

Nucleophilic Attacks on Carbon–Carbon Double Bonds. Part 24.¹ Nucleophilic Substitution of (*E*)- and (*Z*)-3-Chloro-2-phenylpropenonitriles; Comments on the Work of Le Guillanton and Cariou

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The contradictions between the results and conclusions of Le Guillanton and Cariou and those of Rappoport and Topol in studies of the nucleophilic substitution of 3-chloro-2-phenylpropenonitriles are discussed. A mechanism is suggested for the 'racemisation' reaction observed at high ethoxide ion concentrations. Methods for determining the configurations of the substitution products are evaluated.

THE preceding paper² comments on results reported¹ for the nucleophilic substitution of (*E*)- and (*Z*)-3-chloro-2-phenylpropenonitriles. Although we agree that the ϵ value for (*E*)-3-ethoxy-2-phenylpropenonitrile previously reported¹ is probably too low, we have no reason to question our original data concerning the nature and the identity of the isolated compounds, especially since our analytical and spectroscopic data are more extensive than those reported by Le Guillanton and Cariou.² We will therefore restrict our discussion to the differences between the data and the interpretations which are relevant to the stereochemical outcome of the reaction. Since Le Guillanton and Cariou² do not attempt to explain the apparent discrepancy in the two sets of results, we will briefly examine the question within the context of nucleophilic vinylic substitution.³ The main points of disagreement between the two papers which we will discuss are (a) the purity of our (*E*)-3-chloro-2-phenylpropenonitrile, (b) the configurational assignments of the 3-ethoxy-2-phenylpropenonitriles, and (c) the stereochemistry of the substitution by EtO⁻ (and PhO⁻) and by morpholine and piperidine.

(*E*)-3-Chloro-2-phenylpropenonitrile Purity.—This isomer was obtained by Cariou's distillation method,⁴ after separation of the solid *Z*-isomer from an *EZ*-mixture. Le Guillanton and Cariou² reported that in their hands this method gave an *E*-isomer which was *always* contaminated with the *Z*-isomer, implying that the *E*-isomer

in our stereochemical studies was not pure. This is not so. Obviously, the purity of the *E*-isomer obtained in different preparations or in different laboratories may differ, depending on the distillation temperature (since isomerisation may occur on distillation), and on the extent of the initial separation of the *E*- and the *Z*-isomers. Indeed, we actually observed different *E–Z* compositions of the distillate in different preparations. However, the sample of the *E*-isomer eventually used by us¹ was obtained after careful separation of the *Z*-isomer and two distillations, at a lower temperature than that used by Cariou.⁴ It showed no n.m.r. :CH signal for the *Z*-isomer and was therefore $\geq 97\%$ pure. The high purity is corroborated by the high stereospecificity of the isolated product of substitution by toluene-*p*-thiolate ion.

Configurational Assignments of the Vinyl Ethers.—Our configurational assignments for the vinyl ethers were based on u.v. data and on the stereochemistry of the reaction. Furthermore, we expressed reservation concerning the application of Tobey's rule to the n.m.r. data of these compounds. Nevertheless, Le Guillanton and Cariou² suggest a reversal of the configurational assignments, based on the use of n.m.r. additivity rules. We will comment on each of these methods separately.

U.v. data. In the absence of n.m.r. data for model compounds, we previously¹ applied the analogy between the u.v. data of our 3-ethoxy-2-phenylpropenonitriles and the earlier data of Cariou⁴ for the 3-methoxy-ana-

¹ Part 23, Z. Rappoport and A. Topol, *J.C.S. Perkin II*, 1975, 982.

² G. Le Guillanton and M. Cariou, preceding paper.

³ (a) Z. Rappoport, *Adv. Phys. Org. Chem.*, 1969, 7, 1; (b) G. Modena, *Accounts Chem. Res.*, 1971, 4, 73.

⁴ M. Cariou, *Bull. Soc. chim. France*, 1969, 217.

logues. While our work was under consideration for publication, Le Guillanton, Cariou, and Lebouc⁵ reversed their original configurational assignments of the 3-methoxy-analogues. In view of the close similarities between the λ_{max} and ϵ values for each pair of isomers, the u.v. method now seems of little use in configurational assignments without corroborative evidence. The nature of such evidence is discussed below.

Application of Tobey's Rule to 3-Substituted-2-Phenylpropenenitriles.—Le Guillanton and Cariou² calculated the positions of the vinylic proton signals and assigned the stereochemistry for 3-substituted 2-phenylpropenenitriles (substituent X = Cl, OR, or NR₂) by using Tobey's⁶ or Pascual, Meier, and Simon's⁷ additivity rules. This was a main argument for reversing our assignments when X = OR, and the only method of configurational assignment when X = NR₂. They concluded that Pascual's formula and Tobey's rule are applicable, without limitation, to the configurational assignment of (*E*)- and (*Z*)-2-phenylpropenenitriles substituted on C-3.² We disagree with this statement since Tobey himself concluded⁶ that although the additivity rule applies for the chlorine substituent, for the case of two substituents capable of conjugative interaction (and we believe that the CN and OR of our system are such substituents), 'attempts to tabulate σ ' constants ' for asymmetric substituents that will be of any great use in differentiating between closely related ethylenes are ordinarily fruitless.'⁶ Indeed, Tobey refrained from giving a definite σ value for OR.⁶ There is also evidence that the steric interaction of conjugating groups will lead to deviations from the additivity rule when applied to vinyl ethers and enamines.⁸ In agreement with Tobey's analysis we used the rule only for assignments of the 3-chloro-2-phenylpropenenitriles.¹ We feel that its use for systems with strongly interacting substituents is misleading, and we prefer to trust in these cases the empirically observed rule of retention of configuration in nucleophilic vinylic substitution.³

Application of the Stereochemistry of Substitution as a Stereochemical Guide.—It is well established that nucleophilic vinylic substitution *via* 'addition-elimination' proceeds with initial retention of configuration.³ Although post-substitution isomerisation in the substitution by most amines is important,^{3a,9} to our knowledge

⁵ G. Le Guillanton, M. Cariou, and A. Lebouc, *Bull. Soc. chim. France*, 1974, 2980.

⁶ S. Tobey, *J. Org. Chem.*, 1969, **34**, 1281.

⁷ C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, 1966, **49**, 164.

⁸ U. E. Malter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, 1969, **25**, 691, 2023; J. Niwa, *Bull. Chem. Soc. Japan*, 1967, **40**, 1512.

⁹ (a) G. Modena, P. E. Todesco, and S. Tonti, *Gazzetta*, 1959, **89**, 878; (b) F. Scotti and E. J. Frazza, *J. Org. Chem.*, 1964, **29**, 1800; (c) C. H. McMullen and C. J. M. Stirling, *J. Chem. Soc. (B)*, 1966, 1217; (d) J.-C. Chalchat, F. Théron, and R. Vessière, *Bull. Soc. chim. France*, 1970, 4486; (e) J.-C. Chalchat and F. Théron, *ibid.*, 1973, 3361; (f) Y. Shvo, E. C. Taylor, and J. Bartulin, *Tetrahedron Letters*, 1967, 3259; Y. Shvo and H. Shanan-Atidi, *J. Amer. Chem. Soc.*, 1969, **91**, 6683, 6689; (g) W. E. Truce, J. E. Parr, and M. L. Gorbaty, *Chem. and Ind.*, 1967, 660; (h) W. E. Truce and M. L. Gorbaty, *J. Org. Chem.*, 1970, **35**, 2113; (i) W. J. Fanshawe, V. J. Bauer, and S. R. Safir, *ibid.*, 1965, **30**, 1278; (j) J. S. Meek and J. S. Fowler, *ibid.*, 1968, **33**, 985.

there is no case of initial substitution with inversion of configuration. Hence, we suggest that, in the absence of other evidence, the stereochemistry of the substitution can be used to assign configurations. The substitution reactions of (*E*)- and (*Z*)-3-chloro-2-phenylpropenenitriles with EtO⁻ in ethanol gave completely different products under our conditions.¹ Since the u.v. method and Tobey's rule cannot be trusted, we preferred to use the 'retention rule' and ascribed retained configurations to our substitution products. These assignments agree with those suggested by us originally,¹ but are opposite to those of Le Guillanton and Cariou.² If our assignments should be reversed, an explanation will be required for such an unprecedented inversion of configuration in substitution by EtO⁻.

Stereochemistry of the Substitution.—(a) *Ethoxide in ethanol.* We reported that the substitution of (*E*)- and (*Z*)-3-chloro-2-phenylpropenenitriles by EtO⁻ in ethanol is stereospecific, leading to a different ethyl vinyl ether in each case. We isolated 88 and 95% yields of the pure vinyl ethers. We therefore suggested,¹ and still maintain, that *under our conditions* the reaction proceeds with retention of configuration. Le Guillanton and Cariou² reported that in their hands the same reaction gave a ca. 1:1 mixture of the two isomers. They also reported that the two vinyl ethers were always present during the reaction, and that these ethers did not undergo isomerisation during chromatography. No explanation was offered for the contradictory results or for the nature of the 'racemisation' process.

To reconcile these contradictory results we will have to assume that the different stereochemical outcome is due to differences in reaction conditions. Le Guillanton and Cariou² conducted their reaction with 0.85M-ethoxide and 0.4M-chloro-compound, whereas our reaction was conducted with 10-fold lower concentrations of both.

At least three mechanisms (Scheme) which lead to retention at low base concentrations can lead to 'racemisation' at higher base concentrations. (a) An α -elimination to form the vinylic carbene (2), which could then react with ethoxide ion and then with a proton, to give a mixture of the vinyl ethers (3) and (4), finds precedent in some reactions of vinyl trifluoromethanesulphonates.¹⁰ This route was excluded by us¹ owing to the lack of deuterium incorporation into the ethers (3) and (4), but it may operate at higher base concentrations. It is in line with the observation that several substitutions by EtO⁻ which do not give retention proceed by elimination-addition routes.^{3,11,12} (b) An initially formed product of retained configuration [e.g. (3) from (1)] could be nucleophilically isomerised *via* addition-elimination of ethoxide

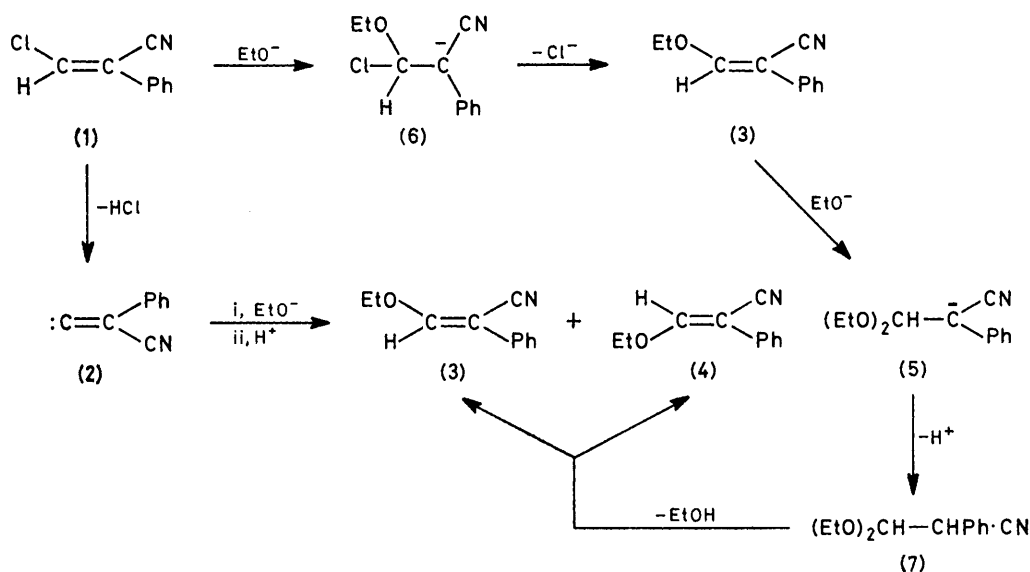
¹⁰ P. J. Stang, M. G. Magnum, D. P. Fox, and P. Haak, *J. Amer. Chem. Soc.*, 1974, **96**, 4562.

¹¹ (a) S. Gheretti, G. Modena, P. E. Todesco, and P. Vivarelli, *Gazzetta*, 1961, **91**, 620; (b) L. DiNunno, G. Modena, and G. Scorrano, *J. Chem. Soc. (B)*, 1966, 1186; (c) F. Théron, *Bull. Soc. chim. France*, 1968, 278; (d) J. Biougne, F. Théron, and R. Vessière, *ibid.*, 1972, 2882; 1975, 2703; J.-C. Chalchat, F. Théron, and R. Vessière, *ibid.*, 1973, 2501.

¹² G. Marchese, G. Modena, and F. Naso, *Tetrahedron*, 1968, **24**, 663, 958.

ion [*i.e.* (3) \rightarrow (5) \rightarrow (4)]. Precedents are known for nucleophilic isomerisation of activated double bonds.¹³ If the nucleophilic attack on (3) to form (5) is slower than the initial attack on (1) to form (6), the second-order

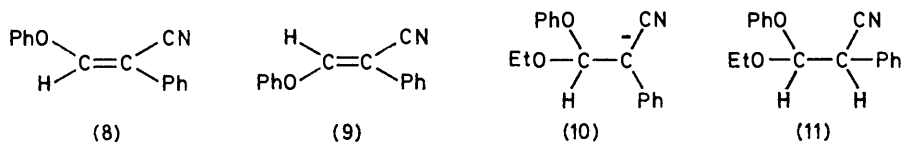
with a much less important expulsion of EtOH to give (8) and (9). In view of the facts that the acetal (7) could eliminate either of its two ethoxy-groups, and that protonation of the resonance-stabilised ion (10) could



isomerisation may be important at high EtO⁻ concentrations, but negligible at low base concentrations. (c) The most likely mechanism involves formation of the alcohol adduct (7), followed by loss of ethanol in the basic medium, *i.e.* (1) \rightarrow (6) \rightarrow (3) \rightarrow (5) \rightarrow (7) \rightarrow (3) \rightarrow (4). This will be accompanied by deuterium incorporation under appropriate conditions and again will be more important in the more basic medium. This

lead to several stereoisomers of (11), the formation of *ca.* 1 : 1 mixtures of the *E*- and *Z*-ethers is not surprising.

Le Guillanton and Cariou apparently extrapolated their data to our kinetic results at low base concentrations in ethanol: they state that 'the choice of ethanol as a solvent for the kinetic measurements is unfortunate.'² Analysis of the PhOH + EtO⁻ \rightleftharpoons PhO⁻ + EtOH equilibrium combined with the kinetic results at our base



route, which still calls for initial retention of configuration, finds precedent, for example, in the substitution of *trans*- β -chloro-4-nitro- or 2,4-dinitro- β -bromo-styrenes by EtO⁻.¹² Moreover, this mechanism also explains the solvent effect on the analogous reaction with phenoxide ion. In acetonitrile-triethylamine we found that this reaction leads to retention¹ and this was verified by Le Guillanton and Cariou.² However, they reported that the products of reaction in ethanol were mainly the ethers (3) and (4), formed in addition to some of the racemised phenyl ethers (8) and (9). This solvent effect is consistent with (i) retention [*e.g.* (1) \rightarrow (8)] by nucleophilic attack of PhO⁻ in the aprotic solvent; (ii) racemisation *via* formation of the mixed acetal (11) in the protic media at high base concentrations [(1) \rightarrow (8) \rightarrow (10) \rightarrow (11)], followed by a preferential expulsion of the better leaving group (PhO) to give mainly (3) and (4), concurrent

concentrations shows that the main reaction under our conditions is with the PhO⁻ ion.*

(b) *Amines in acetonitrile.* Le Guillanton and Cariou found that the substitution reactions of the (*E*)- and (*Z*)-chloro-compounds by piperidine or morpholine gave initially a different product in each case.² The products from the *E*-isomers isomerised later to the enamines derived from the *Z*-isomers. They suggested that the initial substitution for both isomers proceeds with retention of configuration, although neither the reason for this conclusion, nor any evidence except for R_F values and δ (^1C H) values was given as a support for the identification of the compounds formed as substitution pro-

¹³ S. Patai and Z. Rappoport, *J. Chem. Soc.*, 1962, 396; Z. Rappoport, C. Degani, and S. Patai, *ibid.*, 1963, 4513; Z. Grünbaum, S. Patai, and Z. Rappoport, *J. Chem. Soc. (B)*, 1966, 1133; D. J. Kroeger and R. Stewart, *ibid.*, 1970, 217.

ducts. Although these authors gave no reference to it, it is well documented that the initial substitution step by amines gives retention of configuration,^{3a,9} as concluded from a study of the reactions of amines where the barrier for the *E-Z*-enamine isomerisation is high.^{9g-j} Le Guillanton and Cariou's results suggest that even with piperidine and morpholine, where the barrier for rotation in the enamino-nitriles is expected to be low,^{9f} the initial substitution product can be detected. Since this novel observation is unprecedented, this conclusion requires corroboration.

Provided that the compounds formed are indeed the

isomeric enamino-nitriles, our method of configurational assignment by applying the 'retention rule' leads to the same assignment as suggested by Le Guillanton and Cariou, apparently on the basis of Tobey's rule. We isolated only the stable isomer from these reactions in EtOH and *tentatively* assigned its configuration by analogy.¹ If the initial reaction products are the enamino-nitriles, our configurational assignments for the isomers isolated by us should now be reversed.

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