# Structures of three minor alkaloids of *Fumaria officinalis* L.

D. B. MacLean, R. A. Bell, J. K. Saunders, and C.-Y. Chen
*Department of Chemistry, McMaster University, Hamilton, Ontario*

AND

R. H. F. Manske
*Research Laboratories, UniRoyal Limited, Guelph, Ontario*

Received April 28, 1969

The structures of fumaricine, fumaritine, and fumariline, minor alkaloids of *F. officinalis*, have been deduced by spectroscopic methods and by comparison with model systems. Nuclear Overhauser effects observed in these systems aided in the solution of the structural problem. The three alkaloids have a common ring system and are structurally related to ochotensimine.

Canadian Journal of Chemistry, 47, 3593 (1969)

In 1938 Manske (1) examined *Fumaria officinalis* L. for its alkaloid content. He isolated and identified several isoquinoline alkaloids, namely protopine, cryptopine, ± stylopine, + and ± scoulerine, and sinactine. Besides these alkaloids of established structure he reported the presence of two new alkaloids, F-37 ($C_{21}H_{23}NO_5$) (**1**) and F-38 ($C_{20}H_{19}NO_6$). In the interim Manske (2) has isolated two other minor alkaloids from this source corresponding in composition to $C_{20}H_{21}NO_5$ (**2**) and to $C_{20}H_{17}NO_5$ (**3**). Compound **2** is a lower homologue of **1** since it yields **1** upon methylation with diazomethane. The names, fumaricine, fumaritine, and fumariline have been assigned to **1**, **2**, and **3** respectively.

In two earlier short communications (3, 4) we described briefly the studies which led to the assignment of structures to **1** and **3**. Here we give a full account of our work and provide evidence for the assignment of the hydroxyl and methoxyl groups in **2**.

We were unable to carry out meaningful chemical degradations of these alkaloids and were forced to rely on physical methods for our structural assignments. The infrared (i.r.) spectrum of **3** showed a band at $\nu_{max}$ ($CHCl_3$) 1709 $cm^{-1}$ suggesting the presence of a carbonyl group. Its presence was confirmed by reduction of **3** to an alcohol **4** ($C_{20}H_{19}NO_5$) with sodium borohydride or with lithium aluminium hydride. The i.r. spectrum of **4** lacked a band in the carbonyl region but had a band in the hydroxyl region. The ultraviolet (u.v.) spectrum of **4** was virtually superimposable on that of **1** $\lambda_{max}$ (EtOH) 207, 235, and 288 mμ, (log ε 4.74, 3.94, and 3.74) but distinctly different from that of **3** $\lambda_{max}$ (EtOH) 203, 237, 263, 294, and 355 mμ, (log ε 4.60, 4.31, 4.05, 3.66, and 3.51). The change in the u.v. spectrum resulting from the reduction suggested that the carbonyl group of **3** was conjugated, probably to an aromatic system. The i.r. spectrum of **1** had no bands in the carbonyl region but had a band in the hydroxyl region, $\nu_{max}$ ($CS_2$) 3560 $cm^{-1}$, which did not shift upon dilution suggesting that the hydroxyl group was internally hydrogen bonded.

The proton magnetic resonance (p.m.r.) spectra of **1** and **3** showed that both compounds had one *N*-$CH_3$ group and four aromatic protons, that **1** had two methoxyl groups and one methylenedioxy group, and that **3** had two methylenedioxy groups. The substituents on **2** and **4** follow from their relationship to **1** and **3**, respectively.

From an examination of their mass spectra (Fig. 1) it is apparent that **1**, **2**, and **4** have a common fragmentation pattern. The major fragment ion in each spectrum shows the shift in mass expected for the different substituents in each of them. (That the spectrum of **3** is very different is a consequence of the difference in its functionality from the other alkaloids.) It seems likely, therefore, that **1** and **3** have a common ring system but differ in their substituents and in their oxidation state. The mass spectra, aside from indicating a common ring system for the alkaloids, did not provide much structural information. The spectra were, however, sufficiently different from the spectra of known isoquinoline systems to suggest that the alkaloids belonged to a hitherto unreported structural group. Compound **4** is isomeric with chelidonine (5) but a comparison of its spectrum (Fig. 1*e*) with that of **4** showed that the two compounds must have different ring systems.

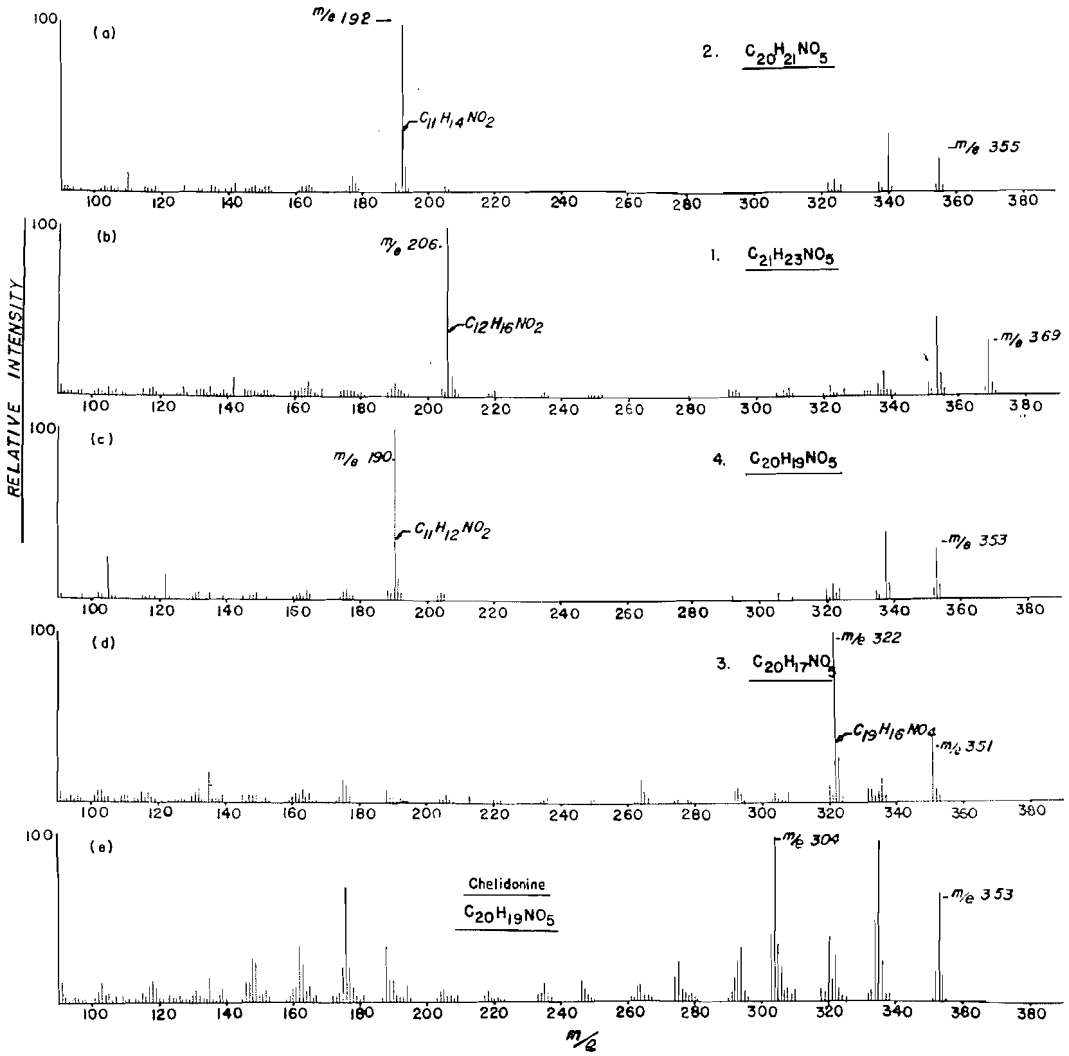


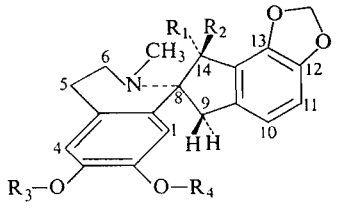

FIG. 1. Mass spectra of (a) fumaritine, (b) fumaricine, (c) dihydrofumariline, (d) fumariline, and (e) chelidonine.

It was through an examination of the 100 MHz p.m.r. spectra of **1**, **2**, **3**, and **4** and an examination of the nuclear Overhauser effects (N.O.E.) (6) in these systems that we were able to arrive at structures for the alkaloids. The salient features of the spectra of **3** and **4** which are discussed first are summarized in Table I. Each spectrum shows four aromatic protons, two ortho and coupled to each other (H-10 and H-11) and two singlets (H-1 and H-4) which are uncoupled. Each has two methylenedioxy groups and one $\diagdown N\text{—}CH_3$. Both show an AB quartet in the region expected of benzylic protons (H-9A, H-9B) which have a large coupling constant but which are uncoupled to neighboring aliphatic protons. In the spectrum of **4** there is a singlet (H-14) attributed to the hydrogen geminal to the hydroxyl group which is absent, as expected, in the spectrum of **3**. This proton is also uncoupled to neighboring aliphatic protons. In each spectrum there are signals corresponding in area to four additional aliphatic protons which lie in the region 2.6–3.6 δ and which are not readily analyzed.

Decoupling experiments carried out on **3** show that H-10 and H-11 are long-range coupled to

TABLE I

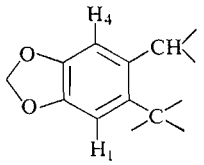
The p.m.r. signals of **1**, **2**, **3**, and **4** in p.p.m. (δ)



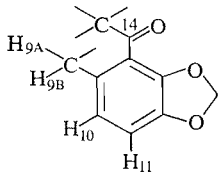
| | **1** $R_3 = R_4 = CH_3$ $R_1 = H, R_2 = OH$ | **2** $R_3 = CH_3, R_4 = H$ $R_1 = H, R_2 = OH$ | **3** $R_3 + R_4 = CH_2$ $R_1 + R_2 = O$ | **4** $R_3 + R_4 = CH_2$ $R_1 = H, R_2 = OH$ |
|---|---|---|---|---|
| H-1 | 6.39 | 6.47 | 6.16 | 6.38 |
| H-4 | 6.57 | 6.59 | 6.54 | 6.56 |
| H-10* | 6.68 | 6.68 | 6.86 | 6.68 |
| H-11* | 6.73 | 6.74 | 7.07 | 6.75 |
| H-9† | 3.29 | 3.29 | 3.50 | 3.23 |
| | | | 3.32 | 3.31 |
| H-14 | 5.44 | 5.42 | — | 5.42 |
| 2-OMe | 3.49 | — | — | — |
| 3-OMe | 3.81 | 3.85 | — | — |
| 2,3 —O, —O, $CH_2$ | — | — | 5.80 | 5.80 |
| 12,13 —O, —O, $CH_2$ | 5.91 | 5.95 | 6.12 | 5.90 |
| >N—$CH_3$ | 2.40 | 2.41 | 2.36 | 2.38 |

*$J_{H_{10}H_{11}}$ = 8.0 Hz for **1**, **2**, **3**, and **4**.
†$J$ = 18 Hz for **3** and **4**.

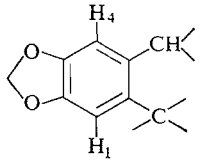
the protons of the benzylic AB quartet centered at 3.41 but that the coupling to H-10 is stronger and that H-4 is long-range coupled to an aliphatic proton centered near 3.0 but that H-1 is not coupled or only weakly so.



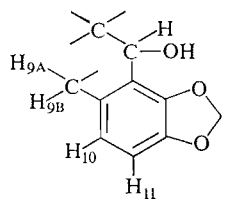
*3a*



*3b*



*4a*

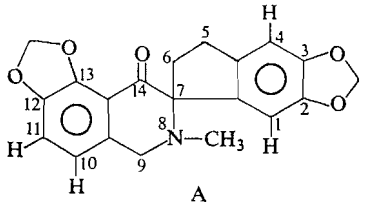


*4b*

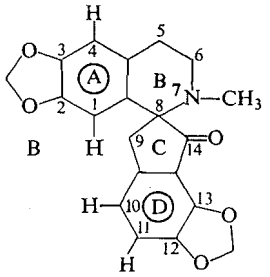
The spectral data suggest the following structural units, *a* and *b*, in **3** and **4**. The carbonyl group is placed in conjugation with the ring carrying H-10 and H-11 since both of these protons undergo an appreciable upfield shift on conversion of ketone **3** to alcohol **4** as does one of the methylenedioxy groups. The carbonyl group is placed adjacent to the methylenedioxy group in **3***b* for the following reasons. The chemical shift difference between H-10 and H-11 is expected of aromatic protons *meta* and *para* to a carbonyl group (7), but is smaller than expected for protons *ortho* and *meta* to a carbonyl group which would be the case if the carbonyl and methylene groups were interchanged in **3***b*. More definitive, however, was the appreciable n.O.e. observed at H-10 in **3** when the protons at C-9 were irradiated (*vide infra*).

The observation that the hydrogen geminal to the OH group of **4***b* at C-4 is uncoupled to neighboring aliphatic protons suggests that a quaternary carbon is adjacent to the >CHOH group

of **4** and to the >=O group of **3**. This conclusion is supported by the fact that **3** did not exchange hydrogen for deuterium in basic or in acidic media. The benzylic methylene protons of **3** and **4** are uncoupled to neighboring aliphatic protons and must, therefore, be adjacent to a quaternary carbon or to nitrogen. There are two



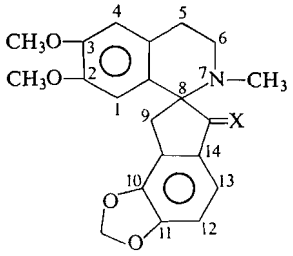
A



B

structures, A and B, into which these structural units can be incorporated and which appear to meet the requirements of the spectral data discussed thus far. Ring system A has not to our knowledge been encountered in nature although this skeleton has been reported as a transformation product of cryptopine (8). Ring system B is related to that found in ochotensimine, **5**, (9).

Structure A contains a substituted 2,3-dihydro-4 (1*H*) isoquinolone system. Derivatives of this system have recently been synthesized by Grethe *et al.* (10, 11). In these compounds the carbonyl absorption for the most part fell in the range 1680–1700 $cm^{-1}$ which is at lower frequency than the carbonyl absorption observed in **3**. In the p.m.r. spectrum (11) of 2-benzyl-2,3-dihydro-7-methoxy-4 (1*H*) isoquinolone, the two sets of benzylic methylene protons absorb at δ 3.75 and 3.85, both of which are at lower field than in our compound **3**. In other isoquinoline alkaloids, for example, chelidonine (12) and the protoberberines (13), the methylene protons lying between nitrogen and phenyl are observed at lower field than we observe in **3**. Thus, the examination of the model systems casts doubt on the validity of structure A.



**5.** ochotensimine X = $CH_2$
**6.** X = O

While this work was in progress the synthesis of ochotensimine, **5**, was reported by McLean *et al.* (14). An intermediate in this synthesis is compound **6** which served as an ideal model of structure B. The carbonyl absorption of **6**, $\nu_{max}$ ($CHCl_3$) 1711 $cm^{-1}$, appears at virtually the same frequency as that of **3**. The 100 MHz p.m.r. spectrum of **6** shows a marked similarity to that of **3**. The spectra were reproduced in our earlier communication and need not be repeated here. The major difference in the two spectra, aside from the differences arising from the substituents, lies in the chemical shift of the low-field proton of the aromatic AB quartet. In **6** this proton is centered at 7.46 δ, in **3** at 7.07 δ. In **6** the low-field proton is *ortho* to the carbonyl group. It appears, therefore, that in **3** the low-field proton is *para* to the carbonyl group and such a difference is expected (7). The proton *meta* to the carbonyl has approximately the same chemical shift in each, at 6.86 and 6.91 in **3** and **6**, respectively, as do the aromatic protons at C-1 and C-4 which appear at 6.16 and 6.54 in **3** and at 6.11 and 6.57 in **6**. Similarly, we found the same chemical shift for the protons of the benzylic AB quartet in each of **3** and **6**. The remarkable similarity in the spectral properties of the two compounds leads us to the conclusion that B and not A is the proper formulation of **3**.

In order to substantiate our conclusions regarding the structure of **3**, and at the same time to ascertain the substitution pattern of **1**, we examined **1**, **3**, and **6** for N.O.E. The potential of N.O.E. in structural and stereochemical studies was pointed out by Anet and Bourn (6) who were the first to use the method in this sense. It has since been applied successfully in the examination of other systems (15). Examination of a model of **6** showed that there were a number of uncoupled

protons lying within 3.0 Å of one another for which N.O.E. should be observed. (There is no ambiguity with respect to the structure of **6** since it has been converted in a single step to ± ochotensimine; the structure of natural ochotensimine was established by X-ray analysis (9).) We, therefore, measured N.O.E. in **6** and wherever possible, measured the same interactions in **1** and **3**.

Model studies on **6** showed that irradiation of the protons at C-9 or the methoxyl protons at C-2 should increase the area of the proton at C-1. Similarly, irradiation at the C-3 methoxyl or at the C-5 protons should affect the proton at C-4, and irradiation of the $N$-$CH_3$ should affect one of the protons at C-9. In all cases these predictions were borne out experimentally and the results were reported previously (4). It is important to note that irradiation at C-9 should not and did not affect either of the protons of the aromatic AB quartet. Similar effects have also been observed in ochotensimine (16).

With these results at hand for **6** we looked for similar effects in **3**. We found all that were possible in the light of the altered substitution pattern and, in addition, we observed a sizeable effect (4) at the aromatic proton C-10 when the protons of C-9 were irradiated, thereby confirming the assignment of the substituents in ring D which we had drawn from chemical shift data.

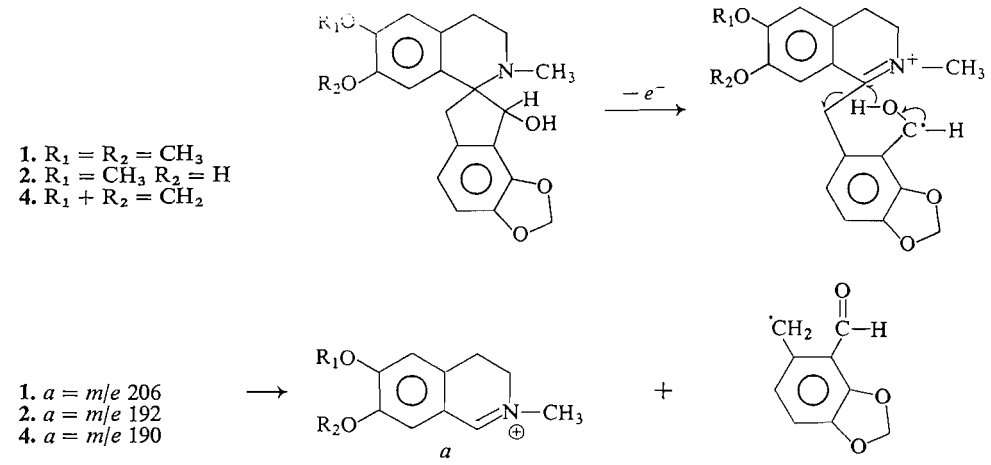
Turning now to fumaricine, we stated earlier that its i.r., u.v., and mass spectra suggested that it has the same ring system as **4**. Its p.m.r. spectrum is compared in Table I with that of **4** and the two spectra are also remarkably similar. Nuclear Overhauser effects measured on **1** were similar to those in **6** except that irradiation at C-9 resulted in an increase in area of the signal attributed to H-10. This finding led us to assign the same substitution pattern to **1** as to **3** and **4**. In our original paper we concluded that the —OH group of **1** was internally hydrogen-bonded to the nitrogen, on the basis of its i.r. spectrum and coupling constant to the hydroxyl proton. We have since found that there is an observable N.O.E. (14%) for the proton at C-14 when the signal due to the $N$-$CH_3$ group is irradiated. We must, therefore, revise our original assignment and place the OH group *trans* to the $N$-$CH_3$ group. Apparently the hydroxyl group of **1** is π-bonded to the aromatic ring (17) and not to nitrogen as we originally suspected. Since the signal of the proton at C-14 of **4** has the same chemical shift as that of **1** and shows the same behavior, namely, a broad signal which sharpens on addition of $D_2O$, it seems probable that the configuration of **4** at C-14 is identical with **1**.

Since **2** is converted to **1** by treatment with diazomethane there is only one structural feature of **2** which remains to be resolved, namely the assignment of the $OCH_3$ group to C-2 or C-3. This assignment was readily made by ascertaining which of the protons, at C-1 or C-4, exhibits an increase in area when the —$OCH_3$ group of **2** is irradiated. The resonances of the protons of **2** are recorded in Table I. The lower-field and broader signal observed at 6.59 δ has been assigned to C-4 by analogy with the spectra of **1**, **3**, **4**, and **6** and it is this signal which increases in area by 24% when the —$OCH_3$ group is irradiated. We, therefore, assign the —$OCH_3$ to C-3 and the OH group to C-2 in **2**.

In the mass spectra of **1**, **2**, and **4** there is only one intense fragment ion, designated *a*, which is found at *m/e* 206 in **1**, at *m/e* 192 in **2**, and at *m/e* 190 in **4**. Exact mass measurements have confirmed the composition of this ion in **1**. A mechanism for the formation of ion *a* is shown in Scheme 1. Compound **4**, deuterated at C-14, was prepared by the reduction of **3** with sodium borodeuteride and its spectrum examined. It was found that *a* still appeared at *m/e* 190 although the molecular ion was at *m/e* 354. When, however, the hydroxyl hydrogen of **4** was exchanged with deuterium it was found that ion *a* was partially shifted to *m/e* 191 in the spectrum of the deuterated compound. These deuteration studies lend support to the mechanism proposed in Scheme 1.

The spectrum of **3** is distinctly different from **1**, **2**, and **4** in that it does not show an intense ion in the low mass region. The major fragment ion appears at *m/e* 322. High resolution mass spectrometry has shown that this peak is a singlet and that it corresponds in composition to $C_{19}H_{16}NO_4$. It is apparently formed by loss of CO followed or preceded by loss of H. The OH function in the five-membered ring appears to be a necessary structural feature for fragmentation leading to ions of type *a*. Their presence in **1**, **2**, and **4** lends further support to that already given for a tetrahydroisoquinoline system in these alkaloids.

Ions of type *a* are also characteristic of the benzylisoquinoline (18) and phthalide isoquinoline alkaloids (19). In these systems the molecular ion is of very low intensity and thus they are




SCHEME 1

readily differentiated from fumaricine and its analogues.

The spectrum of chelidonine is worthy of comment. The major fragment ions appear at *m/e* 335, 320, and 304. That at *m/e* 335 is formed through loss of $H_2O$, that at 320 through loss of $CH_3$ from *m/e* 335, and surprisingly that at *m/e* 304 through loss of $CH_3NH_2$ from *m/e* 335. The composition of these ions has been confirmed by exact mass measurement.

## Experimental

*Materials and Methods*

The isolation and properties of the alkaloids used in this investigation have been described elsewhere (1, 2).

The mass spectra were recorded on a Hitachi Perkin–Elmer RMU-6A mass spectrometer. Samples were introduced through the direct inlet system. Accurate mass measurements (20) were carried out on a CEC-21-110B double-focussing mass spectrometer. The measurements were made by reference to appropriate peaks in the spectrum of perfluorokerosene (21). Observed values agreed with calculated values within ±0.005 mass units. Exchange of the OH group of **4** was carried out using $CH_3OD$.

The p.m.r. spectra were recorded using the frequency sweep mode of a Varian HA-100 spectrometer. Samples were dissolved in $CDCl_3$ using added TMS as the internal locking signal. Chemical shifts were measured relative to TMS using a V4315 frequency counter incorporated in the instrument. Double irradiation was achieved by employing a Hewlett–Packard 201C audio generator at the desired frequency. For N.O.E. measurements degassed solutions were used and a procedure similar to that of Anet and Bourn (6) was employed. A Perkin–Elmer 521 spectrometer was used to record i.r. spectra and a Cary 14 spectrometer was used for u.v. spectra.

*Reduction of 3 with Lithium Aluminium Hydride*

Compound **3** (58 mg) was dissolved in dry ether and added to an excess of $LiAlH_4$ in dry ether and the mixture heated under reflux for 20 min. Excess hydride was destroyed with water, the ether layer separated, and the aqueous layer extracted several times with fresh ether. The combined ether extract was evaporated to dryness yielding a residue which was recrystallized from ether, m.p. 129–133° (45 mg). The i.r. spectrum showed the presence of hydroxyl absorption but there was no band in the carbonyl region. The mass spectrum showed a molecular ion at *m/e* 353.1248; calcd. for $C_{20}H_{19}NO_5$, 353.1263. The compound showed a single spot on thin-layer chromatography.

*Reduction of 3 with Sodium Borohydride*

Compound **3**, dissolved in methanol, was added to a solution of sodium borohydride in methanol and the mixture allowed to stand at room temperature for several hours. The solution was evaporated to dryness, water was added to the residue, and the aqueous suspension extracted into chloroform. Evaporation of the chloroform extract gave a residue which had spectroscopic properties identical with the product of $LiAlH_4$ reduction of **3**.

Reduction with sodium borodeuteride was carried out in an analogous manner.

## Acknowledgment

We wish to thank Professor Stewart McLean for providing us with a generous sample of compound **6**. We thank the National Research Council of Canada for financial support of this work and McMaster University for the award of a University Fellowship to C.-Y. Chen.

1. R. H. F. MANSKE. Can. J. Research, **16B**, 438 (1938).
2. R. H. F. MANSKE. Can. J. Chem. **47**, 1103 (1969).

3. J. K. SAUNDERS, R. A. BELL, C.-Y. CHEN, D. B. MACLEAN, and R. H. F. MANSKE. Can. J. Chem. **46**, 2873 (1968).
4. J. K. SAUNDERS, R. A. BELL, C.-Y. CHEN, D. B. MACLEAN, and R. H. F. Manske. Can. J. Chem. **46**, 2876 (1968).
5. R. H. F. MANSKE. The alkaloids. Vol. IV. Academic Press, Inc., New York. 1954. p. 253.
6. F. A. L. ANET and A. J. R. BOURN. J. Amer. Chem. Soc. **87**, 5250 (1965).
7. J. W. EMSLEY, J. FEENEY, and L. H. SUTCLIFFE. High resolution nuclear magnetic resonance spectroscopy. Vol. II. The Pergamon Press Ltd., Oxford. 1966. p. 750.
8. D. W. BROWN and S. F. DYKE. Tetrahedron Letters, 3975 (1966).
9. S. MCLEAN, M.-S. LIN, A. C. MACDONALD, and J. TROTTER. Tetrahedron Letters, 3819 (1964). S. MCLEAN, M.-S. LIN, and R. H. F. MANSKE. Can. J. Chem. **44**, 2249 (1966).
10. G. GRETHE, H. L. LEE, M. USKOKOVIĆ, AND A. BROSSI. J. Org. Chem. **33**, 491 (1968).
11. G. GRETHE, H. L. LEE, M. USKOKOVIĆ, AND A. BROSSI. J. Org. Chem. **33**, 495 (1968).
12. C.-Y. CHEN and D. B. MACLEAN. Can. J. Chem. **45**, 3001 (1967).
13. C.-Y. CHEN and D. B. MACLEAN. Can. J. Chem. **46**, 2501 (1968).
14. S. MCLEAN, M.-S. LIN, and J. WHELAN. Tetrahedron Letters, 2425 (1968).
15. R. H. MARTIN and J. C. NOULS. Tetrahedron Letters, 2727 (1968), and references cited therein.
16. J. K. SAUNDERS and R. A. BELL. Can. J. Chem. **46**, 3421 (1968).
17. K. NAKANISHI. Infrared absorption spectroscopy. Holden-Day Inc., San Francisco. 1962. p. 30.
18. H. BUDZIKIEWICZ, C. DJERASSI, and D. H. WILLIAMS. Structure elucidation by mass spectrometry. Vol. I. Holden-Day Inc., San Francisco. 1954. p. 174.
19. A. L. BURLINGAME. Ph.D. Thesis, Massachusetts Institute of Technology. 1963.
20. K. S. QUISENBERRY, T. T. SCOTMAN, and A. O. NIER. Phys. Rev. **102**, 1071 (1956).
21. F. W. MCLAFFERTY. Anal. Chem. **28**, 306 (1956).