# Kinetic and *X*-Ray Crystallographic Studies of the Steric Course of *N*-Benzylation of Piperidines: Quaternization by Preferential Equatorial Attack†

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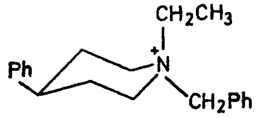
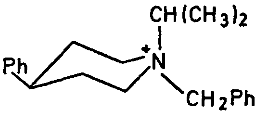
*Summary* The effects of solvent and of substituents at the piperidine nitrogen and in the benzyl ring on the relative and absolute rates of *N*-benzylation of piperidines are discussed with the aid of *X*-ray analysis of the major products from the benzylation of 1-ethyl-4-phenylpiperidine and 1-isopropyl-4-phenylpiperidine.

THE steric course of alkylation of tertiary bases has been highly controversial. Although *X*-ray crystallography has now shown that the product of axial attack predominates in the methylation of 1-ethyl-[1-3] and 1-benzyl-4-phenylpiperidine,[4] interpretations in other systems are less firmly based. In a paper[5] dealing with benzylations, McKenna and his co-workers conclude that preferred axial attack occurs for all primary alkylations, and House *et al.* report predominant axial benzylation.[6] However, we interpreted[2] benzylations in terms of predominant equatorial attack as did Bottini.[7]

We have now studied product ratios and kinetic rates for the reactions of *N*-methyl-, *N*-ethyl-, and *N*-isopropyl-4-phenylpiperidine with $p$-X·$C_6H_4CH_2Cl$ (X = OMe, H, $NO_2$) in methanol, acetonitrile, acetone, and benzene. Orientation of products in the *N*-Et and *N*-$\mathrm{Pr^i}$ series was determined by *X*-ray analysis of the predominant products formed by reaction with benzyl chloride, and of those in the *N*-Me series by using a previous *X*-ray report.[4]



(1)



(2)

1-Benzyl-1-ethyl-4-phenylpiperidinium chloride (**1**) crystallises from acetonitrile as orthorhombic crystals, $a = 9{\cdot}41$, $b = 17{\cdot}94$, $c = 20{\cdot}47$ Å, $U = 3455{\cdot}6$ Å$^3$, $Z = 8$, space group *Pbca*. 2040 independent non-zero reflections were collected using the Weissenberg technique (Cu-$K_\alpha$ radiation, $\lambda = 1{\cdot}5418$ Å). The structure was solved by direct methods and all the non-hydrogen atoms were refined anisotropically by least-squares. The hydrogen atoms have not yet been included in the structure-factor calculation. The current *R* value is 0·13.

1-Benzyl-1-isopropyl-4-phenylpiperidinium chloride (**2**) crystallises from acetonitrile as monoclinic crystals, $a = 27{\cdot}778$, $b = 9{\cdot}483$, $c = 19{\cdot}911$ Å, $\beta = 133{\cdot}3°$, $U = 3833{\cdot}0$ Å$^3$, $Z = 8$, space group *C*2/*c*. 2089 independent non-zero reflections were collected on a Siemens AED automatic four-circle diffractometer using the "ω-scan" mode (Mo-$K_\alpha$ radiation, $\lambda = 0{\cdot}7107$ Å). The structure was solved by direct methods and refined by least-squares, anisotropically for the non-hydrogen atoms, isotropically for the hydrogen atoms. The final *R* value is 0·05.

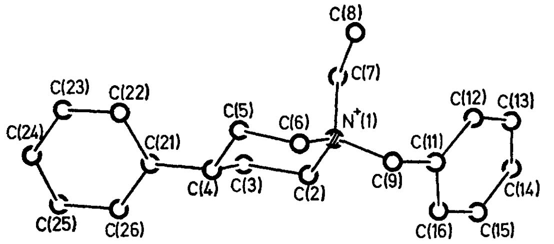


FIGURE 1. *The conformation of the* 1-*benzyl*-1-*ethyl*-4-*phenylpiperidinium cation.*

The structures (Figures 1 and 2) show clearly that the rings are in the chair form with the 4-phenyl groups in the equatorial positions as expected. The ethyl and isopropyl groups occupy the axial positions, and the benzyl groups the equatorial positions proving that these benzylations have occurred predominantly by equatorial attack. The benzyl groups occupy different rotameric positions in the two compounds.

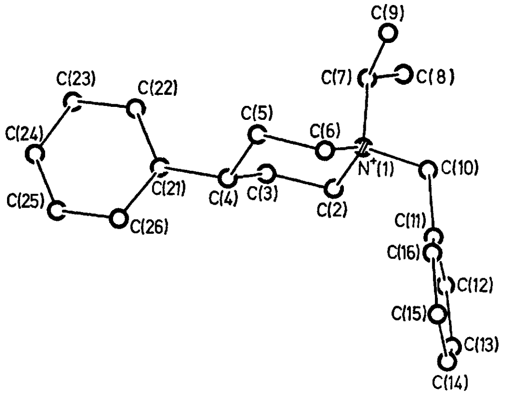


FIGURE 2. *The conformation of the* 1-*benzyl*-1-*isopropyl*-4-*phenylpiperidinium cation.*

A detailed analysis of the kinetic results† indicates that equatorial attack predominates for all the reactions studied, except for $p$-methoxy-benzylation in acetone (and methanol) solvents. The proportion of product formed by equatorial attack is less in methanol but varies little in the other solvents. Whereas the effect of the *N*-substituent on the product ratios is small and apparently random, analysis of the results in terms of the individual rate constants $k_e$ and $k_a$ shows that although both rate constants vary smoothly with the *N*-substituent Me > Et > $\mathrm{Pr^i}$ and with

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† Full details of the work described in this communication will be submitted to *J. C. S. Perkin II* in the form of two papers, dealing with the crystallographic and the kinetic results, respectively.

the benzyl *p*-substituent OMe $\gg$ H $>$ $NO_2$, the variations are considerably greater for $k_a$ than for $k_e$. This behaviour may be rationalised in terms of steric effects. Clearly the balance between predominant axial and equatorial alkylation in piperidines is a delicate one, but for benzylation equatorial attack predominates under most conditions.

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