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

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Summary A degradative sequence which has been used to determine the distribution of radioactivity in the pyrrolidine of nicotine involves, as one of the steps, the oxidation of *NN*-dimethylglycine with lead tetra-acetate; the formaldehyde produced in this reaction, formerly thought to originate entirely from C-2, has been shown to be derived in appreciable amounts from the *N*-methyl groups.

RAPOPORT and his co-workers have reported[1–3] that the short-term exposure of *Nicotiana glutinosa* plants to $^{14}CO_2$ yielded nicotine (I) in which there was an unsymmetrical distribution of radioactivity in the pyrrolidine ring; in general there was a higher level of activity at C-4′ and C-5′ *uniform* labelling of the pyrrolidine ring of nicotine. They were unable to give a reason for the discrepancy between their results and those of Rapoport. We suggested[7] that the degradative scheme[3] used to determine the pattern of labelling in the pyrrolidine ring was not completely valid.

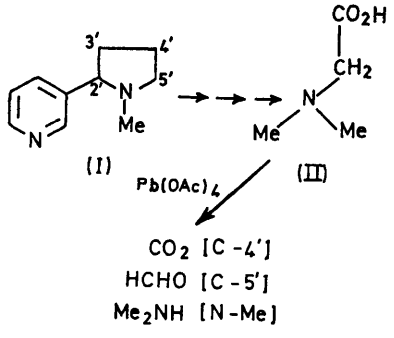
We have now examined one of the steps in this degradative sequence, namely the lead tetra-acetate oxidation of *NN*-dimethylglycine (II) which is derived from C-4′,5′ and the *N*-methyl group of nicotine. In the reported procedure,[3] *NN*-dimethylglycine hydrochloride (0·72 mmole) and lead tetra-acetate (1·0 mmole) are heated in benzene at 55° for 2 h, when CO_2 derived from the carboxyl group is liberated. Addition of water to the reaction mixture yields formaldehyde which is removed by distillation. The residue in the reaction flask is made basic and the resultant dimethylamine collected as *NN*-dimethyl-*p*-bromobenzenesulphonamide. On carrying out this reaction with [*N*-*methyl*-^{14}C]-*NN*-dimethylglycine, using these conditions, we obtained considerable radioactivity in the formaldehyde and found that the final residue of the reaction was a 2:1 mixture of methylamine and dimethylamine (Expt. 1 in the Table). By reducing the reaction time (Expt. 2) the amount of activity in the formaldehyde was decreased. By using equimolecular amounts of the reactants (Expt. 3) the activity of the formaldehyde was reduced but not eliminated. Complementary experiments were carried out with [2-^{14}C]-*NN*-dimethylglycine, when it was found that inactive formaldehyde derived from the *N*-methyl groups lowered the expected activity of the formaldehyde. Others[8] have also observed that formaldehyde can be produced by the oxidation of *N*-methyl groups.

In most of the samples of nicotine obtained by short-term $^{14}CO_2$ feedings[3] the level of activity in the *N*-methyl

TABLE

Expt. No.	Conditions of reaction: Time (min)	Mole ratio (II)/Pb(OAc)$_4$	Relative specific activity [*NN*-dimethylglycine = 100]: $MeNH_2$[a]	Me_2NH[b]	HCHO[c]	$BaCO_3$
[*N*-*methyl*-^{14}C]Dimethylglycine						
1	120	0·72	52	99	25	0·16
2	25	0·72	[d]	98	4·3	0·12
3	120	1·0	48	98	13·5	0·15
[2-^{14}C]Dimethylglycine						
4	120	0·72	2·0	2·4	60	0·25
5	20	0·72	d	2·9	95	0·23
6	120	1·0	1·9	2·3	62	0·27

[a] Assayed as *N*-methylbenzamide.
[b] Assayed as *NN*-dimethylbenzamide or *NN*-dimethyl-*p*-bromobenzenesulphonamide.
[c] Assayed as its dimedone derivative.
[d] Only a trace formed, insufficient for assay.



than at C-2′ and C-3′. These results are not consistent with the earlier observation[4,5] that [2-^{14}C]ornithine afforded nicotine which had equal labelling at C-2′ and C-5′. More recently Byerrum and his co-workers[6] have also carried out short-term feedings of $^{14}CO_2$ to tobacco and have obtained

group was significantly higher than the average activity of the pyrrolidine ring carbons. Thus the use of this degradation would lead to a high value for the reported activity at C-5′.

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