

Rates of Reaction of Steroidal Primary and Secondary Amines with 2,4-Dinitrochlorobenzene

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IN 98.5% ethanol at 99.5°, rate constants for the reaction of 2,4-dinitrochlorobenzene (DNCB) with an excess (~150 molar) of 3 α -, 3 β -, 6 α -, and 6 β -amino-5 α -cholestane all fall within a range of ~2:1, within which the constant for the axial 3 α -, and, more surprisingly, that for the very hindered axial 6 β -amine, are each higher than the constants for the corresponding epimeric equatorial bases: the overall order* is 3 α \gg 6 β > 3 β > 6 α . Rate constants are hardly altered in presence of 0.1M-sodium acetate (significant transition states¹ are therefore associative in character), and the axial > equatorial order for the 3-amines (the 6-amines have not yet been similarly examined) is the same in benzene. The axial 3- and 6-amines also react faster than their equatorial epimers in 98.5% ethanol when the DNCB: amine ratio is 1:2; under these conditions the reactions are in some cases observed to be partly second-order in amine. With the same solvent and 1:2 DNCB: amine ratio the primary

equatorial 7 β -amine reacts faster than its axial 7 α -epimer; it has not yet proved possible to use large excesses of these two bases in the kinetic studies. Because of interfering reactions, extension of the work to steroidal secondary amines was more difficult, but we have shown that in 98.5% ethanol at 99.5° the four isomeric 3- and 6-methylamino-5 α -cholestanes (in large excess) give rate constants falling within a range of ~20:1: each equatorial amine reacts faster than its axial epimer, but the atypical sequence 6 α > 3 β > 3 α > 6 β is observed.

For epimeric primary amines similar but less detailed observations have previously been made with menthylamines² (in reaction with benzoyl chloride in pyridine) and 4-*t*-butylcyclohexylamines³ (in reaction with DNCB). While full analysis of the unexpected relative reactivities is hardly yet possible [the detailed mechanism of the DNCB reaction, including the important question of the timing of the proton transfer step,

* Because of the complication of mixed reaction orders, brevity requires that we emphasize the qualitative sequences of reactivities here, rather than quote and discuss individual rate constants, which we shall do in the full paper. Calculated first-order rate constants for the reaction of DNCB with a large excess of the bases at a standard concentration, for example, would fall into the sequences and ranges quoted.

$e.g.$, $R-NH_2-Ar \xrightarrow{Cl + B} BH + R-NH-Ar (Cl)$,
 is still controversial] a significant related point
 appears to be the reduction in equatorial preference,
 demonstrated both experimentally⁴ and analytically,⁵
 in passing from $-NH_2$ to $-NHR$ at least in the case
 where $R = Me$ (the corresponding position for $-NHMe$
 as against $-NMe_2$ is presently less clear). In our
 work, the equatorial preference of the reacting 3- and
 6-amino-groups at the kinetically important transition-
 state stage during the reaction $R-NH_2 \rightarrow R-NH-Ar$ is
 seen to be less

than for the unreacted groups. The "normal" result
 with the primary 7-amino-steroids may be due to the
 strong "peri"-effect of the 15-methylene group.⁶

The importance of consideration of the actual
 co-ordination-number change in assessment of the
 applicability of the classical axial *versus* equatorial
 reactivity generalisations has been stressed in
 previous papers.⁶

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¹ For the mechanisms of reactions of nucleophiles with 2,4-dinitrohalogenobenzenes, see, *inter alia*, J. F. Bunnett, *Quart. Rev.*, 1958, **12**, 1; S. D. Ross, *Progr. Phys. Org. Chem.*, 1963, **1**, 31; R. E. Parker, *Adv. Fluorine Chem.*, 1963, **3**, 63; J. F. Bunnett and J. J. Randall, *J. Amer. Chem. Soc.*, 1958, **80**, 6020; J. F. Bunnett and R. H. Garst, *ibid.*, 1965, **87**, 3875; C. R. Hart and A. N. Bourns, *Tetrahedron Letters*, 1966, 2995.

² A. K. Macbeth, J. A. Mills, and W. G. P. Robertson, *J. Chem. Soc.*, 1951, 2968.

³ E. L. Eliel, E. W. Della, and T. H. Williams, *Tetrahedron Letters*, 1963, 831.

⁴ H. Feltkamp, N. C. Franklin, K. D. Thomas, and W. Brügel, *Annalen*, 1965, **683**, 64; E. L. Eliel, *Angew. Chem. Internat. Edn.*, 1965, **4**, 761, (Table I, p. 764).

⁵ A. R. Katritzky, Lecture at Chemical Society Anniversary Meetings, Oxford, March, 1966.

⁶ R. Ledger, J. McKenna, and P. B. Smith, *Tetrahedron Letters*, 1963, 1433; J. McKenna, J. M. McKenna, R. Ledger, and P. B. Smith, *Tetrahedron*, 1964, **20**, 2423.