Lead Tetra-acetate Oxidation of *NN*-Dimethylglycine and its Relevance to the Biosynthesis of the Pyrrolidine Ring of Nicotine

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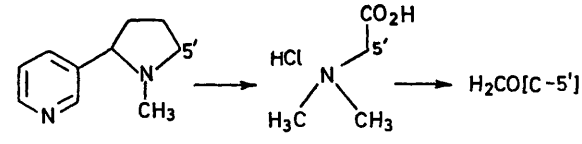
Summary Validity of the degradation of the pyrrolidine ring of nicotine *via* *NN*-dimethylglycine hydrochloride has been confirmed since oxidation of the latter by lead tetra-acetate yields formaldehyde derived 98·7 ± 1·1% from the methylene group.

LEETE, in a recent article in this journal,[1] has criticized our procedure[2] for the degradation of *NN*-dimethylglycine hydrochloride to dimethylamine, formaldehyde, and carbon dioxide. He reports that our oxidation procedure using lead tetra-acetate, in his hands, led to formaldehyde derived from the *N*-methyl groups as well as from the methylene. As support, he cites other observations[3–5] that formaldehyde can be produced by the oxidation of *N*-methyl groups. However, these examples involve ozone[3,4] and periodate[5] as oxidants, not lead tetra-acetate on the amine hydrochloride according to our procedure. He concludes that this contamination from the *N*-methyl group would lead to high values for our reported activity at C-5′ (isolated as formaldehyde) in nicotine biosynthesis with $^{14}CO_2$ and would account for the difference between the unsymmetrical labelling pattern found by us[2] and the symmetrical pattern found by Zielke *et al.*[6]

Apparently Leete overlooked the control experiments we presented[2] which established the validity of our oxidation procedure. One degradation of [2-^{14}C]-*NN*-dimethylglycine



hydrochloride we reported as giving formaldehyde with more than 99% of the initial specific activity (now No. 1, Table). The other control degradation was reported with [β-^{14}C]-β-dimethylaminopropiophenone and ultimately gave formaldehyde with 99·1% of the initial specific activity (now No. 2, Table).

TABLE

Expt. No,	[^{14}C]-*NN*-Dimethylglycine, HCl[a] Labelled carbon	Spec. act.[c]	Formaldehyde[b] Spec. act.[c]	%[d]
1	C-2	$1{\cdot}27\times10^5$	$1{\cdot}26\times10^5$	99·2
2	C-2	57,670	57,154	99·1
3	C-2	57,670	57,561	99·8
4	*N*-CH_3	$5{\cdot}54\times10^6$	$1{\cdot}32\times10^5$	2·4
5	*N*-CH_3	$5{\cdot}54\times10^6$	$7{\cdot}69\times10^4$	1·4

[a] Prepared by reductive alkylation of glycine with formaldehyde as described for the corresponding β-alanine derivative in ref. 2 and isolated as the hydrochloride by sublimation.
[b] Assayed as its dimedone derivative.
[c] Specific activity in d.p.m./mmol.
[d] Per cent of the original dimethylglycine activity found in the formaldehyde.

We have now performed three additional control degradations, the last two with material prepared from glycine and [^{14}C]formaldehyde. All experiments were conducted with *NN*-dimethylglycine hydrochloride, free of glycine and sarcosine by automatic amino-acid analysis and pure by mass spectrometry, n.m.r., and elemental analyses. The oxidation conditions were as specified[2] and were kept constant throughout the reaction.

As can be seen from the Table, in all the degradations the methylene carbon maintained its integrity to the extent of $98{\cdot}7 \pm 1{\cdot}1\%$. The departure from 100% is practically within experimental error (1% of each count) and could have no effect on the reported[2] activities of nicotine at C-5′. Furthermore, this degradation procedure cannot account for the difference between the unsymmetrical[2] and the symmetrical labelling pattern,[6] since in both cases our degradation procedure was used. We have also found symmetrical labelling patterns in some $^{14}CO_2$ biosynthesis experiments, but the factors responsible have not yet been established.

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