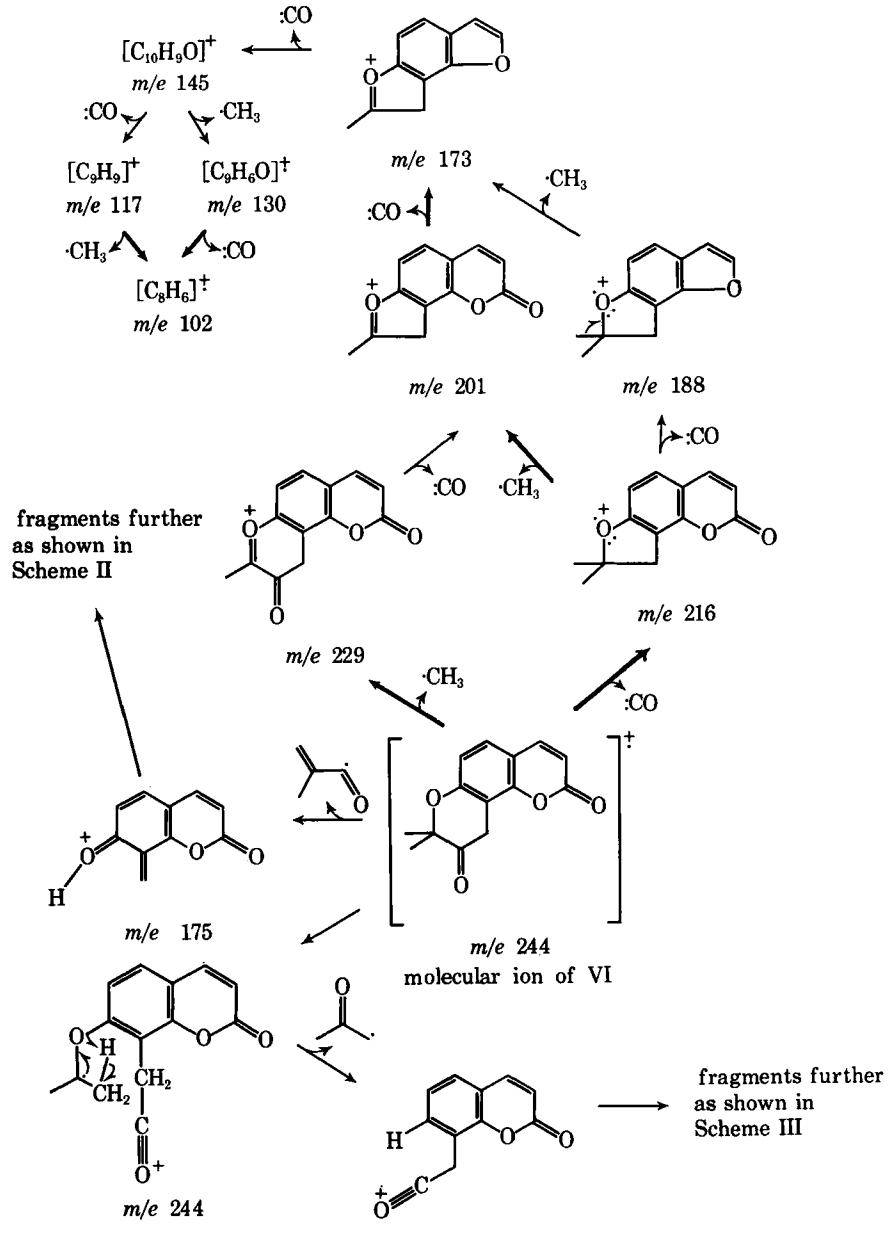


Fig. 5—Mass spectrum of III.



Scheme VII

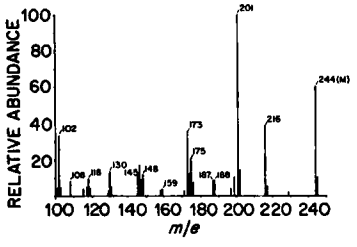


Fig. 6—Mass spectrum of VI.

ion of *m/e* 173 which then fragments further as shown in Scheme VII. Fission of the chroman ring with one hydrogen transfer would result in the ion of *m/e* 175 as in the case of I. A peak at *m/e* 187 could be proposed as resulting from ion formation by the mechanism shown in Scheme VII.

EXPERIMENTAL

Materials—Lomatin (I), its angelate (II), and its senecioate (III) were available in these laboratories

from the studies of Lee and Soine (5). The acetate (V) as well as the ketone (VI) were available in these laboratories from the studies of Gupta and Soine (28).

Deuteration of lomatin was achieved by heating a small amount of it overnight in a sealed tube at 130° in the presence of enough D_2O to form a clear solution during the heating period. After cooling, the crystallized product was removed by filtration and dried. The ratio of the molecular ion peaks (see Fig. 2) indicated approximately 90% incorporation.

Mass Spectra—These were carried out by Mr. A. R. Swanson and Mr. D. L. Hobbs, School of Chemistry, University of Minnesota, employing a mass spectrometer (Hitachi-Perkin-Elmer RMU-6D). The instrument was operated with a source temperature of 250° and an ionizing voltage of 50 ev. The direct sample inlet temperature was 90° in the case of I, deuterated I, II, V, and VI and 135° in the case of III.

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Keyphrases

Coumarins
Lomatin, derivatives—mass spectra
Mass spectra—lomatin, derivatives, fragmentation patterns
Deuterated lomatin—mass spectrum

Radiosynthesis of 3′-Chloro-3-nitrosalicylanilide and Determination of Its Uptake by Lamprey Larvae

By LARRY L. FRENCH and HOWARD A. SWARTZ

Tritium radiosynthesis of 3′-chloro-3-nitrosalicylanilide was accomplished by an exchange reaction with tritiated phosphoric acid-boron trifluoride reagent. Radiochemical purity was established by means of paper chromatography and autoradiography. Residual activity in lamprey larvae was determined at intervals of 1, 2, and 3 hr. The values observed were 3.046, 3.16, and 3.512 percent, respectively, representing a total residue of 0.0182 mg./g., 0.0186 mg./g., and 0.021 mg./g. at the stated time intervals.

THE LAMPREY EEL of the Great Lakes has inflicted considerable damage to the fishing industry of this region, and for many years attempts have been made to kill the eel and inhibit its reproduction.

The lamprey eel is a vertebrate of the Cyclostomi, the "round mouthed" class, constituting the *Petromyzon* genus. Although there are five species indigenous to the Great Lakes region, both

Received April 29, 1968, from Department of Bionucleonics, College of Pharmacy, Butler University, Indianapolis, IN 46208
Accepted for publication September 12, 1968.