# Cyclisation of Nitrile Imides with Alkenyl Substituents: Routes to 1,2-Benzodiazepines and Cyclopropa[*c*]cinnolines

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Treatment of the chloroglyoxylate phenylhydrazones (1) with triethylamine affords 1*H*-1,2-benzodiazepines and/or 1a,7b-dihydro-1*H*-cyclopropa[*c*]cinnolines in substantial yields. Mechanisms are proposed which involve different modes of intramolecular rearrangement of the first-formed nitrile imides (8).

We have reported [1] that the reactions of the chloroglyoxylate hydrazones (1a—c) with triethylamine lead to fully unsaturated 1*H*-1,2-benzodiazepines (2a—c). Later, it was found [2] that, under similar conditions, the related chloro-hydrazones (1j and k) afford 1a,7b-dihydro-1*H*-cyclopropa[*c*]cinnolines (3j and k). This dramatic change in chemical behaviour prompted us to study hydrazones containing a wider variety of substituents at the ethylenic function in order to explore the synthetic applicability of these two different types of intramolecular ring closure and their mechanisms. Compounds (1d—i) were therefore examined.

## RESULTS AND DISCUSSION

As already reported,[1,2] the chloro-hydrazones (1a—c, j, and k) were prepared from the appropriate anilines (4) through diazotization and coupling with ethyl 2-chloroacetoacetate. This sequence was also followed in the preparation of (1e and g), but it was unsuccessful for (1d, f, h, and i): diazotization of the corresponding *ortho*-substituted anilines produced only cinnoline derivatives.[3] Compounds (1d, f, h, and i) were synthesized by a procedure involving (i) diazotization of anilines of type (5), (ii) coupling of the intermediate diazonium salts with ethyl 2-chloroacetoacetate to give compounds (6), and (iii) dehydration of the latter in the presence of toluene-*p*-sulphonic acid.

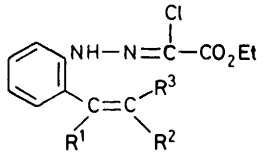
The assignment of the *trans*-configuration of the ethylenic function in compounds (1a, b, and d) is unequivocal in view of the observed coupling constant of

[1] L. Garanti, A. Scandroglio, and G. Zecchi, *Tetrahedron Letters*, 1975, 3349.

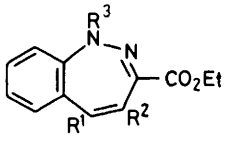
[2] L. Garanti, A. Vigevani, and G. Zecchi, *Tetrahedron Letters*, 1976, 1527.

[3] J. C. E. Simpson and O. Stephenson, *J. Chem. Soc.*, 1942, 353; J. C. E. Simpson, *ibid.*, 1943, 447.

the olefinic protons (16 Hz). Such direct evidence is lacking in the case of (1c): the n.m.r. signal of the olefinic protons is overlapped by the aromatic multiplet; however, the assigned structure was shown to be correct by an independent synthesis of the corresponding *cis*-isomer (*J* 12 Hz). For compounds (1j and k) the



(1)



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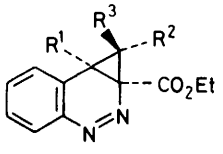

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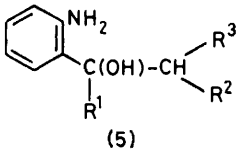
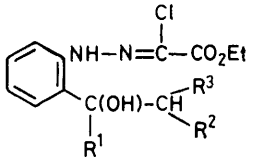
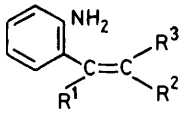


(5)



(6)



(4)

(1a),(2a),(4a) $R^1 = R^3 = H$, $R^2 = CO_2Et$
(1b),(2b),(4b) $R^1 = R^3 = H$, $R^2 = CN$
(1c),(2c),(4c) $R^1 = R^3 = H$, $R^2 = Ph$
(1d),(2d),(5d) (6d) $R^1 = R^3 = H$, $R^2 = Me$
(1e),(2e),(4e) $R^1 = R^2 = R^3 = H$
(1f),(2f),(5f),(6f) $R^1 = Ph$, $R^2 = R^3 = H$
(1g),(2g),(4g) $R^1 = Me$, $R^2 = R^3 = H$
(1h),(3h),(5h),(6h) $R^1 = R^2 = R^3 = Me$
(1i),(3i),(5i),(6i) $R^1 = Ph$, $R^2 = R^3 = Me$
(1j),(3j),(4j) $R^1 = H$, $R^2 = CO_2Et$, $R^3 = Me$
(1k),(3k),(4k) $R^1 = H$, $R^2 = CO_2Et$, $R^3 = Ph$

assigned stereochemistry is consistent with that of the starting materials for their synthesis, *i.e.* α-methyl-[4] and α-phenyl-[5] *o*-nitrocinnamic acids.

The reactions of the chloro-hydrazones (1) with triethylamine (4 mol. equiv.) were carried out in boiling benzene. Since in the early experiments [1] compounds (1a—c) were treated with 1 mol. equiv. of triethylamine, the reactions of these substrates were repeated under the new conditions. Reaction times, products, and yields are reported in Table 1, which also includes the previously communicated results concerning (1j and k).

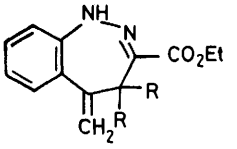
Structural assignments of the products were made on the basis of elemental analyses and i.r. and $^1H$ n.m.r. spectra (see Tables 2 and 3). The strong i.r. absorption at *ca.* 3 300 $cm^{-1}$ of the 1*H*-1,2-benzodiazepines (2) and (7) compares well with literature data for similar compounds,[6,7] and excludes 3*H*- and 5*H*-tautomeric formulae.* Occasionally, further support for the assigned structure was obtained from mass or $^{13}C$ n.m.r. spectra.

TABLE 1

Reactions of chloroglyoxylate phenylhydrazones (1) with triethylamine

| Substrate | Time (h) | Product | Yield (%) |
|---|---|---|---|
| (1a) | 0.25 | (2a) | 68 |
| (1b) | 0.25 | (2b) | 65 |
| (1c) | 2 | (2c) | 54 [a] |
| (1d) | 5 | (2d) | 66 [a] |
| (1e) | 2 | (2e) | 17 [a] |
| (1f) | 6 | (2f) | 75 |
| (1g) | 8 | (2g) + (7a) | 47 + 25 [a] |
| (1h) | 25 | (3h) + (7b) | 65 + 10 [b] |
| (1i) | 15 | (3i) | 68 [a] |
| (1j) | 2 | (3j) | 78 |
| (1k) | 1 | (3k) | 80 |

[a] By silica gel column chromatography with diethyl ether–light petroleum (1 : 1) as eluant. [b] By silica gel column chromatography with 6 : 3 : 1 light petroleum–diethyl ether–triethylamine as eluant.



(7) a; R = H
b; R = Me

The above products are stable compounds with the exception of (2e) and (3h), which decompose to give unidentified substances. A control experiment showed that the isomeric 1,2-benzodiazepines (2g) and (7a), both arising from (1g), are not interconverted in boiling benzene in the presence of triethylamine.

The results so far reported show that the cyclisation leading to 1,2-benzodiazepines occurs with electron-withdrawing as well as electron-donating groups on the ethylenic function of the starting chloro-hydrazones. Only in cases where a double substitution is present at the end of the π-electron system (independent of the nature of the substituents), does formation of cyclopropa-[*c*]cinnolines take place as an alternative pathway. The only exception is compound (1h), which affords both products.

The following considerations help to explain the experimental findings. Since chloro-hydrazones of type (1) are well known to generate nitrile imides in the presence of tertiary amines, the intervention of the intermediates (8) seems unquestionable.† The benzodiazepine skeleton may be formed from these intermediates

* 1,1-Diaryl-3-diazoalk-1-enes have been shown to cyclise giving 3*H*-1,2-benzodiazepines, which however rearrange to the corresponding 1*H*-isomers under basic conditions.[6]

† Nitrile imides bearing an alkenyl substituent have been reported recently to undergo intramolecular 1,3-dipolar cycloadditions.[8] Such a reaction is probably precluded in the case of compounds (8) by geometrical constraints.

[4] K. G. Cunningham, G. T. Newbold, F. S. Spring, and J. Stark, *J. Chem. Soc.*, 1949, 2091.

[5] DeLos F. De Tar, *Org. Synth.*, Coll. Vol. IV, 1963, p. 730.

[6] J. T. Sharp, R. H. Findlay, and P. B. Thorogood, *J.C.S. Perkin I*, 1975, 102.

[7] T. Tsuchiya, J. Kurita, H. Igeta, and V. Snieckus, *J.C.S. Chem. Comm.*, 1974, 640.

[8] L. Garanti, A. Sala, and G. Zecchi, *J. Org. Chem.*, 1977, in the press.

TABLE 2

Physical and analytical data of compounds (2), (3), and (7)

| Compd. | M.p. (°C) | Cryst. solvent | Colour of crystals | Formula | Required (%) C | H | N | Found (%) C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| (2a) | 114 | $Et_2O$–$Pr^i_2O$ | Red | $C_{15}H_{16}N_2O_4$ | 62.5 | 5.6 | 9.7 | 62.6 | 5.5 | 9.8 |
| (2b) | 168 | $Et_2O$–$Pr^i_2O$ | Red | $C_{13}H_{11}N_3O_2$ | 64.7 | 4.6 | 17.4 | 64.8 | 4.6 | 17.6 |
| (2c) | 131 | $Et_2O$–$Pr^i_2O$ | Red | $C_{18}H_{16}N_2O_2$ | 73.9 | 5.5 | 9.6 | 73.7 | 5.4 | 9.7 |
| (2d) | 119 | $Pr^i_2O$ | Red | $C_{13}H_{14}N_2O_2$ | 67.8 | 6.1 | 12.2 | 67.7 | 6.2 | 12.2 |
| (2e) | 105 | $Et_2O$–$Pr^i_2O$ | Red | $C_{12}H_{12}N_2O_2$ | 66.6 | 5.6 | 12.9 | 66.5 | 5.5 | 12.8 |
| (2f) | 180 | $Et_2O$–$Pr^i_2O$ | Red | $C_{18}H_{16}N_2O_2$ | 73.9 | 5.5 | 9.6 | 73.6 | 5.3 | 9.4 |
| (2g) | 105 | $Pr^i_2O$ | Red | $C_{13}H_{14}N_2O_2$ | 67.8 | 6.1 | 12.2 | 67.6 | 6.0 | 12.1 |
| (3h) | 39 | Light petroleum | Pale yellow | $C_{15}H_{18}N_2O_2$ | 69.7 | 7.0 | 10.8 | 69.8 | 7.1 | 10.8 |
| (3i) | 95 | Light petroleum | Pale yellow | $C_{20}H_{20}N_2O_2$ | 75.0 | 6.3 | 8.7 | 74.8 | 6.3 | 8.9 |
| (3j) | 51 | Light petroleum | Pale yellow | $C_{16}H_{18}N_2O_4$ | 63.6 | 6.0 | 9.3 | 63.4 | 6.1 | 9.1 |
| (3k) | 89 | Light petroleum–$Et_2O$ | Pale yellow | $C_{21}H_{20}N_2O_4$ | 69.2 | 5.5 | 7.7 | 69.3 | 5.3 | 7.6 |
| (7a) | 95 | Light petroleum | White | $C_{13}H_{14}N_2O_2$ | 67.8 | 6.1 | 12.2 | 67.6 | 6.0 | 12.1 |
| (7b) | 114 | Light petroleum | White | $C_{15}H_{18}N_2O_2$ | 69.7 | 7.0 | 10.8 | 69.7 | 6.8 | 10.6 |

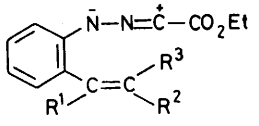
TABLE 3

Spectral data of compounds (2), (3), and (7) [a]

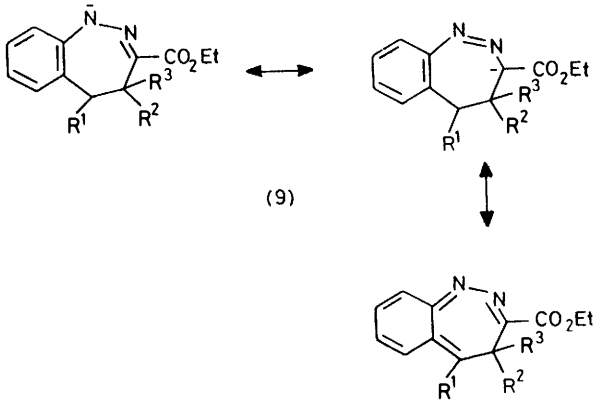
| Compound | $\nu_{max.}$/cm$^{-1}$ [b] | $^1$H N.m.r. (δ) [c] |
|---|---|---|
| (2d) | 3 280 (NH), 1 720 (CO) | 1.27 (3 H, t, $CH_2Me$), 1.88 (3 H, d, *J ca.* 1 Hz, Me), 4.22 (2 H, q, $CH_2Me$), 6.7—7.3 (5 H, m, ArH and CH=), 7.8br (1 H, s, NH) |
| (2e) [d] | 3 260 (NH), 1 720 (CO) | 1.26 (3 H, t, $CH_2Me$), 4.26 (2 H, q, $CH_2Me$), 6.20 (1 H, d, *J* 12 Hz, CH=), 6.5—7.4 (5 H, m, ArH and CH=), 7.9br (1 H, s, NH) |
| (2f) | 3 270 (NH), 1 720 (CO) | 1.10 (3 H, t, $CH_2Me$), 4.07 (2 H, q, $CH_2Me$), 6.4—7.4 (10 H, m, ArH and CH=), 8.0br (1 H, s, NH) |
| (2g) | 3 290 (NH), 1 720 (CO) | 1.26 (3 H, t, $CH_2Me$), 2.17 (3 H, d, *J ca.* 1 Hz, Me), 4.21 (2 H, q, $CH_2Me$), 6.37 (1 H, q, *J ca.* 1 Hz, CH=), 6.7—7.4 (4 H, m, ArH), 7.9br (1 H, s, NH) |
| (3h) | 1 730 (CO) | 0.42 (3 H, s, *endo*-1-Me), 1.37 (3 H, t, $CH_2Me$), 1.61 (3 H, s, Me), 1.72 (3 H, s, Me), 4.37 (2 H, q, $CH_2Me$), 7.2—7.6 (3 H, m, ArH), 7.9—8.2 (1 H, m, ArH) |
| (3i) | 1 740 (CO) | 0.58 (3 H, s, *endo*-1-Me), 1.25 (3 H, t, $CH_2Me$), 1.75 (3 H, s, Me), 4.26 (2 H, q, $CH_2Me$), 6.6—7.6 (8 H, m, ArH), 8.20 (1 H, dd, *J* 8 and 2 Hz, ArH) |
| (7a) | 3 280 (NH), 1 720 (CO) | 1.37 (3 H, t, $CH_2Me$), 3.70 (2 H, s, $CH_2$), 4.34 (2 H, q, $CH_2Me$), 5.00, 5.29 (2 H, AB, *J ca.* 1 Hz, $CH_2$=), 6.7—7.5 (4 H, m, ArH), 8.7br (1 H, s, NH) |
| (7b) [e] | 3 300 (NH), 1 715 (CO) | 1.34 (3 H, t, $CH_2Me$), 1.65, 1.70 (6 H, two s, two Me), 4.30 (2 H, q, $CH_2Me$), 5.0—5.2 (2 H, m, $CH_2$=), 6.6—7.3 (4 H, m, ArH), 8.2br (1 H, s, NH) |

[a] For compounds (2a—c) and (3j and k) see refs. 1 and 2, respectively. [b] Nujol. [c] Solvent $(CD_3)_2CO$ for (2), $CDCl_3$ for (3) and (7). [d] $^{13}$C N.m.r. spectrum [20 MHz; $(CD_3)_2CO$; p.p.m. from internal $Me_4Si$]: δ 14.3, 61.5, 120.5, 125.8, 126.2, 130.4, 131.6, 132.0, 140.8, 148.0, 149.8, and 164.2. [e] Mass spectrum: *m/e* 258 ($M^+$, 18%), 243 (16), 217 (100), 171 (66), and 143 (16).

through intramolecular nucleophilic attack of the olefinic double bond on the electron-deficient carbon atom



(8)



(9)

of the nitrile imide group. This closure, which can be seen as a 1,7-electrocyclic reaction, affords the novel intermediates (9), possessing some dipolar character. Rearrangement of (9) to the final benzodiazepines could occur by prototropic migration from appropriate positions. Thus, fully unsaturated 1*H*-1,2-benzodiazepines (2) are formed when $R^3$ = H, and the formation of 5-methylene-4,5-dihydro-1*H*-1,2-benzodiazepines (7) occurs as a competitive or alternative reaction in cases where $R^1$ = Me.

Since it is reasonable to suppose that all the substrates are able to generate intermediates of type (9), the problem arises as to how these intermediates evolve if prototropic rearrangements are precluded by the absence of hydrogen atoms in the appropriate positions. It may be that the dipolar intermediates (9) collapse to the tricyclic products (3) *via* a disrotatory 1,6-electrocyclic process similar to that involved in the rearrangement of oxepins to benzene oxides [9] and that of diazacycloheptatrienes to diazanorcaradienes.[10] Within this hypothesis, a steric preference must be invoked to account for the stereospecific formation of the isomer with $R^3$ in the *endo* position.

Alternatively, the ring closure leading to (9) may occur in a reversible fashion in cases where a subsequent

[9] G. B. Gill and M. R. Willis, ' Pericyclic Reactions,' Chapman and Hall, London, 1974, p. 154.

[10] A. Steigel, J. Sauer, D. A. Kleier, and G. Binsch, *J. Amer. Chem. Soc.*, 1972, **94**, 2770.

prototropic rearrangement to a stable system is not possible. If so, the tricyclic compounds (3) could arise directly from (8) through a carbene-like concerted cheletropic reaction of the nitrile imide group. Thus, the formation of (3j and k) would parallel the stereospecific addition of singlet carbenes to olefins.[11]

## EXPERIMENTAL

I.r. spectra were measured with a Perkin-Elmer 377 spectrophotometer, and $^1$H n.m.r. spectra with a Varian A-60A instrument ($Me_4Si$ as internal standard). M.p.s were determined with a Büchi apparatus. Light petroleum refers to the fraction of b.p. 40—60 °C. All organic solutions were dried over anhydrous sodium sulphate.

The following amines were prepared according to literature methods: (4a),[12] (4b),[13] (4c),[14] (4e),[15] (4g),[16] (5f),[17] (5h),[18] and (5i).[18]

Spectral (i.r. and n.m.r.) and analytical data of the chlorohydrazones (1) and (6) are available as Supplementary Publication No. SUP 22088 (3 pp.).*

1-(2-*Aminophenyl*)*propan*-1-*ol* (5d).— 2-Aminobenzaldehyde (6.0 g) was treated with ethylmagnesium bromide [from ethyl bromide (16.4 g)] according to the procedure described for (5f).[17] The amine (5d) (6.3 g) was obtained as a viscous oil of *ca.* 95% purity (n.m.r. analysis); δ ($CDCl_3$) 0.93 (3 H, t, *J* 7 Hz, Me), 1.6—2.2 (2 H, m, $CH_2$), 3.5br (3 H, s, $NH_2$ and OH), 4.50 (1 H, t, *J* 7 Hz, CH), and 6.5—7.3 (4 H, m, aromatic).

*Ethyl* 3-(2-*Aminophenyl*)-2-*methylprop*-2-*enoate* (4j).—A solution of tin(II) chloride dihydrate (4.95 g) in concentrated hydrochloric acid (55 ml) was slowly added to a solution of ethyl 3-(2-nitrophenyl)-2-methylprop-2-enoate [4] (5.2 g) in acetic acid (50 ml) at 15 °C. Zinc powder (14.3 g) was then added in portions with stirring and cooling. After 1 h at room temperature, the mixture was filtered and the solution was made alkaline with ammonia and extracted with chloroform. The organic layer was dried and evaporated. The residue was dissolved in anhydrous ether and treated with ethereal hydrogen chloride to afford the *hydrochloride* of the amine (4j) (4.5 g), m.p. 117° (Found: C, 59.7; H, 6.6; N, 5.6. $C_{12}H_{16}ClNO_2$ requires C, 59.6; H, 6.7; N, 5.8%), $\nu_{max.}$ (Nujol) 1 720 $cm^{-1}$ (CO), δ($D_2O$) 1.39 (3 H, t, $CH_2$*Me*), 1.97 (3 H, d, *J ca.* 1 Hz, Me), 4.36 (2 H, q, C*H*$_2$Me), and 7.4—7.8 (5 H, m, aromatic and CH=).

*Ethyl* 3-(2-*Aminophenyl*)-2-*phenylprop*-2-*enoate* (4k).—Ethyl 3-(2-nitrophenyl)-2-phenylprop-2-enoate [19] (13.0 g) was reduced as above to afford the *hydrochloride* of the amine (4k) (11.0 g), m.p. 108° (Found: C, 67.4; H, 5.9; N, 4.7. $C_{17}H_{18}ClNO_2$ requires C, 67.2; H, 6.0; N, 4.6%), $\nu_{max.}$ (Nujol) 1 710 $cm^{-1}$ (CO), δ ($D_2O$) 1.33 (3 H, t, $CH_2$*Me*), 4.34 (2 H, q, C*H*$_2$Me), and 6.8—8.2 (10 H, m, aromatic and CH=).

*Chloro-hydrazones* (1a—c, e, g, j, *and* k) *and* (6).—A solution of sodium nitrite (40 mmol) in water (20 ml) was added to a stirred solution of the substituted aniline (40 mmol) in 0.5N-hydrochloric acid (250 ml) cooled in ice. The mixture was then adjusted to pH 4 with sodium acetate, and ethyl 2-chloroacetoacetate (40 mmol) was added dropwise at 0—5 °C. After 3 h at room temperature, the mixture was extracted with ether and the organic solution was dried and evaporated. The product was isolated from the residue as indicated in Table 4.

*Chloro-hydrazones* (1d, f, h, *and* i).—A solution of the chloro-hydrazone (6) (10 mmol) in dry toluene (400 ml) was treated with toluene-*p*-sulphonic acid (0.2 g) and refluxed under a water separator for 1 h. The mixture was washed with aqueous sodium hydrogen carbonate, dried, and evaporated. The residue was purified as indicated in Table 4.

TABLE 4

Preparation of chloro-hydrazones (6) and (1)

| Compd. | Yield (%) | M.p. (°C) | Isolation procedure [a] |
|---|---|---|---|
| (6d) | 60 | Oil [b] | B [light petroleum–$Et_2O$ (4 : 1)] |
| (6f) | 45 | 132 | A ($Pr^i_2O$) |
| (6h) | 15 | Oil [b] | B [light petroleum–$Et_2O$ (4 : 1)] |
| (6i) | 17 | 97 | B [light petroleum–PhH (4 : 1)] |
| (1a) | 56 | 75 | A (MeOH) |
| (1b) | 59 | 133 | A (EtOH) |
| (1c) | 43 | 55 | B [light petroleum–$Et_2O$ (1 : 1)] |
| (1d) | 29 | 49 | B [light petroleum–$Et_2O$ (9 : 1)] |
| (1e) | 51 | 64 | B [light petroleum–$Et_2O$ (4 : 1)] |
| (1f) | 79 | 67 | A ($Pr^i_2O$) |
| (1g) | 15 | Oil [b] | B [light petroleum–PhH (1 : 1)] |
| (1h) | 44 | 49 | A (MeOH) |
| (1i) | 45 | 74 | A (n-pentane) |
| (1j) | 72 | 96 | A (EtOH) |
| (1k) | 62 | 72 | A ($Pr^i_2O$) |

[a] A, crystallization of the crude product (solvent in parentheses); B, chromatography of the product mixture on silica gel column (eluant in parentheses). [b] Purity better than 95% (n.m.r. analysis).

*Treatment of Chloro-hydrazones* (1) *with Triethylamine*.—A solution of the chloro-hydrazone (1) (15 mmol) and triethylamine (60 mmol) in dry benzene (150 ml) was refluxed for the time given in Table 1. The mixture was washed with water, dried, and evaporated. The residue was handled as indicated in Table 1. In the case of (1h), the mixture was chromatographed, without treatment with water (elution with 6 : 3 : 1 diethyl ether–light petroleum–triethylamine); this was necessary to prevent partial decomposition of (3h).

[7/480 *Received*, 18*th March*, 1977]

* For details of Supplementary Publications see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue.

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