Biosynthesis of the C_{9-10} Unit of Ajmaline and Reserpine

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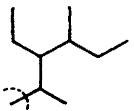
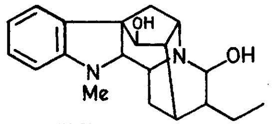
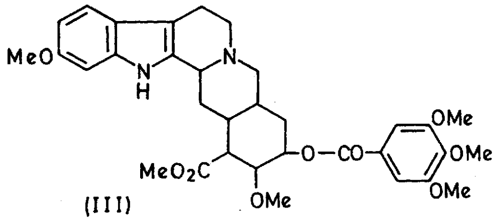
Summary Glycine can be a specific precursor of the C_{9-10} unit (I) of ajmaline (II), and probably of reserpine (III), and may be a fundamental precursor for this unit in alkaloids.

RECENTLY we reported that glycine could be specifically incorporated into the C_{9-10} unit as it occurs in the isoquinoline alkaloid cephaeline in *Cephaelis acuminata*, but that it was a poor precursor of β-sitosterol in the same plant.[1,2] At the same time it was confirmed that while acetic acid acts as a normal precursor of β-sitosterol, it is neither significantly nor specifically incorporated into cephaeline.[2] We now present evidence that glycine is also specifically incorporated into this same C_{9-10} unit as it occurs in indole alkaloids found in *Rauwolfia serpentina*, and hence that it may be a universal precursor of this unit.


(I)



(II)



(III)

Radioactive compounds (0·1 mc) were fed by the wick method to two eighteen-month-old *Rauwolfia serpentina* plants, and the plants were harvested after 7 days. Ajmaline and reserpine were isolated from the whole plant by scavenging with inactive alkaloids (15 mg), and examined for radioactivity.

When sodium [2-^{14}C]acetate was fed, ajmaline with a specific activity of $1\cdot2 \times 10^4$ d.p.m./mM was isolated. It was subjected to a Kuhn–Roth oxidation to yield sodium acetate (C-18 and C-19) which contained 9·5% of the activity of the ajmaline. The reserpine isolated had a specific activity of $6\cdot0 \times 10^3$ d.p.m./mM. It was hydrolysed to yield reserpic acid and 3,4,5-trimethoxybenzoic acid containing 60 and 32%, respectively, of the activity of the reserpine.

These results indicate that extensive randomization of the activity to all parts of the molecule has occurred. They agree with the results found when sodium [2-^{14}C]acetate was fed to *Cephaelis acuminata*,[2] and also with more detailed degradation of alkaloids derived from earlier feedings of sodium [2-^{14}C]acetate to *Rauwolfia serpentina*.[3]

When [2-^{14}C]glycine was fed, ajmaline with a higher specific activity of $5\cdot2 \times 10^4$ d.p.m./mM was isolated, and the sodium acetate obtained after a Kuhn–Roth oxidation contained 15·5% of the activity of the ajmaline. A Schmidt reaction on this sodium acetate yielded inactive barium carbonate (C-19), indicating that the activity was confined specifically to C-18. The reserpine isolated had a specific activity of $1\cdot3 \times 10^4$ d.p.m./mM. It was hydrolysed to reserpic acid and 3,4,5-trimethoxybenzoic acid which contained 83 and 15%, respectively, of the activity of the reserpine.

Since the indole portion of reserpine (less the *O*-methyl group) arises from tryptophan,[4] most of the activity found in the reserpic acid derived from glycine must reside in the C_{9-10} unit. It is, however, reasonable that some activity from C-2 of glycine will be transferred by normal metabolic processes to the one-carbon pool, and hence to the *O*-methyl groups of 3,4,5-trimethoxybenzoic acid. The appearance of only 15—18% of the total activity in the appropriate atoms of cephaeline and ajmaline, instead of the theoretical 20%, may have the same explanation, with some activity reaching the three *O*-methyl groups of cephaeline and the *N*-methyl group of ajmaline by way of the one-carbon pool.

It has been well substantiated that the C_{9-10} unit in alkaloids can arise from geraniol,[5] and from mevalonic acid.[6] However, acetate, the fundamental precursor of geraniol in terpenes, is not specifically converted into this monoterpenoid unit.[2] The similarity of the feeding results in *Cephaelis acuminata* and *Rauwolfia serpentina*, and the specific incorporation of glycine into different alkaloids in different plants, leads us to suggest that glycine may be a fundamental precursor of the C_{9-10} unit in alkaloids.

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[3] E. Leete and J. R. Gear, unpublished results.

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