

## Ring Transformation and Reactions of 2-Amino-4,5-dihydrofuran-3,4-dicarbonitriles

Vicente J. Arán, Miguel A. Pérez, and José L. Soto\*

Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, Madrid-3, Spain

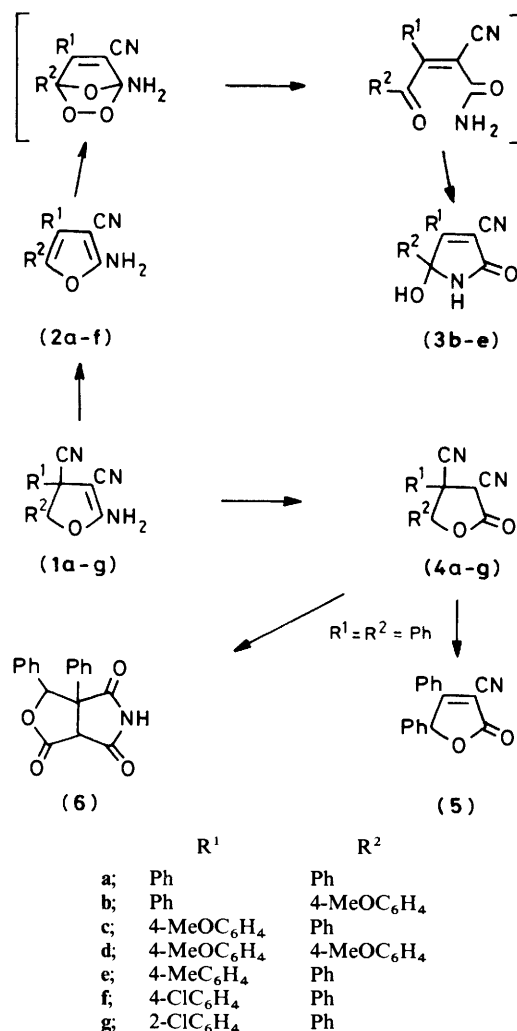
The 2-amino-4,5-dihydrofuran-3,4-dicarbonitriles (**1a–f**) were thermally aromatized to the 2-aminofuran-3-carbonitriles (**2a–f**) which, in turn, underwent photooxidative ring transformation into the 2,5-dihydro-5-hydroxy-2-oxopyrrole-3-carbonitriles (**3b–e**). Mild acidic hydrolysis of the 2-amino-4,5-dihydrofuran-3,4-dicarbonitriles (**1a–g**) led to the tetrahydro-2-oxofuran-3,4-dicarbonitriles (**4a–g**). The representative compound (**4a**) was converted into the 2,5-dihydro-2-oxofuran-3-carbonitrile (**5**) or further transformed into the 3,3a-dihydrofuro[3,4-c]pyrrole-1,4,6-trione (**6**).

The formation of 2-aminofuran-3-carbonitriles *via* intramolecular cyclization of intermediate 4-oxobutanenitriles obtained from propanedinitrile and benzoin<sup>1–3</sup> or chloroketones<sup>4–8</sup> is well documented. However, the generality of this approach is often limited by the availability of differently substituted benzoin. We have reported<sup>9</sup> a preparation of 5-aminofuran-3-carbonitriles of potential interest in the laser field.<sup>10</sup> Recently we described<sup>11</sup> the formation of the 2-amino-4,5-diaryl-4,5-dihydrofuran-3,4-dicarbonitriles (**1a–g**) from 3-aryl-2-cyanopropenenitriles, potassium cyanide, and aromatic aldehydes.

### Results and Discussion

The 2-amino-4,5-diaryl-4,5-dihydrofuran-3,4-dicarbonitriles (**1a–g**) were isolated<sup>11</sup> as the *trans*-diaryl diastereoisomer or as an equimolar mixture of the *trans*- and *cis*-diastereoisomers depending on the substitution and the reaction conditions. By refluxing any of these isomers in ethane-1,2-diol elimination of hydrogen cyanide took place with formation of the 2-amino-4,5-diarylfuran-3-carbonitriles (**2a–f**) in 55–70% yields. This thermal aromatization constitutes a simple and general route to differently substituted 2-aminofuran-3-carbonitriles (**2**) (Scheme).

The 2-aminofuran-3-carbonitriles (**2b–e**) with electron-donating substituents must be protected from light and oxygen. On exposure to air and daylight for 3 days compounds (**2b–e**) underwent ring transformation into the 4,5-diaryl-2,5-dihydro-5-hydroxy-2-oxopyrrole-3-carbonitriles (**3b–e**) in 65–80% yields. This reaction is assumed to proceed *via* a Diels–Alder cycloaddition of singlet oxygen and an intermediate 4-oxobutanamide as depicted in the Scheme. An analogous ring transformation has been reported for 2-furylcarbamates.<sup>12</sup> The pyrrole-3-carbonitrile (**3d**) was also prepared, using a reported procedure,<sup>13</sup> from bis(4-methoxyphenyl)ethanedione and 2-cyanoacetamide *via* the proposed 4-oxobutanamide intermediate mentioned above. The furan-3-carbonitrile (**2a**) underwent slight photooxidation after 10 days and the product (**3a**) was only detected on t.l.c. by comparison with a sample prepared independently.<sup>13</sup> On the other hand, the furan-3-carbonitrile (**2f**) possessing an electron-withdrawing substituent resisted photooxidation under these conditions. The ready photooxidation of the furan-3-carbonitriles (**2b–e**) compared to the reluctance of the isomeric 2,4-diaryl-5-aminofuran-3-carbonitriles<sup>9</sup> is probably due to the high steric hindrance of the neighbouring aryl groups which are not coplanar. The steric hindrance is reduced in the transition state formed on cycloaddition with oxygen. The isomeric 2,4-diaryl-5-aminofuran-3-carbonitriles<sup>9</sup> whose aryl groups can adopt a coplanar arrangement need to be irradiated with a 250 kW nitrogen laser



Scheme.

to achieve an analogous transformation, which does not occur when oxygen is excluded.<sup>10</sup>

The 4,5-dihydrofuran-3,4-dicarbonitriles (**1a–g**) underwent mild hydrolysis under acidic conditions affording the 4,5-diaryltetrahydro-2-oxofuran-3,4-dicarbonitriles (**4a–g**) in 85–97% yields. Related hydrolyses of heterocyclic, carbocyclic, and aliphatic enamionitriles leading to  $\alpha$ -oxonitriles have been reported.<sup>14</sup> The structure of the dihydrofuran-3,4-dicarbo-

nitriles (**4a—g**) was established on the basis of spectral evidence. It was further confirmed by transformation of the representative compound (**4a**) into the known<sup>1</sup> 2,5-dihydro-2-oxo-4,5-diphenylfuran-3-carbonitrile (**5**) by thermal extrusion of hydrogen cyanide. The <sup>1</sup>H n.m.r. spectra indicated that only one diastereoisomer of (**4a—g**) was formed starting either from the *trans*-diarylfurans (**1a—g**) or a *cis/trans*-mixture. The proton at position 3 of the 2-oxofuran-3,4-dicarbonitriles (**4a—g**) appeared as a sharp singlet in deuteriochloroform but was broadened in hexadeuteriodimethyl sulphoxide and was completely exchanged upon addition of deuterium oxide. However, a sharp non-exchangeable singlet was found for the proton at position 5 in both solvents. The mobility of the proton at position 3 allows compounds (**4a—g**) to reach the thermodynamically most stable configuration at this position. Additional information on the configuration of compounds (**4a—g**) can be gathered from their n.m.r. spectra in deuteriochloroform. The chemical shifts of the protons at positions 3 and 5 of the furans (**4a—f**) are between  $\delta$  4.4—4.6 and 5.4—5.6, respectively. However, although the chemical shift of the proton at position 3 of the 4-(2-chlorophenyl)-substituted compound (**4g**) is in the range mentioned, the proton at position 5 is shifted by *ca.* 1 p.p.m. to lower field. This may be explained by the proximity of the *ortho*-chlorine atom to the proton at position 5. Such van der Waal effects lead to deshielding in all cases.<sup>15</sup> On this basis, a *trans*-diaryl, *trans*-dicyano configuration may be assumed for the furans (**4a—g**) in chloroform solution. This stereochemistry is the only one that explains the interaction with the proton at position 5 only, as observed in molecular models. In a *cis*-dicyano configuration an interaction with the proton at position 3 would also be expected.

The acidic hydrolysis of the tetrahydrofuran-3,4-dicarbonitrile (**4a**) under vigorous conditions led to the dihydro-1*H*-furo[3,4-*c*]pyrrole-1,4,6-trione (**6**). The mobility of the proton at position 3 of the furan (**4a**) enables the *cis*-configuration of the carbonitrile groups, necessary for this cyclization, to be adopted.

## Experimental

Exposure to direct light should be avoided in the preparation and storage of the compounds (**2**). I.r. spectra were obtained as KBr pellets on a Perkin-Elmer 257 spectrophotometer. <sup>1</sup>H N.m.r. spectra were recorded on a Varian T-60A spectrometer and <sup>13</sup>C n.m.r. spectra on a Varian CFT 20 spectrometer with tetramethylsilane as an internal standard in the solvents indicated. Mass spectra were obtained on a Varian MAT 711 mass spectrometer at 70 eV. Analytical t.l.c. was performed on silica gel using toluene-ethyl acetate (4:1) as the eluant.

**Preparation of 2-Amino-4,5-diarylfuran-3-carbonitriles (2a—f).**—The appropriate 2-amino-4,5-diaryl-4,5-dihydrofuran-3,4-dicarbonitrile (**1**) (7 mmol) in ethane-1,2-diol (40 ml) was refluxed for 15 min avoiding exposure to direct light. The cold solution was poured slowly with stirring into chilled water (600 ml). The precipitate was collected and recrystallized from benzene to yield the following furan-3-carbonitriles (**2**): 2-amino-4,5-diphenylfuran-3-carbonitrile (**2a**) (65%), m.p. 203—205 °C (lit.,<sup>1</sup> m.p. 204—206 °C); 2-amino-5-(4-methoxyphenyl)-4-phenylfuran-3-carbonitrile (**2b**) (55%), m.p. 178—180 °C (lit.,<sup>6</sup> m.p. 182—183 °C); 2-amino-4-(4-methoxyphenyl)-5-phenylfuran-3-carbonitrile (**2c**) (57%), m.p. 174—176 °C (lit.,<sup>6</sup> m.p. 176—177 °C); 2-amino-4,5-bis(4-methoxyphenyl)furan-3-carbonitrile (**2d**) (55%), m.p. 186—188 °C (Found: C, 71.3; H, 4.8; N, 8.6. C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>3</sub> requires C, 71.2; H, 5.0; N, 8.7%;  $\nu_{\max}$ . 3 470, 3 320, 3 260, and 3 200 (NH), and 2 220 cm<sup>-1</sup> (conj. CN); 2-amino-4-(4-methylphenyl)-5-phenylfuran-3-carbonitrile (**2e**)

(60%), m.p. 189—190 °C (lit.,<sup>6</sup> m.p. 191—192 °C); and 2-amino-4-(4-chlorophenyl)-5-phenylfuran-3-carbonitrile (**2f**) (70%), m.p. 220—222 °C (lit.,<sup>6</sup> m.p. 221—223 °C).

**Preparation of 4,5-Diaryl-2,5-dihydro-5-hydroxy-2-oxopyrrole-3-carbonitriles (3b—e).**—A stirred solution of the corresponding furan-3-carbonitrile (**2**) (3 mmol) in acetonitrile (50 ml) was kept exposed to daylight for 3 days. The solvent was evaporated and the residue was recrystallized to yield the pyrrole-3-carbonitriles (**3b—e**). 2,5-Dihydro-5-hydroxy-5-(4-methoxyphenyl)-2-oxo-4-phenylpyrrole-3-carbonitrile (**3b**) (80%), m.p. 194—196 °C (decomp.) (from ethanol) (Found: C, 70.3; H, 4.7; N, 9.0. C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires C, 70.6; H, 4.6; N, 9.1%;  $\nu_{\max}$ . 3 340 (NH + OH), 2 230 (conj. CN), and 1 715 cm<sup>-1</sup> (CO);  $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$  3.60 (3 H, s, OCH<sub>3</sub>), 7.23 (1 H, s, OH, exchangeable), 6.6—7.7 (9 H, m, ArH), and 9.25 (1 H, s, NH). 2,5-Dihydro-5-hydroxy-4-(4-methoxyphenyl)-2-oxo-5-phenylpyrrole-3-carbonitrile (**3c**) (75%), m.p. 227—229 °C (decomp.) (from acetonitrile) (Found: C, 70.7; H, 4.2; N, 9.3. C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires C, 70.6; H, 4.6; N, 9.1%;  $\nu_{\max}$ . 3 360 and 3 260 (NH + OH), 2 225 (conj. CN), and 1 720 cm<sup>-1</sup> (CO);  $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$  3.67 (3 H, s, OCH<sub>3</sub>), 6.7—7.9 (9 H, m, ArH), 7.33 (1 H, s, OH, exchangeable), and 9.20 (1 H, s, NH). 2,5-Dihydro-5-hydroxy-4,5-bis(4-methoxyphenyl)-2-oxopyrrole-3-carbonitrile (**3d**) (80%), m.p. 232—234 °C (decomp.) (from acetonitrile) (Found: C, 68.1; H, 4.5; N, 8.6. C<sub>19</sub>H<sub>16</sub>N<sub>2</sub>O<sub>4</sub> requires C, 67.9; H, 4.8; N, 8.3%;  $\nu_{\max}$ . 3 340 and 3 240 (NH + OH), 2 225 (conj. CN), and 1 710 cm<sup>-1</sup> (CO);  $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$  3.61 (3 H, s, OCH<sub>3</sub>), 3.67 (3 H, s, OCH<sub>3</sub>), 6.6—7.8 (8 H, m, ArH), 7.25 (1 H, s, OH, exchangeable), and 9.10 (1 H, s, NH);  $m/z$  336 ( $M^+$ , 28%) and 135 (100). 2,5-Dihydro-5-hydroxy-4-(4-methylphenyl)-2-oxo-5-phenylpyrrole-3-carbonitrile (**3e**) (65%), m.p. 218—220 °C (decomp.) (from benzene) (Found: C, 74.7; H, 4.8; N, 9.3. C<sub>18</sub>H<sub>14</sub>N<sub>2</sub>O<sub>2</sub> requires C, 74.5; H, 4.9; N, 9.6%;  $\nu_{\max}$ . 3 260 (NH + OH), 2 230 (conj. CN), and 1 715 cm<sup>-1</sup> (CO);  $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$  2.22 (3 H, s, CH<sub>3</sub>), 6.9—7.7 (9 H, m, ArH), 7.33 (1 H, s, OH, exchangeable), and 9.21 (1 H, s, NH).

**Preparation of 4,5-Diaryl-2,3,4,5-tetrahydro-2-oxofuran-3,4-dicarbonitriles (4a—g).**—A mixture of the 2-amino-4,5-diaryl-4,5-dihydrofuran-3,4-dicarbonitrile (**1**) (6 mmol) and concentrated hydrochloric acid (2 ml) in ethanol (50 ml) was gently warmed to solution, allowed to cool to room temperature, and poured into water with stirring. The precipitate thus formed was collected by filtration and recrystallized to yield the tetrahydrofuran-3,4-dicarbonitriles (**4a—g**).

2,3,4,5-Tetrahydro-2-oxo-4,5-diphenylfuran-3,4-dicarbonitrile (**4a**) (95%), m.p. 182—184 °C (from ethanol) (Found: C, 75.1; H, 4.0; N, 9.6. C<sub>18</sub>H<sub>12</sub>N<sub>2</sub>O<sub>2</sub> requires C, 75.0; H, 4.2; N, 9.7%;  $\nu_{\max}$ . 2 260 (CN) and 1 800 cm<sup>-1</sup> (CO);  $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$  6.00 (1 H, br s, 3-H, exchangeable), 6.13 (1 H, s, 5-H), 6.8—7.7 (10 H, m, ArH);  $\delta_{\text{H}}(\text{CDCl}_3)$  4.41 (1 H, s, 3-H), 5.52 (1 H, s, 5-H), and 6.9—7.5 (10 H, m, ArH);  $\delta_{\text{C}}[(\text{CD}_3)_2\text{SO}]$  45.8 (d, C-3), 59.1 (C-4), 84.6 (d, C-5), 113.1, 114.9 (CN), 125.8—130.6 (Ar), and 166.2 (CO);  $m/z$  288 ( $M^+$ , 5%), 287 (17), 261 (16), and 105 (100).

2,3,4,5-Tetrahydro-5-(4-methoxyphenyl)-2-oxo-4-phenylfuran-3,4-dicarbonitrile (**4b**) (85%), m.p. 160—162 °C (from butan-1-ol) (Found: C, 71.5; H, 4.4; N, 8.8. C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires C, 71.7; H, 4.4; N, 8.8%;  $\nu_{\max}$ . 2 250 (CN) and 1 800 cm<sup>-1</sup> (CO);  $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$  3.63 (3 H, s, OCH<sub>3</sub>), 5.93 (1 H, br, s, 3-H, exchangeable), 6.01 (1 H, s, 5-H), and 6.7—7.6 (9 H, m, ArH).

2,3,4,5-Tetrahydro-4-(4-methoxyphenyl)-2-oxo-5-phenylfuran-3,4-dicarbonitrile (**4c**) (94%), m.p. 182—184 °C (from butan-1-ol) (Found: C, 71.4; H, 4.5; N, 9.0. C<sub>19</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> requires C, 71.7; H, 4.4; N, 8.8%;  $\nu_{\max}$ . 2 260 (CN) and 1 800 cm<sup>-1</sup> (CO);  $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$  3.68 (3 H, s, OCH<sub>3</sub>), 5.83 (1 H, br, s,

3-H, exchangeable), 5.98 (1 H, s, 5-H), and 6.7—7.4 (9 H, m, ArH).

**2,3,4,5-Tetrahydro-4,5-bis(4-methoxyphenyl)-2-oxofuran-3,4-dicarbonitrile (4d)** (96%), m.p. 164—166 °C (from butan-1-ol) (Found: C, 69.1; H, 4.8; N, 7.9.  $C_{20}H_{16}N_2O_4$  requires C, 69.0; H, 4.6; N, 8.0%);  $\nu_{max}$ . 2270 (CN) and 1815  $cm^{-1}$  (CO);  $\delta_H[(CD_3)_2SO]$  3.66 (3 H, s, OCH<sub>3</sub>), 3.72 (3 H, s, OCH<sub>3</sub>), 5.90 (1 H, br s, 3-H, exchangeable), 5.98 (1 H, s, 5-H), and 6.7—7.6 (8 H, m, ArH).

**2,3,4,5-Tetrahydro-4-(4-methylphenyl)-2-oxo-5-phenylfuran-3,4-dicarbonitrile (4e)** (97%), m.p. 190—192 °C (from butan-1-ol) (Found: C, 75.3; H, 4.7; N, 9.6.  $C_{19}H_{14}N_2O_2$  requires C, 75.5; H, 4.7; N, 9.3%);  $\nu_{max}$ . 2250 (CN) and 1800  $cm^{-1}$  (CO);  $\delta_H[(CD_3)_2SO]$  2.27 (3 H, s, CH<sub>3</sub>), 5.85 (1 H, br s, 3-H, exchangeable), 6.00 (1 H, s, 5-H), and 6.6—7.5 (9 H, m, ArH).

**4-(4-Chlorophenyl)-2,3,4,5-tetrahydro-2-oxo-5-phenylfuran-3,4-dicarbonitrile (4f)** (97%), m.p. 192—194 °C (from toluene) (Found: C, 67.2; H, 3.4; N, 8.9; Cl, 11.2.  $C_{18}H_{11}ClN_2O_2$  requires C, 67.0; H, 3.4; N, 8.7; Cl, 11.0%);  $\nu_{max}$ . 2260 (CN) and 1800  $cm^{-1}$  (CO);  $\delta_H[(CD_3)_2SO]$  6.03 (1 H, br s, 3-H, exchangeable), 6.11 (1 H, s, 5-H), and 6.8—7.6 (9 H, m, ArH).

**4-(2-Chlorophenyl)-2,3,4,5-tetrahydro-2-oxo-5-phenylfuran-3,4-dicarbonitrile (4g)** (96%), m.p. 167—169 °C (from 2,2-dimethylpropanol) (Found: C, 66.7; H, 3.5; N, 8.9; Cl, 10.7.  $C_{18}H_{11}ClN_2O_2$  requires C, 67.0; H, 3.4; N, 8.7; Cl, 11.0%);  $\nu_{max}$ . 2240, 2230 (CN) and 1800  $cm^{-1}$  (CO);  $\delta_H[(CD_3)_2SO]$  6.80 (1 H, br s, 3-H, exchangeable) and 6.9—7.3 (10 H, m, ArH + 5-H);  $\delta_H(CDCl_3)$  4.53 (1 H, s, 3-H), 6.48 (1 H, s, 5-H), and 6.6—7.4 (9 H, m, ArH).

**Preparation of 2,5-Dihydro-2-oxo-4,5-diphenylfuran-3-carbonitrile (5)**.—2,3,4,5-Tetrahydro-2-oxo-4,5-diphenylfuran-3,4-dicarbonitrile (**4a**) (1.44 g, 5 mmol) in ethane-1,2-diol (30 ml) was refluxed for 30 min. The cold solution was poured into chilled water (400 ml). The precipitate was collected and recrystallized from propan-1-ol to yield the 2-oxofuran-3-carbonitrile (**5**) (0.72 g, 55%), m.p. and mixed m.p. 141—142 °C (lit.,<sup>1</sup> m.p. 142—143 °C).

**Preparation of 3,3a-Dihydro-3,3a-diphenyl-1H-furo[3,4-c]-pyrrole-1,4,6(5H,6aH)-trione (6)**.—A mixture of the tetrahydrofuran-3,4-dicarbonitrile (**4a**) (3.46 g, 12 mmol), acetic acid (60 ml), water (40 ml), and concentrated sulphuric acid (20 ml) was heated under reflux for 3 h. The cold solution was poured into water. The precipitate thus formed was collected and recrystallized from ethanol to yield the furo[3,4-c]pyrrole-1,4,6-trione (**6**) (2.18 g, 59%), m.p. 227 °C (decomp.) (Found: C, 70.5; H, 4.4; N, 4.8.  $C_{18}H_{13}NO_4$  requires C, 70.4; H, 4.3; N, 4.6%);  $\nu_{max}$ . 3260 (NH), 1820 (lactonic CO), 1765, and 1720  $cm^{-1}$  (imidic CO);  $\delta_H[(CD_3)_2SO]$  4.75 (1 H, s, 3-H), 5.85 (1 H, s, 6a-H), and 7.0—7.6 (10 H, m, ArH);  $m/z$  307 ( $M^+$ , 1%), 202 (11), 201 (100), 173 (61), and 105 (11).

## References

- 1 K. Gewald, *Chem. Ber.*, 1966, **99**, 1002.
- 2 T. Hayashi and M. Kagawa, *Bull. Chem. Soc. Jpn.*, 1970, **43**, 3290.
- 3 J. W. Ducker and M. P. Gunter, *Aust. J. Chem.*, 1974, **27**, 2229.
- 4 T. I. Temnikova and R. N. Kovalevskaya, *Zh. Org. Khim.*, 1965, **1**, 612 (*Chem. Abstr.*, 1965, **63**, 2944).
- 5 T. I. Temnikova and Yu. A. Sharanin, *Zh. Org. Khim.*, 1966, **2**, 2018 (*Chem. Abstr.*, 1967, **66**, 75474).
- 6 T. I. Temnikova, Yu. A. Sharanin, and V. S. Karavan, *Zh. Org. Khim.*, 1967, **3**, 681 (*Chem. Abstr.*, 1967, **67**, 43778).
- 7 G. Westoo, *Acta Chem. Scand.*, 1959, **13**, 692.
- 8 F. Korte and K. Trautner, *Chem. Ber.*, 1962, **95**, 307.
- 9 V. J. Arán and J. L. Soto, *Synthesis*, 1982, 513.
- 10 M. Sánchez and J. M. Guerra, *Opt. Commun.*, 1981, **40**, 144.
- 11 V. J. Arán and J. L. Soto, *An. Quim.*, 1983, **79C**, 340.
- 12 K. Yakushijin, M. Kozuka, Y. Ito, R. Suzuki, and H. Furukawa, *Heterocycles*, 1980, 1073.
- 13 D. M. W. Anderson, F. Bell, and J. L. Duncan, *J. Chem. Soc.*, 1961, 4705.
- 14 E. C. Taylor and A. McKillop, *Adv. Org. Chem.*, 1970, **7**, 60.
- 15 L. M. Jackman and S. Sternhell, 'Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry,' Pergamon Press, London, 1969, p. 72.

Received 2nd December 1983; Paper 3/2134