NUCLEAR METHYLATION OF $\beta$-RESORCYLIC ALDEHYDE

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Under conditions of methylation, certain poly-hydroxy phenyl derivatives exhibit a tendency to undergo substitution in the benzene nucleus. This phenomenon is known as nuclear methylation. Not only is the chemistry of this reaction interesting, but it has also useful applications in synthetic work. For instance, methyl orsellinate was found to be directly and conveniently methylated with the formation of methyl rhizonate (I). In a similar manner rhizonic aldehyde (II) has been prepared readily by the methylation of orcylic aldehyde. Early work of Perkin$^5$ and of Herzig et al.$^4$ on the methylation of $\beta$-resorcylic acid and ester (III) has been reviewed in the above-mentioned paper by Robinson and Shah.$^1$ Their ideas have been confirmed by Jones and Robertson$^5$ by careful comparison of some of the important products of methylation with substances obtained by definite methods of synthesis.

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\begin{align*}
(I) & \quad \text{CH}_3\text{O} / \text{OH} \quad \text{COOCH}_3 \\
(II) & \quad \text{CH}_3\text{O} / \text{OH} \quad \text{CHO} \\
(III) & \quad \text{HO} / \text{OH} \quad \text{COOR} \\
(IV) & \quad \text{CH}_3\text{O} / \text{OH} \quad \text{OCH}_3 \\
(V) & \quad \text{HO} / \text{OH} \quad \text{COOR}
\end{align*}
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Kauffler$^6$ and Perkin$^8$ found that nuclear ethylation is a much less facile process. Robinson and Shah,$^1$ however, were able to effect nuclear ethylation of the methyl ester of resorcylic acid using large excess of the reagents. Nuclear methylation of resocetophenone was effected by Greger,$^7$ Wechler$^8$ and Crabtree and Robinson$^9$ and nuclear ethylation was carried out by Robinson and Shah.$^1$ The constitution of the products was drawn only

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from analogy with the similar reaction with resorcylic acid and ester. The subject was subsequently reinvestigated by Rangaswami and Seshadri,\textsuperscript{10} who confirmed the structures by unequivocal synthesis and by preparation of derivatives. They employed for this purpose resacetophenone and $\omega$-methoxyresacetophenone. An observation regarding nuclear methylation of a phloroglucinol derivative has been recently made by Hems and Todd.\textsuperscript{11} Using phloroisobutyrophenone, they found that the reaction took place even under very mild conditions by boiling the substance in acetone solution with methyl iodide and potassium carbonate; bæckeol (IV) was thus obtained. This may be taken as an instance of very facile nuclear methylation.

The following is an account of past work relating to the nuclear methylation of $\beta$-resorcylic aldehyde. Tiemann and Parrisius\textsuperscript{12} obtained a compound (A) melting at 62–63° by two methods: (i) by the action of chloroform and alkali on mono-methyl resorcinol, and (ii) by the methylation of $\beta$-resorcylic aldehyde with methyl iodide and alcoholic potash. They assigned to it the structure of 2-hydroxy-4-methoxy-benzaldehyde and this has been shown to be wrong by subsequent work. Claisen and Eisleb\textsuperscript{13} showed that by employing methyl iodide and potassium carbonate for the methylation of $\beta$-resorcylic aldehyde, two compounds could be isolated: (i) melting at 62–63° and identical with (A) and (ii) melting at 41–42° (B). The mixture of these two products could be separated by taking advantage of their difference in volatility with steam under different conditions; compound (A) distilled over from a faintly alkaline solution and subsequently after rendering the solution acid, compound (B) could be distilled. The above work was confirmed by OTT and Nauen\textsuperscript{14} who further showed that methylation of $\beta$-resorcylic aldehyde with methyl iodide and alcoholic potash gave compound (A) along with a small quantity of (B), whereas when dimethyl sulphate or methyl bromide and aqueous potash were employed, compound (B) was exclusively formed. The constitution of compound (B) was established by them as 4-O-methyl-resorcylic aldehyde from careful elementary analysis and comparison with a sample obtained from natural products (e.g., from the root of chlorocodon from Natal isolated by Goulding and Pelly).\textsuperscript{15} It is now known to occur widely in the following plants: (i) Decalepis Hamiltonii (Srinivasa Rao and Sesha Iyengar\textsuperscript{16}); (ii) Periploca Gracea (Solacoln, Mavrodin and Hermann\textsuperscript{17}); (iii) Hemidesmus indicus (Dutta, Ghosh and Chopra\textsuperscript{18}). Compound (A) was subsequently taken to be nuclear methylated homologue of (B) and it was assumed to have the structure of 2-hydroxy-3-methyl-4-methoxy-benzaldehyde; this assumption was based on analogy with similar resorcinol derivatives. Its formation in small amounts in the experiments of Tiemann and Parrisius\textsuperscript{12} using chloroform, alkali and mono-methyl resorcinol was