Saxton J. E., Battersby A. R.,

The Alkaloids. Vol. 1.

(A Review of the Literature Published between January 1969 & June 1970)

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The Alkaloids

Volume 1

A Review of the Literature Published between January 1969 and June 1970

Senior Reporter
J. E. Saxton, *Department of Organic Chemistry, The University of Leeds*

Reporters
A. R. Battersby, *Cambridge University*
K. W. Bentley, *Reckitt and Sons Ltd., Hull*
O. E. Edwards, *National Research Council of Canada, Ottawa*
R. Goutarel, *Centre Nationale de la Recherche Scientifique, Gif-sur-Yvette, France*
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Foreword

This volume is the first in the series of annual Specialist Periodical Reports devoted to the chemistry of the Alkaloids. In preparing this first volume our aim has been not simply to record progress during a selected period, but also to include whatever background material and earlier references are necessary to enable the new work to be placed in perspective in its own particular area; in consequence we hope that the reader, whether the alkaloid specialist or the general reader, will be able to read and benefit from the discussions presented here with the minimum of reference to the standard monographs on the subject.

The alkaloid literature has been reviewed up to the end of June 1970, but for convenience most authors have started their literature surveys from January 1969; this inaugural volume, therefore, properly represents a summary of developments in the subject during an eighteen-month period. The whole field of alkaloid chemistry has been reviewed with the exception of the steroidal alkaloids of the *Solanum* and *Veratrum* groups. It has not proved possible owing to limitations of space to include these sub-groups in the present volume, and it is therefore planned to include a review of developments in this area during a two-year period in the second volume.

Although the Specialist Reports will normally consist of comprehensive annual reviews of alkaloid chemistry, we have included in this volume three chapters which, in view of their scope and character, are of a different type. The first of these is an authoritative statement on the biosynthesis of the terpenoid indole alkaloids, the main features of which are now reasonably well understood. It also seemed a most propitious moment in which to review the fascinating group of bisindole alkaloids and it will, I think, be generally agreed that the inclusion here of a definitive review by Professor Schmid and his Zürich colleagues fills a major gap in the alkaloid literature. The third non-recurrent review is by Dr. Schlittler, who has contributed a survey on the applications of alkaloids in the fields of pharmacology and clinical medicine during the last fifteen years, *i.e.* during the 'post-reserpine' period. In these Reports the pharmacology of the alkaloids will not normally be discussed, but it is appropriate to remember that the actual or reputed physiological activities of plant extracts and their widespread use in folk medicine have frequently provided the stimulus for the initial chemical investigations; and while the fascinating chemistry subsequently

revealed has proved sufficient intellectual reward to the academician, the occasional discovery of substances of clinical value has provided a welcome bonus.

This volume is the result of a cordial and enthusiastic collaboration between a team of alkaloid specialists in which I have done little more than plan the volume, plead for assistance, co-ordinate the final results, and exercise general editorial supervision. It is appropriate, therefore, that I should record here my gratitude to my collaborators for their eager participation and for the efforts they made to ensure the prompt submission of their contributions.

Aside from the deliberate omission of part of the steroid field it is likely that there will also be inadvertent omission of some minor sub-groups of alkaloids, or of material from comparatively inaccessible journals. I shall be pleased to receive information concerning any such omissions, and constructive criticisms or suggestions concerning the preparation of future Reports will also be welcomed.

J. E. SAXTON

Contents

1

Biosynthesis—I. General

BY R. B. HERBERT

This review covers the biosynthesis of alkaloids other than those derived from tryptophan and a C_9 or C_{10} terpenoid unit, which are surveyed in the succeeding chapter.

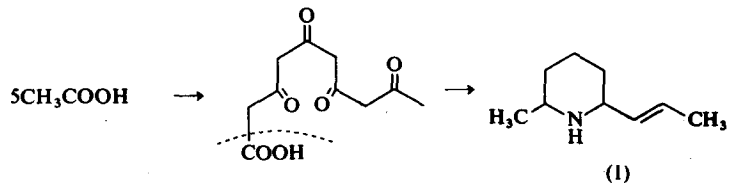
Attention is drawn to reviews which include or are concerned wholly with biosynthesis: Menispermaceae alkaloids,[1] morphine alkaloids,[2] and one which surveys the role of anthranilic acid in the biosynthesis of many alkaloid types.[3] An excellent book on alkaloid biosynthesis edited by Mothes and Schütte has appeared during 1969.[4]

Pinidine and Coniine.—Pinidine (1) is found in various species of pine, including *Pinus jeffreyi*. Inspection would indicate an origin similar to coniine (2) or to *N*-methylpelletierine (13). Whilst the former is biosynthesised by the linear combination of four acetate units,[5] the piperidine ring of the latter is generated from lysine and the side chain from acetate.[6]

The pinidine isolated after feeding [1-^{14}C]acetate to *P. jeffreyi* was degraded to reveal essentially all the activity located at the four positions expected of a linear combination of five acetate units (Scheme 1).[7] On the other hand, a low incorporation of [2-^{14}C]-DL-lysine was obtained, which partial degradation showed was not specific to the piperidine ring of the alkaloid. The incorporation found was rationalised as being the result of catabolism of the lysine to acetate. Thus, the biosynthetic pathway to pinidine is similar to that of the hemlock alkaloid coniine.

The biosynthetic sequence which leads to coniine has been further studied by two different methods. One[8] has involved the use of $^{14}CO_2$ and the other serendipity.[9] As a preliminary to tracer experiments with 5-keto-octanoic acid,

[1] C. W. Thornber, *Phytochemistry*, 1970, **9**, 157.
[2] G. Blaschke, *Mitt. deut. pharm. Ges. D.D.R.*, 1969, **39**, 225. Published in *Arch. Pharm.*, 1969, **302**, 10.
[3] D. Gröger, *Lloydia*, 1969, **32**, 221.
[4] K. Mothes and H. R. Schütte, 'Biosynthese der Alkaloide,'. VEB Deutscher Verlag der Wissenschaften, Berlin, 1969.
[5] E. Leete, *J. Amer. Chem. Soc.*, 1963, **85**, 3523; 1964, **86**, 2509.
[6] R. N. Gupta and I. D. Spenser, *Phytochemistry*, 1969, **8**, 1937.
[7] E. Leete and K. N. Juneau, *J. Amer. Chem. Soc.*, 1969, **91**, 5614.
[8] S. M. C. Dietrich and R. O. Martin, *Biochemistry*, 1969, **8**, 4163.
[9] E. Leete, *J. Amer. Chem. Soc.*, 1970, **92**, 3835.



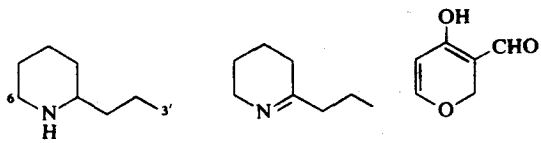
(1)

Scheme 1

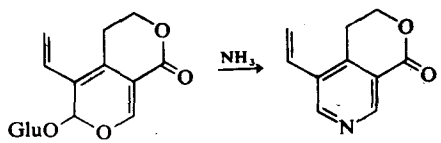
sodium [1-^{14}C]octanoate was administered to hemlock (*Conium maculatum*).[9] The coniine (2) isolated after 24 hours was found, unexpectedly, to be highly radioactive (0.45% incorporation). Further, degradation established that almost all the activity was confined to C-6; a little scrambling of the label was apparent after a feeding extending over 7 days. [8-^{14}C]Octanoate was also specifically incorporated (at the 3′ position) but here the scrambling was more pronounced. Nevertheless, the results clearly indicate a specific and intact incorporation of octanoic acid into coniine, presumably *via* 5-keto-octanoic acid.

The validity of the reported[10] incorporation of Δ^1-piperideine and its 2-carboxy-derivative into γ-coniceine (3), which is clearly in conflict with an acetate derivation for coniine, must be further doubted as incorporation of Δ^1-piperideine in hemlock could not be repeated,[9] nor was any trace of this compound found during $^{14}CO_2$ experiments.[8]

Earlier results with $^{14}CO_2$ in hemlock have been refined and a primary rôle for γ-coniceine in the formation of the other *Conium* alkaloids seems clear.[8] A biosynthetic sequence from γ-coniceine (3) → coniine (2) → *N*-methylconiine is consistent with the findings.



(2) (3) (4)



(5) (6)

An interesting non-nitrogenous base was discovered during these experiments on *Conium maculatum*. It was also isolated from *Sedum sarmentosum* and *Punica*

[10] B. T. Cromwell and M. F. Roberts, *Phytochemistry*, 1964, 3, 369; B. T. Cromwell in 'Biosynthetic Pathways in Higher Plants,' ed. J. B. Pridham and T. Swain, Academic Press, New York, 1965, pp. 147–157.

granatum and its structure has been assigned as 3-formyl-4-hydroxy-2*H*-pyran (4).[11] This pyran was rapidly labelled during the $^{14}CO_2$ experiments in *C. maculatum* and its disappearance coincided with the appearance of alkaloids. This suggested a possible rôle for (4) in the biosynthesis of hemlock alkaloids. In addition, attention was drawn to the structural similarity of (4) to various piperidine and pyridine alkaloids, not least of which is nicotine; also the ease of amination of pyrones and the conversion of gentiopicrin (5) into gentianine (6).[12]

***Nicotiana* Alkaloids.**—Experiments with $^{14}CO_2$ have also been used in consideration of the origin of the pyridine ring of nicotine (27)[13] and correlated with similar work on the pyrrolidine ring of this alkaloid.[14] When *Nicotiana glutinosa* or *N. rustica* were grown in an atmosphere of $^{14}CO_2$, the greatest incorporation of $^{14}CO_2$ into the pyridine ring occurred at positions 4, 5, and 6, which were labelled to a similar extent; the incorporation at position 2 was much smaller, and similar to that at position 3. The results are in agreement with the derivation of this ring from glyceraldehyde (C_3) and aspartic acid (C_2).[15] The modes of formation of both of these precursors would lead to an equal incorporation of $^{14}CO_2$ into all the carbon atoms of each unit. The difference in activity between the two units is a measure of different dilution or incorporation rates or both.

[6-^{14}C]-Δ^1-Piperideine has been shown to be a precursor of anabasine (14) in *Nicotiana glauca*.[16] The incorporation (1.2%) was significantly higher than from cadaverine or lysine with *N. glauca* growing under similar conditions. Degradation established the presence of the label at C-6′, with C-2′, in particular, being inactive. Pelletierine (15), produced by condensation of [6-^{14}C]-Δ^1-piperideine with ethyl acetoacetate in the laboratory, was labelled solely at C-6, indicating that the 1,2-double bond is not capable of tautomeric shift to the 1,6-position.

As both lysine and Δ^1-piperideine lead to unequal labelling of C-2′ and C-6′ in anabasine, and the biosynthetic sequence must be lysine $\rightarrow$ Δ^1-piperideine (11) $\rightarrow$ anabasine (14), any other precursors for (14) after lysine must be unsymmetrical in nature. Thus cadaverine, although incorporated into anabasine, cannot be a true precursor for the alkaloid.[16] Two other groups of workers[6,8] have also cast doubt on the rôle of cadaverine in alkaloid biosynthesis, and it is worth remembering in general that even if a proposed precursor is specifically incorporated it may not lie on the normal pathway to a particular alkaloid. Rather, it may merely test the adaptability of the plant in the face of an unusual substrate.

The available results, which indicate a biosynthetic pathway to anabasine (14) similar to that to *N*-methylpelletierine, are illustrated (Scheme 2).

[11] O. A. Koleoso, S. M. Dietrich, and R. O. Martin, *Biochemistry*, 1969, **8**, 4172.
[12] H. G. Floss, U. Mothes, and A. Rettig, *Z. Naturforsch.*, 1964, **19b**, 1106.
[13] H. R. Zielke, C. M. Reinke, and R. U. Byerrum, *J. Biol. Chem.*, 1969, **244**, 95.
[14] H. R. Zielke, R. U. Byerrum, R. M. O'Neal, L. C. Burns, and R. E. Koeppe, *J. Biol. Chem.*, 1968, **243**, 4757.
[15] D. Gross in 'Biosynthese der Alkaloide,' VEB Deutscher Verlag der Wissenschaften, Berlin, 1969, pp. 243–248.
[16] E. Leete, *J. Amer. Chem. Soc.*, 1969, **91**, 1697.