

Novel Reactions of Carbon Suboxide. Part 8.¹ Kinetic Study of the Reaction with Substituted 2-Hydroxybenzaldehyde Oximes

Leonardo Bonsignore, Giuseppe Loy, and Mario Secci*

Istituto di Chimica Farmaceutica, Tossicologica ed Applicata, Università, Via Ospedale 72, I-09124 Cagliari, Italy

Salvatore Cabiddu and Gioanna Gelli*

Istituto di Chimica Organica, Università, Via Ospedale 72, I-09124 Cagliari, Italy

The kinetics of the reaction of carbon suboxide with aryl-substituted 2-hydroxybenzaldehyde oximes to give coumarin derivatives have been studied. A Hammett plot gave a ρ value of *ca.* -1.5 , indicating that the reaction was promoted by electron-releasing groups *para* to the oxime function. Increasing the dielectric constant of the solvent raises the reaction rate; we have therefore proposed the formation of an ionic intermediate, after fast attack of carbon suboxide on the phenol hydroxy group.

In previous work²⁻⁷ carbon suboxide has been observed to react with aromatic azomethines, oximes, and hydrazones, bearing *ortho*-hydroxy, -amino, and -mercapto substituents, to give benzopyran, quinoline, and benzothiopyran derivatives. Some of us^{2,3} suggested that these reactions proceed by the rearrangement of an eight-membered-ring mesoionic intermediate, initially formed by attack of the carbon suboxide on the substrate; such an intermediate was isolated in some cases. However, Gotthardt and Hoffmann^{6,7} proposed that the same products were formed by rearrangement of a four-membered-ring intermediate (not isolated), obtained by [2 + 2] cycloaddition following initial attack by carbon suboxide.

In order to elucidate the mechanism, we undertook a kinetic study of the reaction of the 4- or 5-substituted 2-hydroxybenzaldehyde oximes (**1**) with carbon suboxide (**2**).

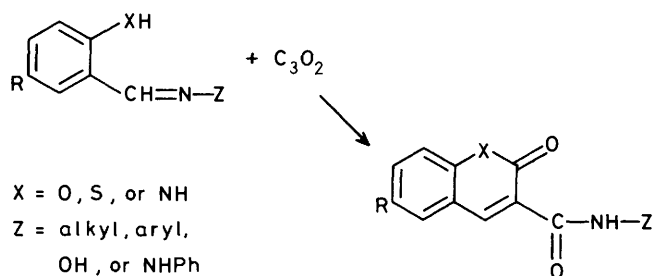
Results and Discussion

The coumarin derivatives (**3**) produced were characterized by two i.r. absorption bands at 1780 cm^{-1} and in the range $1710\text{--}1690\text{ cm}^{-1}$ corresponding, respectively, to lactone and amide carbonyl groups. The kinetic study was carried out by measuring the appearance rate of the i.r. band at 1780 cm^{-1} . Very similar coefficients were obtained when the band at $1710\text{--}1690\text{ cm}^{-1}$ was used. Attempts to calculate the reaction rate from observation of the decreasing intensity of the band at 3400 cm^{-1} (phenol OH) failed. This decrease was more rapid than the appearance of the carbonyl bands: in most cases a decrease corresponding to almost two half-lives was observed during mixing of the reaction solutions.

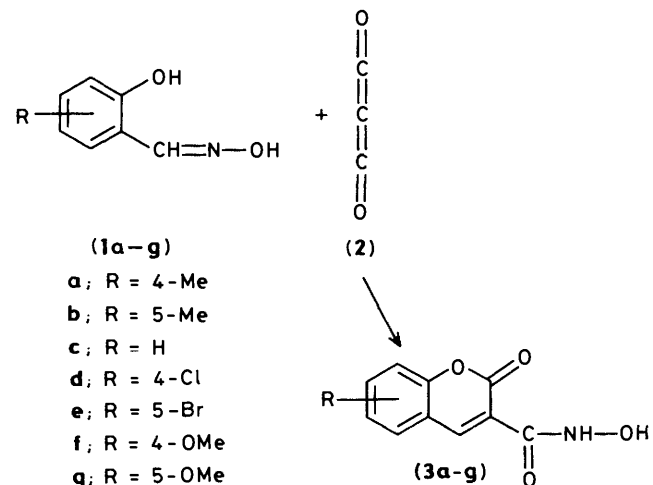
Standard kinetic runs were carried out in a 1,1,2,2-tetrachloroethane-diethyl ether mixture (8.5:1.5 v/v), in the temperature range $32.0\text{--}60.0\text{ }^{\circ}\text{C}$. Solvents such as tetrachloroethane, chloroform, and carbon tetrachloride are also suitable, but neat diethyl ether, used in previous work, does not allow analysis by i.r. spectroscopy.

Kinetic runs were initially carried out in commercial chloroform (reagent grade), containing 0.5% (v/v) ethanol as stabilizing agent. Observed kinetic coefficients were higher than those obtained with chloroform stabilized with 60 p.p.m. of 2-methylbut-2-ene (used to avoid decomposition of carbon suboxide by the acidic hydrogen of ethanol; carbon suboxide reacts with carboxylic acids, alcohols, *etc.* to give malonic acid derivatives^{8,9}).

Because the presence of oxygenated solvents seemed to facilitate the reaction, we started to add definite amounts of diethyl ether to the chlorinated solvent. The amount of 15% (v/v) was chosen after some preliminary experiments with



Scheme 1.



chloroform containing 5% and 10% of diethyl ether. The reaction rate was the same as with mixtures containing 10 or 15% of diethyl ether.

Kinetic measurements were also carried out in neat 1,1,2,2-tetrachloroethane and in neat chloroform (Table 2): the kinetic coefficients were much lower than those observed when the mixture with diethyl ether was used.

The reactant concentrations were $1.5 \times 10^{-2}\text{ mol l}^{-1}$ for 2-hydroxybenzaldehyde oximes (**1**) and *ca.* $3.0 \times 10^{-2}\text{ mol l}^{-1}$ for carbon suboxide (**2**): in the case of the kinetic runs in neat 1,1,2,2-tetrachloroethane or chloroform the concentration of (**2**) was $6.0 \times 10^{-2}\text{ mol l}^{-1}$.

Ring substitution on the oxime (**1**) was studied by measuring the kinetics of the reactions of (**2**) with the series of oximes (**1a-e**).

Table 1. Kinetic coefficients $10^3k/l \text{ mol}^{-1} \text{ s}^{-1}$ for reactions of oximes (**1**) (0.015 mol l^{-1}) with carbon suboxide (**2**) (*ca.* 0.03 mol l^{-1}) in 1,1,2,2-tetrachloroethane–diethyl ether (8.5:1.5 v/v)^a

<i>T</i> /°C	Compound				
	(1a) 4-Me	(1b) 5-Me	(1c) H	(1d) 4-Cl	(1e) 5-Br
32.0		10.14 ± 0.07			2.30 ± 0.02
40.0	21.34 ± 0.16	14.80 ± 0.66	11.99 ± 0.20	4.91 ± 0.06	3.07 ± 0.02
50.0	32.93 ± 1.13	22.47 ± 0.66	19.29 ± 0.49	7.93 ± 0.18	4.78 ± 0.14
60.0	50.40 ± 0.91	34.34 ± 0.05	28.48 ± 0.26	11.82 ± 0.25	7.71 ± 0.21

Activation parameters:

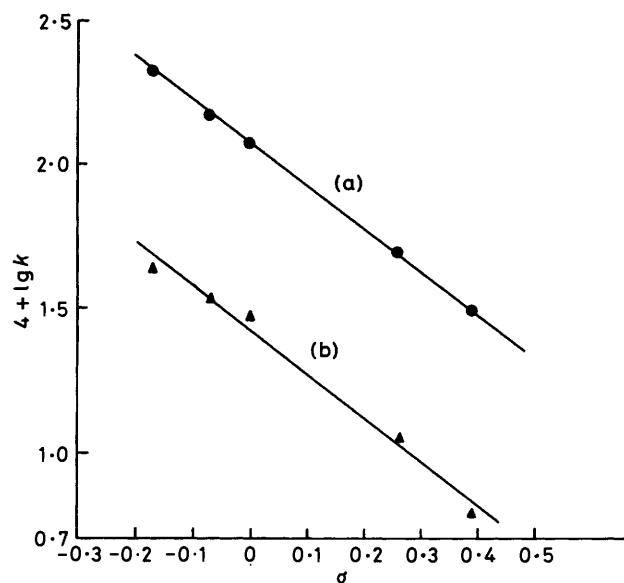
(1a) + (2): $\lg A = 4.55 \pm 0.08$; $E_{\text{act}} = 37.3 \pm 0.5 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -165 \pm 2 \text{ J mol}^{-1} \text{ K}^{-1}$
 (1b) + (2): $\lg A = 4.28 \pm 0.06$; $E_{\text{act}} = 36.7 \pm 0.4 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -172 \pm 2 \text{ J mol}^{-1} \text{ K}^{-1}$
 (1c) + (2): $\lg A = 4.35 \pm 0.24$; $E_{\text{act}} = 35.6 \pm 1.5 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -171 \pm 7 \text{ J mol}^{-1} \text{ K}^{-1}$
 (1d) + (2): $\lg A = 4.06 \pm 0.21$; $E_{\text{act}} = 38.2 \pm 1.3 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -176 \pm 6 \text{ J mol}^{-1} \text{ K}^{-1}$
 (1e) + (2): $\lg A = 3.76 \pm 0.27$; $E_{\text{act}} = 37.6 \pm 1.7 \text{ kJ mol}^{-1}$; $\Delta S^\ddagger = -182 \pm 8 \text{ J mol}^{-1} \text{ K}^{-1}$

^a Errors shown are standard deviations.**Table 2.** Kinetic coefficients for reactions of the oximes (**1**) (0.015 mol l^{-1}) with carbon suboxide (**2**) (*ca.* 0.06 mol l^{-1}) at 40.0 °C in 1,1,2,2-tetrachloroethane

Compound	$10^3k/l \text{ mol}^{-1} \text{ s}^{-1}$
(1a) 4-Me	4.40 ± 0.16
(1b) 5-Me	3.39 ± 0.06
(1c) H	2.94 ± 0.03 ^a
(1d) 4-Cl	1.11 ± 0.01
(1e) 5-Br	0.62 ± 0.01

^a An analogous run in chloroform gave $10^3k = 0.63 \pm 0.05 \text{ l mol}^{-1} \text{ s}^{-1}$.**Table 3.** Kinetic coefficients $10^3k/l \text{ mol}^{-1} \text{ s}^{-1}$ for the reactions of some oximes (**1**) (0.015 mol l^{-1}) with carbon suboxide (**2**) (*ca.* 0.045 mol l^{-1}) in various solvents, at 50 °C

Solvents (85:15, v/v)	Compound		
	(1a)	(1b)	(1c)
CCl ₄ –Et ₂ O	7.45 ± 0.05	5.18 ± 0.10	3.92 ± 0.03
CHCl ₃ –Et ₂ O	18.41 ± 0.06	12.13 ± 1.16	11.01 ± 0.13

**Figure 1.** Hammett plots for the reactions of (**1a**–**e**) with (**2**) in (a) 1,1,2,2-tetrachloroethane–diethyl ether (8.5:1.5) and (b) 1,1,2,2-tetrachloroethane at 40.0 °C

Systematic measurements at 40.0 and 50.0 °C (Table 1) showed a progressive decrease in the kinetic coefficients on going from (**1a**) to (**1e**). Hammett plots were drawn using σ_p and σ_m values; they are linear showing negative slopes (ρ) of -1.49 ± 0.01 at 40.0 °C and -1.47 ± 0.04 at 50.0 °C. The Hammett plots for reactions in 1,1,2,2-tetrachloroethane–diethyl ether and in neat tetrachloroethane are drawn in Figure 1. An analogous ρ value (-1.53 ± 0.09) was obtained

from the Hammett plots of kinetic coefficients observed for reaction in neat 1,1,2,2-tetrachloroethane (Table 2).

The measurements were extended to other temperatures; activation parameters, obtained by Arrhenius and Eyring plots, are summarized in Table 1. When the methoxy group was used as substituent, no measure of kinetic coefficients was possible: a yellow complex was immediately observed on mixing the solutions of (**2**) and (**1f**) or (**1g**). An analogous complexation was observed on treatment of solutions of methoxy- or dimethylamino-benzene with (**2**). Because of this complex the concentration of available carbon suboxide for the addition reaction was unknown; in fact repeated runs on (**1f** and **g**), using the total concentration of (**2**), gave poor results and low values on the Hammett plot; moreover plots of $\ln c(\mathbf{2})/c(\mathbf{1})$ versus time were often not linear. Attempts to calculate the extent of complexation of ¹H n.m.r. analysis, failed.

An indication of the solvent effect on the reaction is given by comparison of kinetic coefficients for (**1a**, **b**, and **c**) measured at 50.0 °C, in chloroform (dielectric constant $D = 4.80$) and carbon tetrachloride ($D = 2.24$) as well as the usual 1,1,2,2-tetrachloroethane ($D = 8.08$), all in the presence of 15% (v/v) of diethyl ether ($D = 4.34$). A linear dependence of $\ln k$ on $(D - 1)/(2D + 1)$ (where D is obtained by linear combination of the dielectric constant of the chlorinated solvent with that of diethyl ether), as expected for a reaction between dipolar molecules,¹⁰ was observed (Figure 2), and tetrachloroethane, which has the highest dielectric constant, proved the best of the three solvents. This suggests that the transition state of the rate-controlling step of the reaction is more polar than the reactant system.

In order to elucidate the action of diethyl ether on the reaction, blank experiments on phenol and 4-methylphenol were carried out by treatment of their solutions in 1,1,2,2-tetrachloroethane–diethyl ether and in neat tetrachloroethane with a suitable amount of (**2**).

In the presence of diethyl ether the phenol hydroxy group i.r.

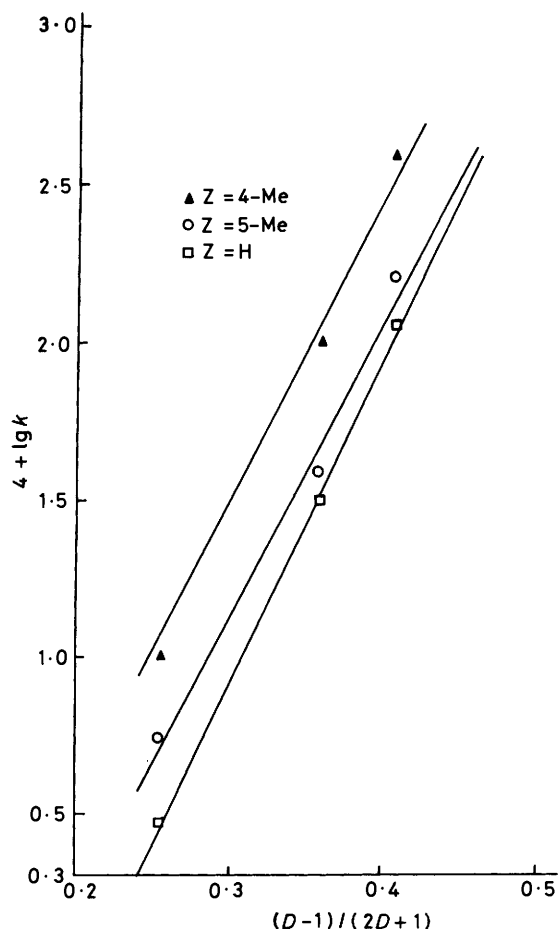


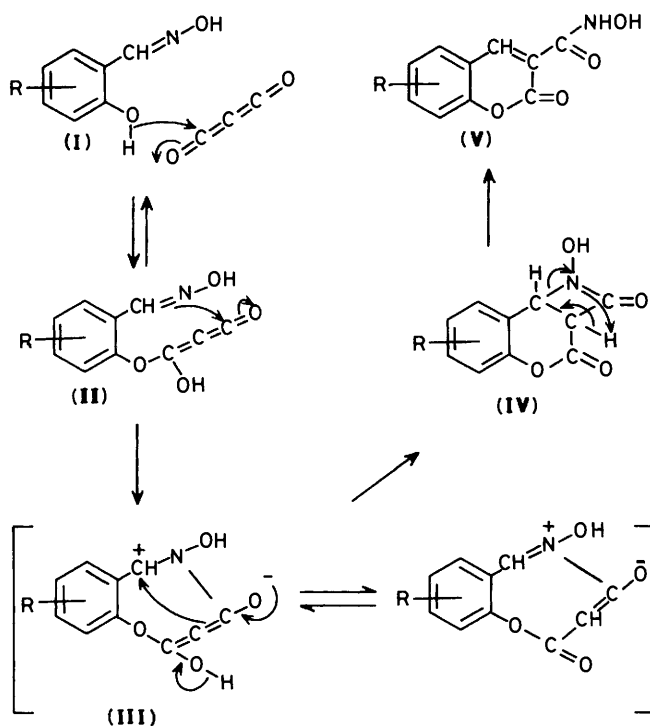
Figure 2. Linear dependence of the kinetic coefficient on the dielectric constant of the solvent

band disappeared, in few minutes, to the extent of 70%, while in the neat chlorinated solvent the extent of disappearance was only 13%.

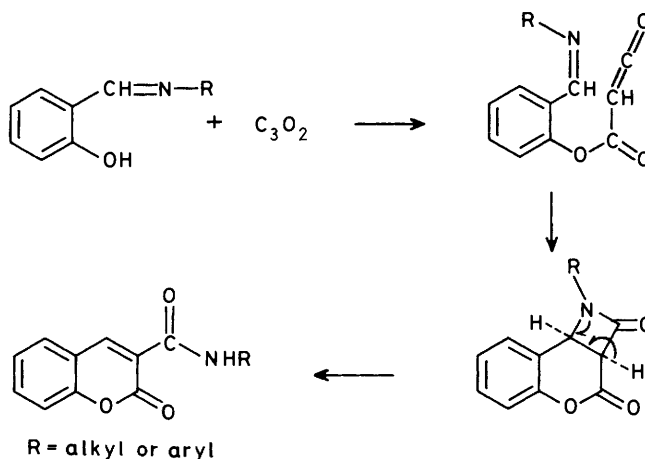
Therefore it seems likely (see Scheme 2) that the first fast step of the reaction of (1) with (2) is attack of the carbon suboxide on the phenol hydroxy group to give an enol intermediate (II); in fact, the band of the hydroxy group disappears immediately, as just described. Because the reaction is promoted by electron-releasing substituents *para* to the oxime function and by the more polar solvents, we suggest that a rate-determining step follows, *i.e.* attack of the carbonyl carbon on oxime nitrogen, providing an ionic, eight-membered-ring intermediate (III), which gives the coumarin derivative (V) through the intermediate (IV).

An ionic eight-membered-ring intermediate was isolated in the case of the reaction of carbon suboxide with azomethines;³ in the present case, the intermediate (III) is formed in diethyl ether or in diethyl ether-chloroform solution, but attempts at isolation and characterization were unsuccessful, because of its transformation into compound (V).

For analogous reactions, Gotthardt and Hoffmann^{6,7} have proposed attack of C_3O_2 on OH to give a ketene, followed by $[2 + 2]$ cycloaddition (Scheme 3). This mechanism seems unlikely, under our conditions, because (i) during the kinetic runs the band at 1780 cm^{-1} (lactone) appears gradually, whereas the proposed ketene formation would be immediate; and (ii) formation of the proposed cyclic imide would probably involve a $[\pi_2s + \pi_2a]$ cycloaddition, which appears unlikely in our case on the basis of molecular models.



Scheme 2.



Scheme 3.

Experimental

M.p.s. were measured with a hot-stage microscope. I.r. spectra were recorded with a Perkin-Elmer 1310 spectrophotometer, and ^1H n.m.r. spectra with a Varian FT 80A instrument (Me_4Si as internal standard). Elemental analyses were carried out on a Carlo Erba 1106 Elemental Analyzer. Reagent-grade commercially available reagents and solvents were used.

The carbon suboxide was prepared from pyrolysis of di-*O*-acetyltartaric anhydride.¹¹ The concentration of carbon suboxide in the various solvents employed was determined by treatment with water and titration of the resulting malonic acid with 0.01M-NaOH (phenolphthalein as indicator).¹² The 2-hydroxybenzaldehyde oxime (1c) (Fluka A.G.) was crystallized before use; the derivatives (1a,b and d-g) were prepared as described in the literature from the corresponding 2-hydroxy aldehydes,¹³⁻¹⁷ and were purified and dried rigorously.

The *N*-hydroxy-2-oxo-2*H*-1-benzopyran-3-carboxamides (3a-g) (coumarins) were obtained as previously described²

from 2-hydroxybenzaldehyde oximes (**1a—g**) and carbon suboxide. The reaction yields were calculated after purification by column chromatography and recrystallization; the crude product consists solely of the mesoionic intermediate and the coumarin derivative.

N-Hydroxy-7-methyl-2-oxo-2H-1-benzopyran-3-carboxamide (**3a**) (58%) had m.p. 128–130 °C (from EtOH) (Found: C, 60.1; H, 4.1; N, 6.3. $C_{11}H_9NO_4$ requires C, 60.3; H, 4.1; N, 6.4%); $\nu_{max.}(CHCl_3)$ 3 570 and 3 220 (NH and OH), and 1 770 and 1 680 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 2.30 (s, 3 H, Me), 3.63 (s, 1 H, OH), 6.66–7.23 (m, 3 H, Ph), 8.43 (s, 1 H, 4-H), and 10.7 (s, 1 H, NH).

N-Hydroxy-7-methoxy-2-oxo-2H-1-benzopyran-3-carboxamide (**3f**) (63%), purified by column chromatography on silica gel [eluant hexane–ethyl ether (3:1)], had m.p. 154–155 °C (from EtOH) (Found: C, 56.25; H, 3.95; N, 5.9. $C_{11}H_9NO_5$ requires C, 56.2; H, 3.9; N, 6.0%); $\nu_{max.}(CHCl_3)$ 3 520 and 3 340 (NH and OH), and 1 750, 1 715, and 1 680 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 3.93 (s, 3 H, Me), 6.54–7.71 (m, 3 H, Ph), 8.40 (s, 1 H, 4-H), 8.78 (s, 1 H, OH), and 8.90 (s, 1 H, NH).

7-Chloro-*N*-hydroxy-2-oxo-2H-1-benzopyran-3-carboxamide (**3d**) (68%) had m.p. 135 °C (from EtOH) (Found: C, 50.0; H, 2.5; N, 5.75. $C_{10}H_6ClNO_4$ requires C, 50.1; H, 2.5; N, 5.8%); $\nu_{max.}(CHCl_3)$ 3 550 and 3 210 (NH and OH), and 1 755, 1 720, and 1 690 cm^{-1} (C=O); $\delta_H(CDCl_3)$ 6.17 (s, 1 H, OH), 6.38–7.43 (m, 3 H, Ph), 8.14 (s, 1 H, 4-H), and 9.29 (s, 1 H, NH).

Kinetics.—Solutions of (**1**) and (**2**) were mixed in appropriate proportions [$c(1)_0 = 0.015 \text{ mol l}^{-1}$; $c(2)_0 = ca. 0.03 \text{ mol l}^{-1}$]. The mixture was quickly introduced into a thermostatically controlled 1 mm sodium chloride cell (Beckmann FH-01 variable-temperature cell), positioned in an i.r. spectrophotometer. The temperature was maintained constant to within ± 0.2 °C. Quantitative determinations of [(**3**)] were made on the band at 1 780 cm^{-1} , using the baseline method and molar extinction coefficients obtained by calibration, straight lines.

Kinetic runs were carried out up to quantitative formation of the product, but the concentration values to 1–2 half-lives were employed to calculate the rate coefficients by a second-order rate equation (i)

$$\{1/[c(2) - c(1)_0]\} \ln \{[c(2)_0 - c(3)]/[c(1)_0 - c(3)]\} = kt + \text{const.} \quad (i)$$

Most runs were carried out in 1,1,2,2-tetrachloroethane–diethyl ether (8.5:1.5, v/v), in the temperature range 32.0–60.0 °C. In one case (**1b**), chloroform and carbon tetrachloride–diethyl ether were also used as solvents. Kinetic runs were also carried out, at 40.0 °C, in 1,1,2,2-tetrachloroethane and, in one case (**1c**), in chloroform as solvent. Average results from duplicate runs are given in Tables 1 and 2.

Acknowledgements

We thank Prof. P. Beltrame for discussions. This work was supported by the National Council of Research (CNR, Rome) and by the Italian Ministry of Education (M.P.I.).

References

- 1 Part 7, L. Bonsignore, S. Cabiddu, G. Loy, and D. Secci, *Heterocycles*, 1987, **26**, 1619.
- 2 L. Bonsignore, S. Cabiddu, G. Loy, and M. Secci, *Tetrahedron Lett.*, 1983, **24**, 5013.
- 3 L. Bonsignore, S. Cabiddu, G. Loy, and M. Secci, *Heterocycles*, 1984, **22**, 2587.
- 4 L. Bonsignore, S. Cabiddu, G. Loy, and M. Secci, *Synthesis*, 1984, 266.
- 5 L. Bonsignore, S. Cabiddu, G. Loy, and M. Secci, *J. Heterocycl. Chem.*, 1985, **22**, 463.
- 6 H. Gotthardt and N. Hoffmann, *Liebigs Ann. Chem.*, 1985, 529.
- 7 H. Gotthardt and N. Hoffmann, *Liebigs Ann. Chem.*, 1985, 901.
- 8 G. Haggeloch and E. Feess, *Chem. Ber.*, 1951, **84**, 730.
- 9 T. Kappe and E. Ziegler, *Angew. Chem., Int. Ed. Engl.*, 1974, **13**, 491.
- 10 E. S. Amis, 'Kinetics of Chemical Change in Solution,' MacMillan, New York, 1949, p. 175.
- 11 L. Crombie, P. A. Gilbert, and R. P. Houghton, *J. Chem. Soc. C*, 1968, 130.
- 12 E. A. Pauw, *Recl. Trav. Chim. Pays-Bas*, 1936, **55**, 215.
- 13 P. Chuit and F. Bolsing, *Bull. Soc. Chim. Fr.*, 1906, **35**, 136.
- 14 C. Postmus, I. A. Kaye, C. A. Graig, and R. S. Matthews, *J. Org. Chem.*, 1964, **29**, 2693.
- 15 K. Auwers and A. J. Walker, *Ber. Dtsch. Chem. Ges.*, 1898, **31**, 3037.
- 16 F. Spath and K. Klager, *Ber. Dtsch. Chem. Ges.*, 1934, **67**, 859.
- 17 J. Shinoda, *J. Chem. Soc.*, 1927, 1983.

Received 10th July 1987; Paper 7/1237