

A Specialist Periodical Report

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# The Alkaloids

Volume 6

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# The Alkaloids

Volume 6

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A Review of the Literature Published  
between July 1974 and June 1975

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## Foreword

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This sixth volume of *Specialist Periodical Reports* devoted to the chemistry of alkaloids follows the policies developed so successfully in Volumes 1—5 by my predecessor as Senior Reporter, Dr. J. E. Saxton. The aim once again is to make the surveys comprehensive, this time covering the literature published during July 1974—June 1975.

Indole and isoquinoline alkaloids continue to play a dominant role. The aporphinoids, comprising proaporphines, aporphines and related dimers, are treated separately, partly in order to reduce the burden on contributors; aristolactams and aristolochic acids, which have not been reviewed since 1961, also are discussed in this chapter. This year the quinolizidine alkaloids, including the sesquiterpenoid *Nuphar* bases and the appropriate Lythraceae alkaloids, as well as azaphenalenes of plant and insect origin are reviewed together. Amaryllidaceae, *Erythrina*, imidazole, purine and peptide alkaloids are omitted from this volume, but it is expected that the chemistry of these groups covering the period 1974—1976 will be surveyed in Volume 7.

Comments on the presentation of the alkaloid reports are welcome, and reporters will appreciate receiving reprints of articles, particularly those published in less accessible journals. I wish to express my gratitude to the new contributors as well as to the old hands for the accuracy and prompt dispatch of manuscripts, and to Dr. Saxton for his indispensable advice.

March 1976

M. F. GRUNDON

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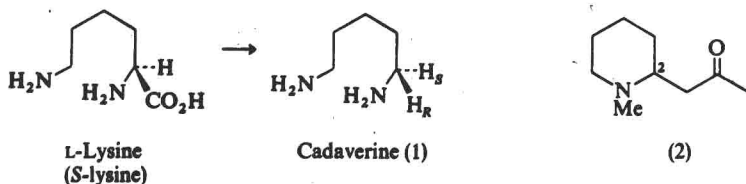
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## 1 Introduction

The number of papers appearing on alkaloid biosynthesis continues to be large. In reviewing this work the practice of referring to previous Reports is continued and, in order to make this background material more conveniently accessible, these Reports are listed as references 1—5. Access to work reported before 1969 is most easily gained through two excellent and comprehensive reviews<sup>6,7</sup> and reference is made to these where appropriate. The reader is also recommended to consult the alternative annual survey on alkaloid biosynthesis,<sup>8</sup> where the approach is different from the one adopted here.

## 2 Piperidine, Pyridine, and Pyrrolidine Alkaloids

**Piperidine Alkaloids (General).**—As part of a study of the role of cadaverine (1) in the biosynthesis of piperidine alkaloids samples of (1), stereospecifically labelled with tritium at C-1, were tested as precursors for *N*-methylpelletierine (2).<sup>9</sup> These samples were prepared by decarboxylation of L-lysine through the action of L-lysine



<sup>1</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1971, Vol. 1.

<sup>2</sup> J. Staunton, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1972, Vol. 2.

<sup>3</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1973, Vol. 3.

<sup>4</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1974, Vol. 4.

<sup>5</sup> R. B. Herbert, in 'The Alkaloids', ed. J. E. Saxton (Specialist Periodical Reports), The Chemical Society, London, 1975, Vol. 5.

<sup>6</sup> 'Biosynthese der Alkaloide', ed. K. Mothes and H. R. Schütte, VEB Deutscher Verlag der Wissenschaften, Berlin, 1969.

<sup>7</sup> I. D. Spenser, in 'Comprehensive Biochemistry', ed. M. Florkin and E. H. Stotz, Elsevier, Amsterdam, 1968, Vol. 20, p. 231.

<sup>8</sup> E. Leete, in 'Biosynthesis', ed. T. A. Geissman (Specialist Periodical Reports), The Chemical Society, London, 1972—1975, Vols. 1—3.

<sup>9</sup> E. Leistner and I. D. Spenser, *J. Amer. Chem. Soc.*, 1973, **95**, 4715; R. B. Herbert, in ref. 5, p. 5.

decarboxylase (isolated from *Bacillus cadaveris*). Although this reaction was known to proceed stereospecifically<sup>10</sup> it was not known at the time if the result was retention or inversion of configuration. It has recently been shown,<sup>11</sup> however, that the consequence of the enzymic decarboxylation is retention of configuration, and so [1A-<sup>3</sup>H]cadaverine<sup>9</sup> is (1R)-[1-<sup>3</sup>H]cadaverine. It follows then, from the earlier conclusion<sup>9</sup> about cadaverine incorporation into *N*-methylpelletierine (2), that it is the 1-*pro-R* proton from cadaverine (1) which is retained at C-2 of (2) and the 1-*pro-S* hydrogen atom which is lost.

**Anatabine and Anabasine.**—Although the biosynthetic pathway to anabasine (3) has been delineated in detail,<sup>12,13</sup> little evidence had been obtained until recently on the way in which anatabine (8) is formed: [2-<sup>14</sup>C]lysine and [2-<sup>14</sup>C]-4-hydroxylysine were found not to label anatabine<sup>14</sup> and results with <sup>14</sup>CO<sub>2</sub> indicated that anabasine was not a precursor of anatabine.<sup>15</sup>

In a recent study,<sup>16</sup> [2-<sup>14</sup>C]lysine was fed to *Nicotiana glutinosa*, and although it was specifically incorporated into anabasine (3) in the expected manner it did not label the anatabine (8), thus according with the previous result.<sup>14</sup>

Nicotinic acid (6) is well established as a precursor of the pyridine ring of nicotine<sup>13,17</sup> and is also a precursor of this moiety in anabasine.<sup>13,18</sup> [6-<sup>14</sup>C]Nicotinic acid, as might therefore be expected, gave radioactive anatabine, but surprisingly the activity was divided equally between C-6 and C-6' ([carboxy-<sup>14</sup>C]nicotinic acid failed to label any of the alkaloids significantly).<sup>16</sup> It follows that nicotinic acid (6) is the source for both rings of anatabine and the equal distribution of label indicates that the two units from which the alkaloid is formed are closely related, if not identical.

The manner in which the two nicotinic acid units may be joined (Scheme 1) is suggested<sup>16</sup> by analogy with the probable intermediacy of a dihydronicotinic acid in nicotine biosynthesis.<sup>17</sup> It is further suggested that anatabine (4) and nicotelline (5) are trimers of the dihydro-derivative (7).<sup>16</sup>

The anabasine obtained after feeding [6-<sup>14</sup>C]nicotinic acid was found to be labelled almost exclusively in the pyridine ring, so no significant conversion of anatabine (8) into anabasine (3) occurs.<sup>16</sup>

In accord with previous conclusions<sup>12,13</sup> about the relationship between lysine and anabasine (3), lysine has been found to be a precursor for (3) in *Anabasis aphylla* along a pathway which does not involve symmetrical intermediates.<sup>19</sup> Aspartic acid was found to serve as a precursor for both rings of anabasine<sup>20</sup> whilst lysine was incorporated into lupinine,<sup>19</sup> again in accord with previous results.

<sup>10</sup> S. Mandeles, R. Koppelman, and M. E. Hanke, *J. Biol. Chem.*, 1954, **209**, 327.

<sup>11</sup> E. Leistner and I. D. Spenser, *J.C.S. Chem. Comm.*, 1975, 378.

<sup>12</sup> R. B. Herbert, in ref. 5, p. 5; ref. 4, p. 4.

<sup>13</sup> (a) D. Gross, in ref. 6, p. 234; (b) I. D. Spenser, in ref. 7, p. 253.

<sup>14</sup> T. Kasaki, S. Mizusaki, and E. Tamaki, *Phytochemistry*, 1968, **7**, 323.

<sup>15</sup> W. L. Alworth and H. Rapoport, *Arch. Biochem. Biophys.*, 1965, **112**, 45.

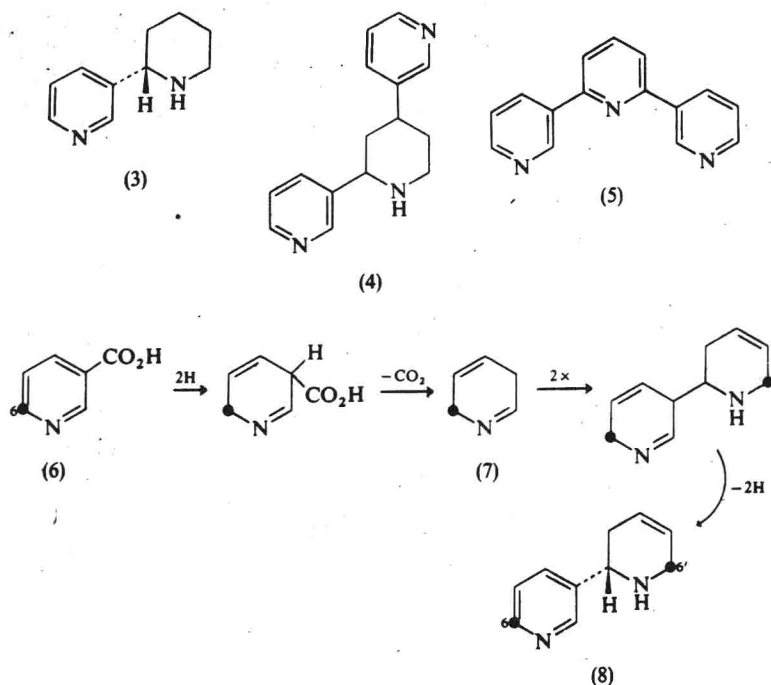
<sup>16</sup> E. Leete, *J.C.S. Chem. Comm.*, 1975, 9.

<sup>17</sup> R. B. Herbert in ref. 4, p. 7 and refs. cited.

<sup>18</sup> M. L. Solt, R. F. Dawson, and D. R. Christman, *Plant Physiol.*, 1960, **35**, 887.

<sup>19</sup> M. Y. Lovkova, E. I. Nurimov, and G. S. Il'in, *Biokhimiya*, 1974, **39**, 388 (*Chem. Abs.*, 1974, **81**, 132882).

<sup>20</sup> M. Y. Lovkova, E. I. Nurimov, and G. S. Il'in, *Biokhimiya*, 1974, **39**, 523 (*Chem. Abs.*, 1974, **81**, 166 429).



Scheme 1

**Lobeline.**—The results of feeding experiments with DL-[2-<sup>14</sup>C]lysine and DL-[2-<sup>14</sup>C]phenylalanine in *Lobelia inflata* have shown that these amino-acids are both specific precursors for the alkaloid lobeline (13).<sup>21,22</sup> In further experiments, DL-[3-<sup>14</sup>C]phenylalanine, [3-<sup>14</sup>C]cinnamic acid, and [3-<sup>14</sup>C]-3-hydroxy-3-phenylpropionic acid [as (9)] have been found to be specific precursors for lobeline (13).<sup>23</sup> These results are consistent with the anticipated pathway<sup>24</sup> to lobeline illustrated in Scheme 2, with benzoylacetic acid (10) as the intermediate which couples with Δ<sup>1</sup>-piperidine to give the intermediate (11). The probability of 3-hydroxy-3-phenylpropionic acid (9) being an intermediate in lobeline biosynthesis is increased by the isolation of this acid from *L. inflata*.<sup>25</sup>

In contrast to the biosynthesis of many other piperidine alkaloids, the incorporation of [2-<sup>14</sup>C]lysine into lobeline (13) was found to be symmetrical, i.e. C-2 and C-6 were equally labelled. Symmetrization of the label could occur on formation of lobelanine (12), a known late precursor,<sup>22,26</sup> or at a possible earlier intermediate,

<sup>21</sup> M. F. Keogh and D. G. O'Donovan, *J. Chem. Soc. (C)*, 1970, 2470.

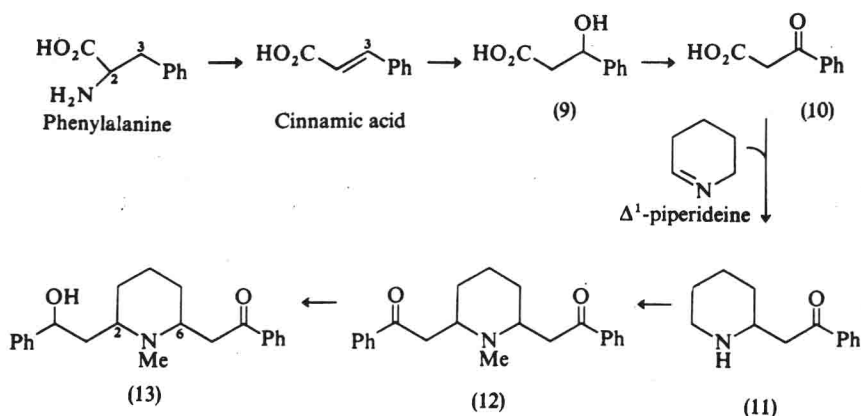
<sup>22</sup> R. B. Herbert, in ref. 3, p. 27.

<sup>23</sup> D. G. O'Donovan, D. J. Long, E. Forde, and P. Geary, *J.C.S. Perkin I*, 1975, 415.

<sup>24</sup> Cf. M. H. Zenk, in 'Biosynthesis of Aromatic Compounds', Proceedings of the 2nd meeting of F.E.B.S., ed. G. Billek, Pergamon Press, Oxford, Vol. 3, 1966, p. 45; M. H. Zenk, in 'Pharmacognosy and Phytochemistry', ed. H. Wagner and L. Hörhammer, Springer-Verlag, Berlin, 1971, p. 314; R. N. Gupta and I. D. Spenser, *Canad. J. Chem.*, 1967, 45, 1275.

<sup>25</sup> H. Wieland, W. Koschira, E. Dane, J. Renz, W. Schwarze, and W. Linde, *Annalen*, 1939, 540, 103.

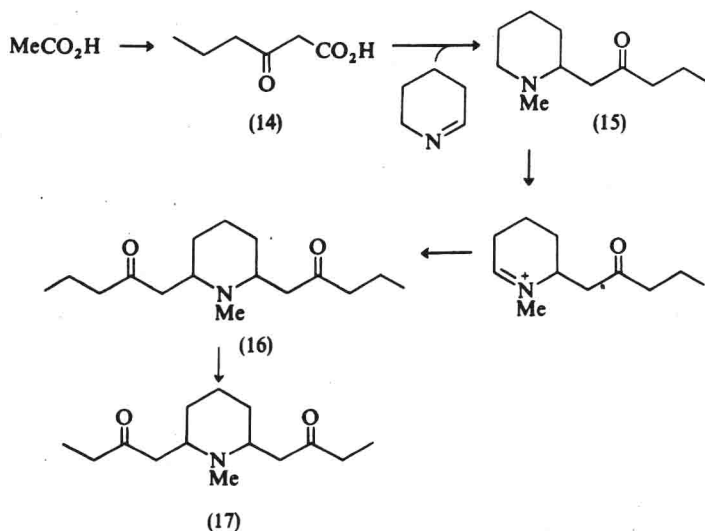
<sup>26</sup> D. G. O'Donovan and T. Forde, *J. Chem. Soc. (C)*, 1971, 2889.



Scheme 2

cadaverine (1). Cadaverine was found, however, to be a much less efficient precursor for lobeline than lysine or  $\Delta^1$ -piperidine, which argues strongly that it is not an obligatory intermediate in lobeline biosynthesis (*cf.* the discussion on piperidine alkaloid biosynthesis in ref. 12) and thus symmetrization of lysine label occurs *via* lobelanine (12).

The biosynthesis of *Lobelia* alkaloids with  $C_4$  units at C-2 and C-6 can be accounted for in terms of the pathway shown in Scheme 3,<sup>23</sup> in which it is envisaged

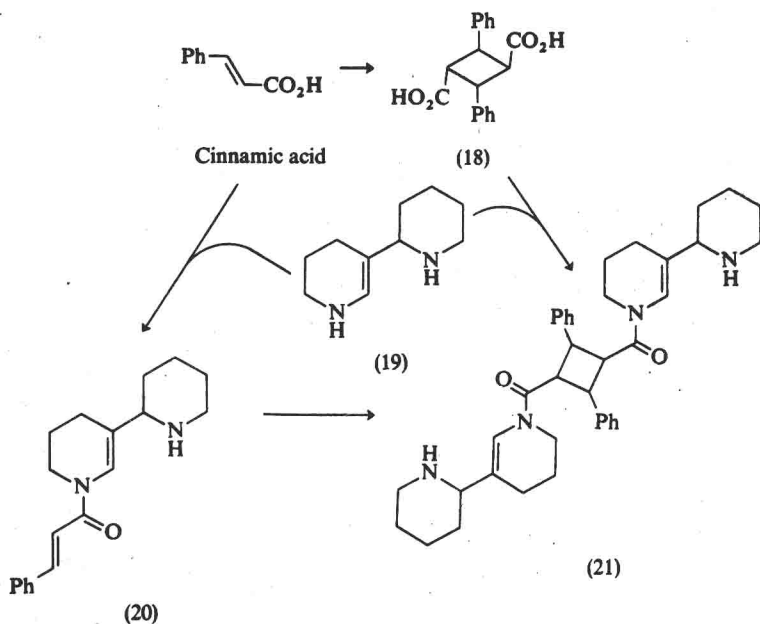


Scheme 3

that acetate-derived 3-oxohexanoic acid (14) condenses with  $\Delta^1$ -piperidine to afford, after methylation, the keto-amine (15) which is oxidized and condensed with a further molecule of 3-oxohexanoic acid (14). Truncation of the (16) formed affords

the alkaloid (17). Evidence for the validity of this pathway has been adduced from the results of feeding  $[2-^{14}\text{C}]$ lysine and  $[1-^{14}\text{C}]$ acetate.<sup>23</sup> The former precursor provides the piperidine ring of (17) as expected and acetate the side chains, with one half of the activity on the carbonyl groups as required by the hypothesis.

**Santiaguine.**—The origin of the curious  $\alpha$ -truxillic acid (18) moiety of santiaguine (21), an alkaloid of *Adenocarpus* species, has been shown to be cinnamic acid. This moiety arises, the available evidence has suggested, during the biosynthesis of santiaguine as a result of the dimerization of adenocarpine (20).<sup>27</sup> An alternative route to santiaguine, which involves the dimerization of cinnamic acid, followed by condensation of the  $\alpha$ -truxillic acid formed with tetrahydroanabasine (19), had not been explored, however. Recent results<sup>28</sup> demonstrate that  $\alpha$ -truxillic acid (18) exists free in *Adenocarpus foliosus*, is specifically labelled by cinnamic acid, and is itself specifically incorporated into santiaguine (21). Thus two distinct pathways to santiaguine may operate (Scheme 4) but it appears, from the relative incorporation efficiencies, that the route *via* adenocarpine (20) is, at least, the major one.



Scheme 4

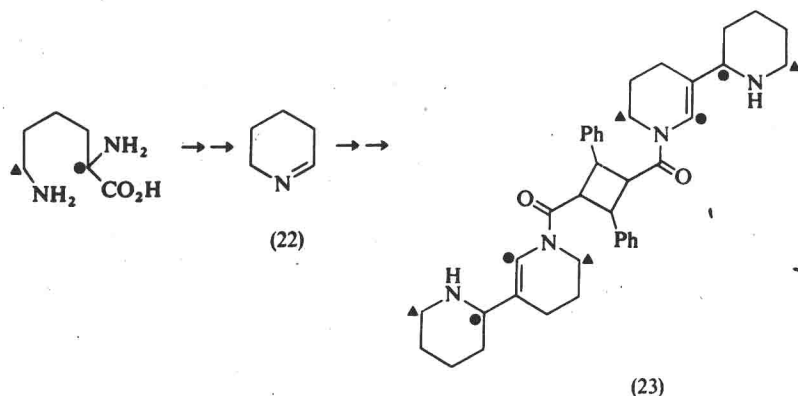
$\alpha$ -Truxillic acid (18) can be formed photochemically *in vitro*, from cinnamic acid,<sup>29</sup> but it seems that such a route is not operative *in vivo*, for no significant difference in the incorporation of labelled adenocarpine (20) into santiaguine (21) could be observed with plants grown in light or darkness.<sup>28</sup>

<sup>27</sup> D. G. O'Donovan and P. B. Creedon, *J. Chem. Soc. (C)*, 1971, 1604; R. B. Herbert in ref. 3, p. 27.

<sup>28</sup> D. G. O'Donovan and P. B. Creedon, *J.C.S. Perkin I*, 1974, 2524.

<sup>29</sup> H. I. Bernstein and W. C. Quimby, *J. Amer. Chem. Soc.*, 1943, **65**, 1845; E. H. White and H. C. Dunathan, *ibid.*, 1956, **78**, 6055.

The origins of the tetrahydroanabasine (19) moieties of santiaguine have been examined in feeding experiments with DL-[2-<sup>14</sup>C]- and DL-[6-<sup>14</sup>C]-lysine. Tracer was incorporated specifically and unsymmetrically into each of the heterocyclic rings (Scheme 5). Labelled  $\Delta^1$ -piperideine (22) was incorporated in like manner and is thus a likely intermediate in the formation of each piperidine ring (Scheme 5). These results are in accord with the carefully delineated pattern of piperidine alkaloid



Scheme 5

biosynthesis.<sup>9,12,13,30</sup> Application of the model developed<sup>9</sup> to explain the incorporation of lysine and cadaverine into these alkaloids allows one to include cadaverine as a precursor for santiaguine, as the tracer results suggest.<sup>31</sup> [The generation of the tetrahydroanabasine skeleton of (21) from lysine makes a notable contrast with the formation of anatabine (8) from nicotinic acid; see above].

The above experiments have thrown up a point of practical interest and possible application elsewhere. When radioactive  $\Delta^1$ -piperideine was fed to *A. foliosus* followed by labelled cinnamic acid, the incorporation of the latter was 10 times as high as previously found. This was tentatively attributed to stimulation of alkaloid biosynthesis by the presence of both precursors necessary for alkaloid synthesis.<sup>28</sup>

**Quinolizidine Alkaloids.**—Previous results demonstrate that the quinolizidine skeleton in its entirety derives from lysine.<sup>32</sup> Further research has indicated that lysine is a precursor of all the alkaloids of this type in five species of Leguminosae.<sup>33</sup> From the levels of activity observed in the individual alkaloids it was concluded that saturated alkaloids are precursors for those with a pyridone ring. This was supported by the observation<sup>34</sup> that label from radioactive sparteine (24) and lupanine (25) appeared in more highly oxidized alkaloids. (This compares with a similar situation in the biosynthesis of matrine-type alkaloids.<sup>35</sup>) A metabolic grid for the biosynthesis of quinolizidine alkaloids from lysine was proposed,<sup>36</sup> based on these results,

<sup>30</sup> R. B. Herbert, in ref. 1, p. 4; ref. 3, p. 25; ref. 4, p. 1; J. Staunton, in ref. 2, p. 20 and refs. cited.

<sup>31</sup> H. R. Schütte, K. L. Kelling, D. Knöfel, and K. Mothes, *Phytochemistry*, 1964, 3, 249.

<sup>32</sup> I. D. Spenser, in ref. 7, p. 262; H. R. Schütte, in ref. 6, p. 324.

<sup>33</sup> E. K. Nowacki and G. R. Waller, *Phytochemistry*, 1975, 14, 155.

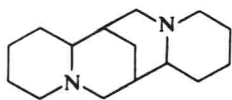
<sup>34</sup> E. K. Nowacki and G. R. Waller, *Phytochemistry*, 1975, 14, 161.

<sup>35</sup> A. A. Takanaev, *Khim. Rast. Veshcherv.*, 1972, 31 (*Chem. Abs.*, 1973, 79, 765).

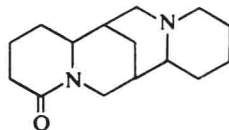
<sup>36</sup> E. K. Nowacki and G. R. Waller, *Phytochemistry*, 1975, 14, 165.



other more convincing evidence,<sup>32,37,38</sup> and the taxonomical distribution of quinolizidine alkaloids.

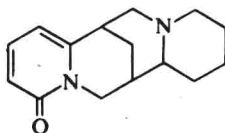


(24)



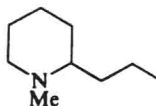
(25)

In young *Lupinus nanus* plants added cadaverine but not putrescine or hexamethylenediamine lowered the incorporation of lysine into thermopsine (26). (In flowering plants the difference between cadaverine and the other two diamines was less marked.<sup>33</sup>) These results provide further evidence for the intermediacy of cadaverine in quinolizidine biosynthesis.<sup>32,38,39</sup>

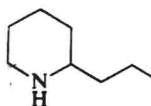


(26)

**N-Methylconiine.**—Feeding experiments with L-[Me-<sup>14</sup>C]methionine in *Conium maculatum* varieties have established that the methyl group of methionine serves as the source of the N-methyl group of methylconiine (27).<sup>40</sup> This adds further to the picture of coniine biosynthesis<sup>41</sup> and provides an additional example of transmethylation in plants. In further experiments,<sup>42</sup> an enzyme was isolated from *C. maculatum* that was capable of catalysing the transfer of a methyl group from S-adenosylmethionine to coniine (28), with the formation of N-methylconiine (27). The enzyme was partially purified and characterized in part.



(27)



(28)

**Ricinine.**—Quinolinic acid (29) is known to be a precursor of ricinine (32).<sup>43,44</sup> The results of other studies have indicated that the pyridine nucleotide cycle (Scheme 6)

<sup>37</sup> Y. D. Cho and R. O. Martin, *Canad. J. Biochem.*, 1971, **49**, 971.

<sup>38</sup> R. B. Herbert, in ref. 3, p. 30.

<sup>39</sup> B. A. Abdusalomov, A. A. Takanaev, Kh. A. Aslanov, and A. S. Sadykov, *Biochemistry (U.S.S.R.)*, 1971, **36**, 239.

<sup>40</sup> M. F. Roberts, *Phytochemistry*, 1974, **13**, 1841.

<sup>41</sup> E. Leete and J. O. Olson, *J. Amer. Chem. Soc.*, 1972, **94**, 5472; E. Leete, *ibid.*, 1964, **86**, 2509; M. F. Roberts, *Phytochemistry*, 1971, **10**, 3057; R. B. Herbert, in ref. 4, p. 10; ref. 1, p. 1; J. Staunton, in ref. 2, p. 26.

<sup>42</sup> M. F. Roberts, *Phytochemistry*, 1974, **13**, 1847.

<sup>43</sup> K. S. Yang and G. R. Waller, *Phytochemistry*, 1965, **4**, 881.

<sup>44</sup> L. A. Hadwiger, S. E. Badieli, G. R. Waller, and R. K. Gholsion, *Biochem. Biophys. Res. Comm.*, 1963, **13**, 466.