Stereochemistry of Nucleophilic Substitution of (*E*)- and (*Z*)-3-Chloro-2-Phenylpropenonitriles; Criticism of a Paper by Rappoport and Topol

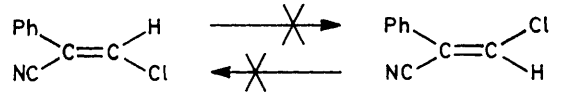
By **Georges Le Guillanton** * and **Michel Cariou**, Laboratoire de Synthèse et Electrochimie Organiques, E.R. C.N.R.S. no. 14, Université Catholique de l'Ouest, B.P. 858, 49005, Angers Cedex, France

Contrary to a report by Rappoport and Topol nucleophilic substitution of (*E*)- and (*Z*)-3-chloro-2-phenylpropenonitriles does not always proceed with retention of configuration. Strong bases, such as sodium ethoxide in ethanol and sodium phenoxide in tetrahydrofuran, cause complete racemisation,' whereas reactions with weak bases, such as morpholine, piperidine, and phenol–triethylamine, proceed with retention of configuration. Moreover the (*E*)- and (*Z*)-vinylic ethers thus obtained do not undergo isomerisation; however the (*E*)-enaminonitriles do isomerise to the stable *Z*-form. The choice of ethanol as solvent for kinetic measurements is unfortunate, since it is itself involved in such substitution reactions. Physical and spectroscopic data reported by Rappoport and Topol are corrected, and the assignment of *E*- and *Z*-configurations to the 3-ethoxy-2-phenylpropenonitrile isomers is reversed.

RECENTLY Rappoport and Topol [1] have reported a study of the stereochemistry of nucleophilic substitution of (*E*)- and (*Z*)-3-chloro-2-phenylpropenonitriles (1) by various reagents (arenethiolate, azide, ethoxide, phenoxide, piperidine, and morpholine). These authors noticed an ' almost exclusive retention of configuration in the substitution by four anionic nucleophiles which cover an appreciable reactivity difference, and the formation of an identical product from (*E*)- and (*Z*)-RCl (1) in the reaction with the amines.' We have re-examined their experiments. Our results are at variance with theirs, and we believe that the substitution proceeds sometimes with and sometimes without retention of configuration, according to the nature of the nucleophilic species. Our evidence is presented below.

Complete Separation of E- *and* Z-*Isomers of* 3-*Chloro*-2-*phenylpropenonitrile* (1) *by Chromatography*.—Rappoport and Topol prepared the chloro-compound (1) and separated the *E*- and *Z*-isomers according to Cariou's procedure.[2] This permits easy separation of the crystalline *Z*-isomer in a pure state, but in our hands the liquid fraction, obtained by distillation, is not, contrary to the report by Rappoport and Topol, the pure *E*-isomer (it is always contaminated with a small amount of *Z*-isomer).[3]

We have completely separated the *E*- and *Z*-isomers by silica gel chromatography. For each isomer, purity was



(*Z*)-(1) (*E*)-(1)

checked by t.l.c., g.l.c., and n.m.r.; chemical shifts of the olefinic proton of each pure isomer differ slightly from the earlier data [1,3] [δ ($CDCl_3$) for (*Z*)-(1) 7.20; for (*E*)-(1) 7.12].

We have not observed isomerisation of the nitriles (1) after more than a year at room temperature.

Configurational Assignments by Spectroscopy.—Rappoport and Topol raise the question of the configurational assignment for (*E*)- and (*Z*)-3-ethoxy-2-phenylpropenonitriles (2). They base their assignment on Cariou's work,[4] who, for 3-methoxy-2-phenylpropenonitrile, on the basis of u.v. spectra alone, assigns the *Z*-configuration to the isomer having the higher ε value. In the case of the ether (2) also, from very different but erroneous ε

(*Z*)-(2) (*E*)-(2)

values (see later) for each isomer (6 500 and 15 400), they conclude that the *Z*-isomer is the one with the higher ε value, though this assignment is inconsistent with one which can be made by comparison of observed chemical shifts of olefinic protons with those empirically calculated by Tobey's additivity rule; [5] furthermore for the chloro-compound (1) they assign configuration in agreement with this latter rule.

In 1974, we completely separated (*E*)- and (*Z*)-3-methoxy-2-phenylpropenonitriles [6] and, on the basis of empirical calculation of chemical shifts of olefinic protons, according to Pascual's formula,[7] we concluded that Cariou's assignment based on u.v. spectra must be reversed; the same holds true for the ether (2). Pascual's formula and Tobey's rule lead to the same statement: the *Z*-isomer is the one for which the olefinic proton signal appears at lower field. In 1975, Brémond [8] confirmed the validity of these assignments by calculations of screening constant variations.

We have noticed also,[6] for *E*-isomers, an effect due to anisotropy of the C–O bond, which acts on aromatic protons *ortho* to the olefinic substituent by shifting their signals to lower field. There is no such effect for *Z*-isomers.

Physical and Spectroscopic Data.—We have separated (*E*)- and (*Z*)-3-ethoxy-2-phenylpropenonitriles (2), pre-

[1] Z. Rappoport and A. Topol, *J.C.S. Perkin II*, 1975, 982.
[2] M. Cariou, *Bull. Soc. chim. France*, 1969, 217.
[3] G. Le Guillanton and A. Daver, *Bull. Soc. chim. France*, 1973, 724.
[4] M. Cariou, *Bull. Soc. chim. France*, 1969, 198.
[5] S. Tobey, *J. Org. Chem.*, 1969, **34**, 1281.
[6] G. Le Guillanton, M. Cariou, and A. Lebouc, *Bull. Soc. chim. France*, 1974, 2980.
[7] C. Pascual, J. Meier, and W. Simon, *Helv. Chim. Acta*, 1966, **49**, 164.
[8] M. Brémond, Diplôme d'Etudes Approfondies, Faculté des Sciences de Nantes, 1975.

pared in an unambiguous way from sodium 2-cyano-2-phenylvinyl oxide and ethyl bromide in dimethylformamide. The properties of the products lead us to conclude, in addition to the reversed configuration assignment for the ethers (2), that the u.v. data published by Rappoport and Topol are erroneous; we also notice a different chemical shift for the olefinic proton of the *Z*-isomer (Table 1).

Moreover, Rappoport and Topol do not raise the question of configurational assignment for isomers of 3-phenoxy-2-phenylpropenonitrile (3); they state that they

TABLE 1

U.v. and n.m.r. data for the ether (2)

	$\lambda_{max.}$(EtOH)/nm	ε	δ($CDCl_3$)	$\delta_{calc.}$[7]	Ref.
(*Z*)-(2)	268	12 700	7.34	7.41	This work
	268.5	6 500	7.22		1
(*E*)-(2)	266	17 500	7.07	7.14	This work
	266	15 400	7.07		1

obtain the *Z*-isomer alone. We note a disagreement between our formerly published values [6] and theirs (Table 2).

Isomerisations.—Rappoport and Topol state that for the products obtained by nucleophilic substitution of the chloro-compound (1) g.l.c. using Carbowax or t.l.c. using silica or alumina columns always resulted in *E* ⇌ *Z* isomerisation. This implies in effect that they observed that some products were mixtures of isomers. They refer solely to i.r. spectroscopy for detecting the presence or otherwise of two isomers. In our opinion, this method is inadequate.

Neither for the chloro-compound (1) nor for the ethers (2) and (3) have we noticed any transformation of one

TABLE 2

Data for the ether (3)

PhC(CN):CH·OPh

	M.p. (°C)	$\lambda_{max.}$(EtOH)/nm	ε	δ($CDCl_3$)	$\delta_{calc.}$[7]	Ref.
(*Z*)-(3)	61	281.5	16 250	7.58	7.37	6
	33	267	15 000	7.07		1
(*E*)-(3)	49	275	22 800	7.10 < δ < 7.43	7.10	6

isomer into another, by t.l.c. or g.l.c. or on a silica gel column.

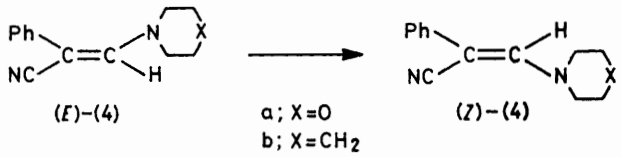
Nevertheless, as established by Rappoport and Topol and by others,[9] in the case of the enamines (4) it is possible to isolate only one isomer; they assign the *E*-configuration to this isomer. We find that two isomers are produced during the reaction, but one of them isomerises into the other, stable form. We have shown the existence of the unstable isomer by t.l.c. and have assigned to it the *E*-configuration by n.m.r. (see later).

The isomerisation (*E*)-(4) ⟶ (*Z*)-(4) in solution at room temperature is complete only after several days; it is rapid however when the solution is warmed or the solvent removed.

Reactions Re-examined.—We have re-examined six types of nucleophilic substitution of both *E*- and *Z*-isomers of the chloro-compound (1) (with EtONa–EtOH, PhONa–THF, PhONa–EtOH, PhOH–Et_3N–MeCN, morpholine–MeCN, and piperidine–MeCN). Reactions were performed at room temperature, according to Rappoport and Topol's procedure. All extractions and purifications were also carried out at room temperature, in order to prevent any thermal isomerisation. Isomers formed during the reaction were detected by t.l.c. and g.l.c. Percentages of isomers were determined by g.l.c., or by separation on a silica gel column or by n.m.r. which also permits identification. In CCl_4 or $CDCl_3$, signals of aromatic protons sometimes mask signals of olefinic protons, but if an aromatic solvent (C_6D_6 or C_5D_5N) is used signals are widely separated.[8] Within the limits of experimental errors, such chromatographic and spectrographic methods gave closely similar results.

(a) *Sodium ethoxide in ethanol.* The action of ethoxide is not stereoselective: irrespective of the chloro-compound isomer used, a *ca.* 1 : 1 mixture of *E*- and *Z*-isomers of the ether (2) is always obtained.

(b) *Sodium phenoxide in tetrahydrofuran.* The action of phenoxide is not stereoselective: a *ca.* 1 : 1 mixture of



isomers of the ether (3) is obtained; this is a further example of non-stereoselectivity (Rappoport and Topol did not study this reaction).

(c) *Sodium phenoxide in ethanol.* Rappoport and Topol made their kinetic measurements in ethanol; in the case of sodium phenoxide we noticed that not only is the reaction not stereoselective, but it gives rise almost exclusively to the ether (2), instead of the expected ether (3); each ether comprises a *ca.* 1 : 1 mixture of *E*- and *Z*-isomers. Ethoxide is a stronger and more reactive base than phenoxide, which accounts for the fact that the ether (2) is the chief product. The u.v. and n.m.r. data which are described by them as those of the ether (3) are related to those of the ether (2).

(d) *Phenol–triethylamine in acetonitrile.* Rappoport and Topol carried out this reaction only with the (*Z*)-chloro-compound (1); we performed it with the two isomers. Like them we note that the substitution proceeds with retention of configuration.

(e) *Morpholine or piperidine in acetonitrile.* Despite the instability of the *E*-isomer of the enamines (4), we have shown that substitution by morpholine or piperidine proceeds, with retention of configuration, by t.l.c. less than 10 min after the beginning of the reaction, and by recording n.m.r. spectra less than 1 h later.

Conclusion.—We believe that Rappoport and Topol have incorrectly concluded that various nucleophiles react with the chloro-compound (1) with retention of configuration. We have noted a complete 'racemisation' in reaction with strong bases (EtONa–EtOH and

[9] A. Novelli, A. P. G. V. De Varela, and J. D. Bonafede, *Tetrahedron*, 1968, **24**, 2481.

PhONa–THF) and retention of configuration in reactions with weak bases (morpholine, piperidine, and phenol–triethylamine).

Pascual's formula [7] and Tobey's rule [5] are applicable, without limitation, to the configurational assignment of (*E*)- and (*Z*)-2-phenylpropenonitriles substituted on C-3.

Except for the (*E*)-enamines (4), all products are stable and do not undergo isomerisation in contact with materials used in chromatography.

EXPERIMENTAL

I.r. spectra were recorded with a Perkin–Elmer 257 spectrophotometer, u.v. spectra with a Beckman Acta C III spectrophotometer, and n.m.r. spectra with a Perkin-Elmer–Hitachi R-24 (60 MHz) instrument (with Me_4Si as internal standard). T.l.c. was carried out on pre-coated plates (Merck silica gel 60 F 254, 0.25 mm thick; elution with cyclohexane–ethyl acetate, 3 : 1). Isomers were separated by chromatography on a silica gel column (Merck H, type 60). Except where stated otherwise, cyclohexane–ethyl acetate (3 : 1) was used as eluant. G.l.c. was carried out on an Aerograph Autoprep 705 instrument with Inox $\frac{1}{4}$ in columns containing the following stationary phases: silicon QF1 (20%) for the chloro-compound (1); FFAP (5%) for the ether (2); silicone SE30 (20%) for the ether (3). M.p.s were taken with a Kofler hot-stage apparatus.

Preparation and Separation of (E)- *and* (Z)-3-*Chloro*-2-*phenylpropenonitriles* (1).—These were prepared according to Cariou's method.[2] The crystalline *Z*-isomer was filtered off and recrystallised from light petroleum. In order to obtain the pure *E*-isomer, an enriched fraction of the liquid isomer was purified by column chromatography (i.d. 7.5 cm; 510 g of silica for 15.6 g of mixture). The *E*-isomer was eluted first (cyclohexane–ethyl acetate, 9 : 1). Some constants have already been reported.[3]

Preparation and Separation of (E)- *and* (Z)-3-*Ethoxy*-2-*phenylpropenonitriles* (2).—A solution of sodium 2-cyano-2-phenylvinyl oxide (16.7 g, 0.1 mol), prepared according to Lamant,[10] and ethyl bromide (32.7 g, 0.3 mol) in dimethylformamide (100 ml) was warmed on a water-bath for 4 h. Benzene (250 ml) and water (100 ml) were added and the solution was decanted, washed with water, dried (Na_2SO_4), and evaporated to leave an oily mixture of *E*- and *Z*-isomers of the ether (2) (15.6 g, 90%); $\nu_{max.}$ ($CHCl_3$) 2 210 (CN) and 1 620 cm^{-1} (C=C). This mixture (1 g) was separated by column chromatography (i.d. 3.4 cm; 100 g of silica) to give the *E*-isomer (78%) and the *Z*-isomer (22%); δ ($CDCl_3$) (*E*)-(2) 7.07 (1 H, s, :CH), 4.17 (2 H, q, CH_2·O), 1.40 (3 H, t, CH_3), 7.80—7.60 (2 H, m, Ph), and 7.45—7.25 (3 H, m, Ph); (*Z*)-(2) 7.34 (1 H, s, :CH), 4.18 (2 H, q, CH_2O), 1.41 (3 H, t, CH_3), and 7.40 (5 H, s, Ph).

Action of Nucleophilic Reagents on (E)- *and* (Z)-3-*Chloro*-2-*phenylpropenonitriles* (1).—All reactions and treatments were conducted at room temperature.

(a) *Sodium ethoxide in ethanol.* To a solution of sodium ethoxide (0.04 mol) [from sodium (1 g)] in ethanol (50 ml), the chloro-compound (1) (3.27 g, 0.02 mol) was added. The reaction was very fast, even at room temperature. T.l.c. always showed two spots, whichever chloro-isomer was used (R_F 0.18 and 0.24). After 3 h, ethanol was evaporated off, then ether (100 ml) and water (50 ml) were added. The ethereal layer was washed several times with water, dried ($MgSO_4$), and evaporated. The residue (3.4 g, 100%) consisted of (*E*)- and (*Z*)-3-ethoxy-2-phenylpropenonitrile (2). G.l.c. showed 50% of *E*-isomer and 50% of *Z*-isomer from (*Z*)-(1) and 47% of *E*-isomer and 53% of *Z*-isomer from (*E*)-(1). N.m.r. (C_6D_6) indicated 48% of *E*-isomer [δ 6.40 (1 H, s, :CH)] and 52% of *Z*-isomer [δ 6.65 (1 H, s, :CH)] from (Z)-(1) and 46% of *E*-isomer and 54% of *Z*-isomer from (*E*)-(1). Separation of mixtures by chromatography on silica (i.d. 5.2 cm; 300 g of silica) afforded 1.7 g of *E*-isomer (53%) and 1.5 g of *Z*-isomer (47%) from (*Z*)-(1), and 1.6 g of *E*-isomer (50%) and 1.6 g of *Z*-isomer (50%) from (*E*)-(1). T.l.c., g.l.c., and n.m.r. showed that the two separated isomers were essentially pure.

(b) *Sodium phenoxide in tetrahydrofuran.* To a solution of sodium phenoxide (4.64 g, 0.04 mol) in tetrahydrofuran (50 ml), the chloro-compound (1) (3.27 g, 0.02 mol) was added. T.l.c. always showed two spots, whichever chloro-isomer was used (R_F 0.42 and 0.36). After 7 h, the solution was worked up as above, giving a residue (4.4 g, 100%), consisting in both cases of a mixture of (*E*)- and (*Z*)-3-phenoxy-2-phenylpropenonitrile (3). G.l.c. showed 45% of *E*-isomer and 54% of *Z*-isomer from (*Z*)-(1), and 43% of *E*-isomer and 57% of *Z*-isomer from (*E*)-(1). N.m.r. (C_5D_5N) indicated 45% of *E*-isomer [δ 7.85 (1 H, s, :CH)] and 55% of *Z*-isomer [δ 8.10 (1 H, s, :CH)] from (*Z*)-(1) and 43% of *E*-isomer and 57% of *Z*-isomer from (*E*)-(1). Separation by chromatography on a silica gel column (i.d. 5.2 cm; 400 g of silica) gave 2 g (52%) of *E*-isomer and 1.8 g (48%) of *Z*-isomer from (*Z*)-(1), and 2.3 g (55%) of *E*-isomer and 1.9 g (45%) of *Z*-isomer from (*E*)-(1). The two isomers have already been described.[6]

(c) *Sodium phenoxide in ethanol.* Sodium phenoxide (4.64 g, 0.04 mol), then the chloro-compound (1) (3.27 g, 0.02 mol), were dissolved in ethanol (100 ml). An hour later, t.l.c. showed four spots (R_F 0.18, 0.24, 0.36, and 0.42). The last two spots were hardly visible but had the same intensity. The usual work-up gave a residue (3.6 g) essentially made up of (*E*)- and (*Z*)-3-ethoxy-2-phenylpropenonitrile (2): 42% of *E*-isomer and 58% of *Z*-isomer from (*Z*)-(1), and 55% of *E*-isomer and 45% of *Z*-isomer from (*E*)-(1). The detection of the expected 3-phenoxy-2-phenylpropenonitrile (3) was difficult; it must represent *ca.* 5% of the mixture. Estimation of the isomers of 3-phenoxy-2-phenylpropenonitrile (3) was not possible by n.m.r. in C_5D_5N, because the concentration was too low. N.m.r. in C_6D_6 permitted estimation of the isomers of 3-ethoxy-2-phenylpropenonitrile (2): 40% of *E*-isomer and 60% of *Z*-isomer from (*Z*)-(1) and 55% of *E*-isomer and 45% of *Z*-isomer from (*E*)-(1). Chromatography on a silica gel column (i.d. 5.2 cm; 300 g of silica) afforded the two isomers of the ether (2): 1.6 g (45%) of *E*-isomer and 1.4 g (44%) of *Z*-isomer from (*Z*)-(1), and 1.8 g (56%) of *E*-isomer and 1.4 g (44%) of *Z*-isomer from (*E*)-(1). The isomers were well characterised by t.l.c., g.l.c., u.v., i.r., and n.m.r. Only traces of the ether (3) were recovered.

(d) *Phenol–triethylamine in acetonitrile.* When using Rappoport and Topol's conditions [1 equiv. of chloro-compound (1), 1 equiv. of phenol, and 1 equiv. of triethylamine], we established by g.l.c., that after 80 h at 30 °C, part of chloro-compound (1) was not consumed. When 2 equiv. of phenol (3.8 g, 0.04 mol) and 2 equiv. of triethylamine (4.0 g, 0.04 mol) to 1 equiv. of chloro-compound (1) (3.27 g, 0.02 mol) were used in acetonitrile (50 ml), reaction was complete after 30 h at 30 °C. T.l.c. indicated the formation of only one isomer (R_F 0.42) from (*Z*)-(1) and only one isomer

[10] M. Lamant and M. Lemoine, *Bull. Soc. chim. France*, 1961, 1144.

(R_F 0.36) from (*E*)-(1). After work-up the isomer obtained in each reaction was pure, as seen by t.l.c., g.l.c., and n.m.r. The yield was quantitative. (*Z*)-(1) furnished the (*Z*)-isomer of the ether (3), m.p. 61 °C (from light petroleum); (*E*)-(1) furnished the *E*-isomer of the ether (3), m.p. 49 °C (from light petroleum).

(e) *Morpholine or piperidine in acetonitrile.* In a test-tube, to a solution of (*Z*)-(1) (33 mg, 0.2 mmol) in acetonitrile (0.4 ml), morpholine (35 μl, 0.4 mmol) was rapidly added. Similar experiments were carried out with (*E*)-(1) and morpholine, (*Z*)-(1) and piperidine (39.5 μl, 0.4 mmol), and (*E*)-(1) and piperidine. The amine hydrochloride was rapidly precipitated. After 10 min t.l.c. indicated total disappearance of the chloride (1): one spot (R_F 0.15) for reaction between (*Z*)-(1) and morpholine; one spot (R_F 0.09) for reaction between (*E*)-(1) and morpholine; one spot (R_F 0.45) for reaction between (*Z*)-(1) and piperidine; one major spot (R_F 0.34) and a minor one (R_F 0.45) for reaction between (*E*)-(1) and piperidine. After this time, $CDCl_3$ (1 ml) with Me_4Si (2%) and water (1 ml) were added to each mixture. The organic layer was washed three times with water (1 ml), and dried (Na_2SO_4). N.m.r. spectra were recorded for the four solutions (the remaining acetonitrile did not interfere with the observation of chemical shifts of olefinic protons). Enamines were pure: δ 6.98 (1 H, s, :CH) for (*Z*)-enamines (4a and b); δ 6.73 (1 H, s, :CH) for (*E*)-enamines (4a and b). One week later, the n.m.r. spectrum of the (*Z*)-enamine remained unchanged, whereas for the enamine initially in the *E*-configuration, the signal of the olefinic proton had shifted to δ 6.98; this was due to $E \longrightarrow Z$ isomerisation, confirmed by t.l.c.

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