Novel Photochemical Demethylation of Cocaine and Related Compounds

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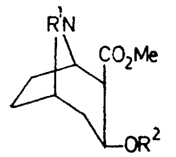
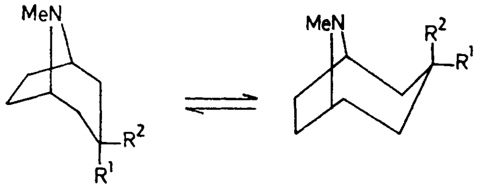
Summary The benzoate chromophore activation of the bicyclic *N*-methylamines, cocaine, *p*-toluoyl-(—)-ecgonine methyl ester, benzoyltropine, and benzoylpseudotropine, during irradiation resulted in the removal of the *N*-methyl group; demethylation failed to occur with the monocyclic *N*-methylamines, 3- and 4-*N*-methylpiperidinobenzoates.

The reported photochemical degradation of cocaine (I)[1] has been examined to find the primary products: norcocaine (II) HCHO, and $PhCO_2H$. This unique demethylation is also observed for three other bicyclic *N*-methylamines, *p*-toluoyl-(—)-ecgonine methyl ester, benzoyltropine (V), and benzoylpseudotropine (IV), but is not observed for the monocyclic *N*-methylamines, 3- and 4-*N*-methylpiperidinobenzoates under conditions identical with the cocaine reaction.

Irradiation was carried out with a Rayonet photochemical reactor equipped with 300 nm lamps and a Corex filter. After irradiation of 0·5 g of (I) in 12 ml MeOH for 43 h under N_2 with subsequent evaporation of MeOH, (II) was separated in a 20% yield by rapid chromatography on neutral alumina together with 70% recovered (I) and 7% $PhCO_2H$. Slow chromatography on neutral or basic alumina produced mainly (III) through the known base-catalysed process.[2] Norcocaine (II) was identified by its m.p. (80—82 °C), mixed m.p.,[3] mass spectrum (M^+ 289), and the absence of the *N*-methyl proton signal (at δ 2·5) in the n.m.r. spectrum. Norcocaine (II) was independently prepared for comparison from (I) by permanganate oxidation to (III)[4] followed by rearrangement by HCl in dry dioxan.[5] HCHO was identified in the reaction solution by directly preparing its dimedone derivative, m.p. 188—189 °C[6] and quantitative determination by the Nash reagent.[7] It was formed in near molar ratios to that of (II). $PhCO_2H$ was isolated by base extraction and identified by its m.p. (121—122 °) and mixed m.p.



(I) R^1 = Me, R^2 = COPh
(II) R^1 = H, R^2 = COPh
(III) R^1 = COPh, R^2 = H



(IV) R^1 = H; R^2 = CO_2Ph
(V) R^1 = CO_2Ph; R^2 = H

The stereochemistry at C-2 and C-3 remained unchanged during the irradiation since not only was the recovered (I) identical with the starting material, but (II) is the same as norcocaine produced by independent synthesis.[4,5] $PhCO_2H$ formation appears to be a competing reaction to the demethylation since its yield is lower than that of (II), and $PhCO_2H$ formation but no demethylation occurs during the irradiations of 3- and 4-*N*-methylpiperidinobenzoates.

Though charge transfer is mechanistically implied in the cocaine irradiations, no spectral evidence for a separate singlet charge transfer state could be obtained by observing absorption and fluorescence spectra of (I) in various solvents. However, cocaine hydrochloride and cyclohexyl benzoate are photochemically stable to the irradiation conditions used for (I). Since the demethylation occurs for (IV) as well as (V), where the benzoyl group does not come in close proximity to the *N*-methyl reaction centre in either conformer, the reaction is intermolecular in character. The specificity of the reaction for bicyclic compounds with *N*-methyl bridges compared to the monocyclic ones is apparently due to the operation of Bredt's rule on a proposed imine intermediate.

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