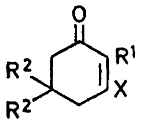
Nucleophilic Substitution by Piperidine in Some 3-Halogenocyclohex-2-enones

By **D. Pitea** *† and **G. Favini**, Istituto di Chimica Fisica, Università, 95125, Catania, Italy

Reactions of 3-chlorocyclohex-2-enone, 3-chloro- and 3-bromo-5,5-dimethylcyclohex-2-enone, and 3-chloro-2-methylcyclohex-2-enone with piperidine in ethanol and dimethylformamide were studied kinetically at 30—90 °C. Substitutions are free from side reactions. Solvent effects are rather small. Measured rate coefficients for 3-chlorocyclohexenone are larger than those of 3-chloro-5,5-dimethylcyclohexenone showing a different degree of coplanarity in the vinyl-carbonyl skeleton. The chloro- and bromo-5,5-dimethylcyclohexenones react at similar rates. Owing to the α-methyl group, rate-coefficient ratios between 3-chloro- and 3-chloro-2-methyl-cyclohexenone have values of 2—2·6 × 10^2.

NUCLEOPHILIC substitutions on vinyl halides activated by electron-withdrawing groups[1] are interesting. β-Halogenovinyl ketones are highly reactive towards nucleophiles.[2] Separate *cis*- and *trans*-isomers are now available[3] and a few *cis–trans* pairs have been studied,[4-6] but the influence of *s-cis*- and *s-trans*-conformations was not taken into account.[4-6]

Displacements tend to take place with retention of the initial geometrical configuration *via* a direct substitution,



(I) $R^1 = R^2 = H$ a; $X = Cl$
(II) $R^1 = H$; $R^2 = Me$ b; $X = Br$
(III) $R^1 = Me$; $R^2 = H$ c; $X =$ Piperidine

although *cis*-isomers in reaction with methoxide ion (in methanol) undergo elimination–addition.[6b]

We are engaged in a study of nucleophilic substitutions in β-halogenovinyl ketones with fixed conformation. We now report the reactions of 3-halogenocyclohex-2-enones (Ia), (IIa), (IIb), and (IIIa) with piperidine in ethanol and *NN*-dimethylformamide.

EXPERIMENTAL

U.v. spectra were recorded on a Hitachi–Perkin-Elmer model 124 spectrophotometer.

Highly pure *NN*-dimethylformamide was further purified according to Moe.[7] Dry ethanol was purified by a standard method.[8] Commercial piperidine was stored over KOH pellets and distilled before use. The fraction of b.p. 106—107° was collected.

3-Halogenocyclohex-2-enones.— 3-Chlorocyclohex-2-enone (Ia), 3-chloro- and 3-bromo-5,5-dimethylcyclohex-2-enone (IIa) and (IIb), and 3-chloro-2-methylcyclohex-2-enone (IIIa) were prepared and purified as described.[9] U.v. $(\pi-\pi^*)$ (ethanol): (Ia), $\lambda_{max.}$ 237 (ε 13,500); (IIa), 236 (12,400); (IIb), 243 (12,870); and (IIIa), 242 nm (13,150).

---

† *Present address:* Istituto di Chimica Fisica dell'Università, Milano, Italy.

[1] For comprehensive reviews see: (*a*) P. B. D. de la Mare, 'Progress in Stereochemistry,' eds. W. Klyne and P. B. D. de la Mare, Butterworths, London, 1958, vol. 2, p. 90; (*b*) S. Patai and Z. Rappoport, 'The Chemistry of Alkenes,' ed. S. Patai, Interscience, London, 1964, ch. 8; (*c*) A. N. Nesmeyanov, M. I. Rybinskaya, and L. V. Rybin, *Russian Chem. Rev.*, 1967, **7**, 453; (*d*) Z. Rappoport, 'Advances in Physical Organic Chemistry,' ed. V. Gold, Academic Press, London, 1969, p. 1.

[2] (*a*) N. K. Kochetkov, *Uspekhi Khim.*, 1955, **24**, 32; (*b*) A. E. Pohland and W. R. Benson, *Chem. Rev.*, 1966, **66**, 161; (*c*) M. I. Rybinskaya, A. N. Nesmeyanov, and N. K. Kochetkov, *Russian Chem. Rev.*, 1969, **9**, 433.

[3] (*a*) D. Landini and F. Montanari, *Chem. Comm.*, 1967, 180; (*b*) A. N. Nesmeyanov, M. I. Rybinskaya, and T. G. Kelekhsaeva, *Zhur. org. Khim.*, 1968, **4**, 921; (*c*) B. Cavalchi, D. Landini, and F. Montanari, *J. Chem. Soc.* (*C*), 1969, 1204.

[4] (*a*) E. Angeletti and F. Montanari, *Boll. sci. Fac. Chim. ind. Bologna*, 1958, **16**, 140; (*b*) W. E. Truce, J. E. Parr, and M. L. Gorbaty, *Chem. and Ind.*, 1967, 660; (*c*) W. E. Truce and M. L. Gorbaty, *J. Org. Chem.*, 1970, **35**, 2113.

[5] (*a*) T. A. Kudryavtseva, N. M. Chirkov, and N. K. Kochetkov, *Doklady Akad. Nauk S.S.S.R.*, 1959, **127**, 108; (*b*) A. N. Nesmeyanov, N. M. Chirkov, and N. K. Kochetkov, *ibid.*, 1963, **148**, 347; (*c*) P. Beltrame, G. Favini, M. G. Cattania, and F. Guella, *Gazzetta*, 1968, **98**, 381.

[6] (*a*) A. N. Nesmeyanov and M. I. Rybinskaya, *Izvest. Akad. Nauk S.S.S.R. Otdel. khim. Nauk*, 1962, 816; *Doklady Akad. Nauk S.S.S.R.*, 1966, **170**, 600; (*b*) D. Landini, F. Montanari, G. Modena, and F. Naso, *J. Chem. Soc.* (*B*), 1969, 243.

[7] N. S. Moe, *Acta Chem. Scand.*, 1967, **21**, 1389.

[8] A. I. Vogel, 'Practical Organic Chemistry,' Longmans, London, 1959, p. 306.

[9] D. Pitea and G. Favini, *J.C.S. Perkin II*, 1972, 142.

3-Piperidinocyclohex-2-enones.— 3-Piperidinocyclohex-2-enone (Ic), 3-piperidino-5,5-dimethylcyclohex-2-enone (IIc), and 3-piperidino-2-methylcyclohex-2-enone (IIIc) were prepared from the corresponding chloro- and bromo-cyclohex-2-enones, under conditions similar to those employed for the kinetic runs. The products are identical to those obtained from the corresponding cyclohexane-1,3-diones.[9] U.v. (π–π^*) (ethanol): (Ic), $\lambda_{\text{max.}}$ 301 (ε 40,000); (IIc), 303 (34,660); and (IIIc), 322 nm (24,380).

Kinetics.—Two different procedures were followed for runs in dimethylformamide and in ethanol.

Weighed amounts of piperidine and halogenocyclohexenone were separately dissolved in dimethylformamide and the thermostatted solutions were mixed in a stoppered Pyrex vessel. Circulation of thermostatted fluid into a jacket kept the reaction vessel at constant temperature ±0·1 °C. Two samples for spectrophotometric analysis were removed and quenched by dilution with Spectrograde ethanol at recorded times. Analyses of each sample were based on absorbance measurement at 300 and 305 nm for compounds (Ic) and (IIc) and at 320 and 325 nm for compound (IIIc).

TABLE 1

Rate coefficients (10^3k/l mol^{-1} s^{-1}) and activation parameters for the reactions of various 3-halogenocyclohex-2-enones ($1{\cdot}2$—$2{\cdot}6 \times 10^{-3}$M) with piperidine ($2{\cdot}4$—$12{\cdot}0 \times 10^{-3}$M) in dimethylformamide

Compound Temp./°C	(Ia)	(IIa)	(IIb)
30	2·87 ± 0·04 [3]		
40	5·51 ± 0·06 [4]		
50	8·82 ± 0·07 [3]	3·47 ± 0·06 [3]	
60	12·0 ± 0·2 [2]	5·19 ± 0·06 [3]	8·39 ± 0·09 [3]
70		7·98 ± 0·10 [4]	13·9 ± 0·2 [3]
80		13·0 ± 0·3 [3]	21·8 ± 0·6 [3]
90			34·5 ± 0·9 [3]
$\Delta E^{\ddagger}$/kcal mol^{-1}	10·6 ± 0·6	9·78 ± 0·54	11·3 ± 0·2
log A	11·9 ± 0·9	9·54 ± 0·80	12·3 ± 0·3
$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} at 50 °C	−33·4 ± 1·8	−38·0 ± 1·6	−32·5 ± 0·6

TABLE 2

Rate coefficients (10^3k/l mol^{-1} s^{-1}) and activation parameters for the reactions of various 3-halogenocyclohex-2-enones ($1{\cdot}0$—$8{\cdot}1 \times 10^{-3}$M) with piperidine ($2{\cdot}8$—$28{\cdot}4 \times 10^{-3}$M) in ethanol

Compound T/°C	(Ia)	(IIa)	(IIb)	(IIIa)
30	7·33 ± 0·09 [3]			0·0281 ± 0·0001 [2]
40	10·9 ± 0·2 [3]			0·0495 ± 0·0005 [3]
50	18·1 ± 0·4 [3]			0·0854 ± 0·0009 [3]
60	28·7 ± 0·6 [3]	3·79 ± 0·03 [3]	3·07 ± 0·06 [3]	0·139 ± 0·003 [4]
66			3·97 ± 0·09 [1]	
70		5·88 ± 0·08 [6]		
72			5·03 ± 0·10 [1]	
80		9·00 ± 0·12 [5]	6·87 ± 0·11 [3]	
90		13·5 ± 0·1 [3]	9·75 ± 0·08 [3]	
$\Delta E^{\ddagger}$/kcal mol^{-1}	9·02 ± 0·38	10·16 ± 0·04	9·22 ± 0·06	10·7 ± 0·1
log A	10·0 ± 0·6	9·78 ± 0·06	8·16 ± 0·09	7·37 ± 0·18
$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1} at 50 °C	−37·0 ± 1·2	−37·6 ± 0·1	−40·8 ± 0·2	−42·3 ± 0·4

For runs in ethanol, weighed amounts of piperidine and halogenocyclohexenone separately dissolved in ethanol were mixed at room temperature and quickly transferred to a series of glass tubes (5 ml in each tube). These were sealed with the contents frozen, transferred to a bath thermostatted to 0·1 °C, and preheated for 15 s before the zero time. Two tubes were withdrawn at each interval and quenched by cooling. A standard volume was diluted with Spectrograde ethanol. The substrate disappearance and the product formation were simultaneously recorded by absorbance measurements at 240 and 300 nm for compounds (Ia) and (Ic), at 235, 240, and 300 nm for compounds (IIa), (IIb), and (IIc), and at 240 and 320 nm for compounds (IIIa) and (IIIc).

In any case, as the dilution quenching was not perfectly efficient, analyses were performed as soon as possible. The reaction solution was left in the thermostat for at least 15 half-lives, and then an ' experimental infinity ' sample was analysed in the usual way; the absorbance was 98 ± 5% of the theoretical. Theoretical values were used for rate coefficient calculations.

For all reactions, most of which were followed to 40—80% completion, results fitted a second-order rate equation; initial concentrations were varied by factors within 2 for substrates and 4 for the nucleophile. Initial concentrations were corrected, when required, for solvent expansion. Rate coefficients were calculated by Margerison's procedure.[10a] For every run, the rate coefficient (k) was obtained by a weighted [10a] least-squares linear regression method; only runs for which the index of determination was $\geqslant 0{\cdot}99$ have been considered. Rate coefficients were tested for homogeneity.[10] Tables 1 and 2 record the weighted mean values (k) of the rate coefficients together with estimated standard errors and (in brackets) the corresponding number of degrees of freedom.

Arrhenius activation energies ($\Delta E^{\ddagger}$), frequency factors (A), and activation entropies ($\Delta S^{\ddagger}$) were obtained by a weighted least-squares regression method [10] and standard formulae.[11]

RESULTS AND DISCUSSION

The reactions of substrates (Ia), (IIa), (IIb), and (IIIa), having fixed *trans-s-trans*-conformation, with piperidine in dimethylformamide and in ethanol gave the expected substitution products (Ic), (IIc), and (IIIc) without detectable side-products. Kinetic results are in Tables 1 and 2.

---

[10] D. Margerison, ' The Practice of Kinetics,' eds. C. H. Bamford and C. F. H. Tipper, Elseiver, Amsterdam, 1969; (*a*) ch. 5; (*b*) method (2) on p. 375.

[11] L. L. Schaleger and F. A. Long, ' Advances in Physical Organic Chemistry,' ed. V. Gold, Academic Press, London, 1963, p. 1.

Compound (Ia) differs from (IIa) only by the lack of the two 5-methyl groups but it is more reactive than (IIa) by a factor of 2—3 in dimethylformamide and 7—9 in ethanol. On the basis of dipole-moment studies [9] it was shown that there is a steric crowding between a 5(*ax*)-methyl group and the carbon atoms C(1), C(2), and C(3) in the coplanar conformation of the vinyl-carbonyl skeleton. It was suggested that such crowding can be relieved by out-of-plane twisting of the carbonyl group and a value of *ca*. 30° was estimated for the interplanar angle. Then the smaller reactivity of (IIa) should be attributed to the reduced coplanarity with the consequent lower efficiency in the transmission of the electronic effect.

As expected for the introduction of an α-methyl group, compound (Ia) reacts more rapidly than (IIIa), $k_{\mathrm{Ia}} : k_{\mathrm{IIIa}}$ being 200—260 in ethanol. In addition to electronic effects,[1d] steric effects may be present.

The reactivity of our compounds with piperidine in ethanol can be compared with that of some β-chlorovinyl ketones.[5c] A comparison of derivative (IIIa) with 1-chloro-2-methylpent-1-en-3-one and 2-chlorocyclopent-1-en-1-yl methyl ketone seems reasonable.

In the first case, an open-chain derivative having unknown conformation and a β-hydrogen must be compared with a cyclic one having fixed *s-trans*-conformation and a β-CH_2 group. 1-Chloro-2-methylpent-1-en-3-one is 50 times more reactive than compound (IIIa). Since, in the reactions of *cis-p*-nitrophenylsulphonyl-β-chloroethylenes with cyclohexylamine and di-n-butylamine in methanol a β-methyl group decreases the substitution rate 11- and 144-fold respectively,[12] the different reactivity could be explained as due essentially to a substituent effect and to a minor extent to the different degree of coplanarity in the vinyl-carbonyl system. Further, 1-chloro-2-methylpent-1-en-3-one has an activation entropy (—31·2 cal mol^{-1} K^{-1} [5c]) higher by *ca*. 11 cal mol^{-1} K^{-1} than (IIIa); surprisingly, this indicates a higher ordering of the transition state, with respect to the initial state, for the cyclic than for the open-chain compound.

In the second case, 2-chlorocyclopent-1-en-1-yl methyl ketone is a *cis*-derivative with unknown conformation. It has been found to be *ca*. 5 times more reactive than (IIIa). The two compounds have similar activation parameters, as expected for the reactions of *cis*- and *trans*-isomers in the substitution at a vinylic centre.[1d]

Chloro- and bromo-derivatives (IIa) and (IIb) react with very similar rates, as is typical of the vinylic displacement when Cl and Br are the leaving halogen.

By examination of the solvent effect, we note that the substrates have comparable reactivities in ethanol and in dimethylformamide, $k(\mathrm{EtOH}) : k(\mathrm{Me_2N{\cdot}CHO})$ being (at 50 °C) 2·1 for (Ia), 0·7 for (IIa), and 0·4 for (IIb). Therefore the solvent effect is scarcely important and, moreover, at least for (Ia) and (IIa), $k(\mathrm{EtOH}) : k(\mathrm{Me_2N{\cdot}CHO})$ ratios approach unity as the temperature increases.

We thank Professor P. Beltrame for discussions. Financial aid of the Italian C.N.R. is acknowledged.

[1/1125 *Received*, 13*th October*, 1971]

[12] L. Maioli, G. Modena, and P. E. Todesco, *Boll. sci. Fac. Chim. ind. Bologna*, 1960, **18**, 66.