Pyryliumolates II—generation of and cycloaddition reactions with isoxazole annulated pyryliumolates

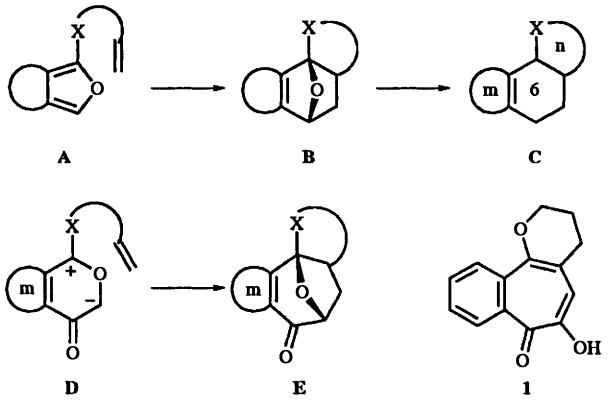
Carsten Plüg and Willy Friedrichsen *

Institute of Organic Chemistry, University of Kiel, Olshausenstraße 40/60, D-24098 Kiel, Germany

Isoxazole annulated pyryliumolates (formed *in situ* from diazo compounds 3 and 6) can be trapped with DMAD to form 1:1 adducts (5, 8) and in minor amount 2:1 adducts (Schemes 4 and 5). Suitably substituted pyryliumolates (7b,c) undergo an intramolecular cycloaddition giving 9 and 10. Compound 10 can be transformed easily to an annulated tropolone (11). Computational studies on 2:1 adducts and on 11 are reported.

Introduction

Intramolecular cycloaddition reactions[2] with *c*-annulated furans (**A**, Scheme 1) offer an attractive route for the preparation of a wide variety of [m-6-n] systems (**B**, **C**).[3,4] An extension of this methodology towards the synthesis of [m-7-n] systems (**E**) seems obvious using pyryliumolates[5,6] of type **D** as precursors. Both *inter*- and *intra*-molecular cycloadditions of pyryliumolates and their annulated derivatives are of course well known.[6] Quite recently we succeeded in the preparation of a benzotropolone (**1**, Scheme 1)[1] and it seemed appropriate to use this procedure[7,8] to prepare [m-7-n] heterocycles with m = 5. In this paper the generation of the corresponding pyryliumolates (**4**, **7**; Schemes 2 and 3) and some inter- and intra-molecular cycloadditions are reported.

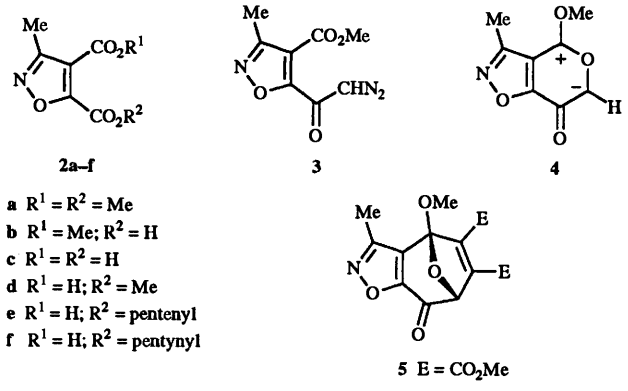


Scheme 1

Preparative results

As starting material for the *in situ* generation of **4** and **7** the isoxazole derivative **2a**[9] was used. Selective saponification (potassium hydroxide, 0 °C, 1 h) gives the monoester **2b**[10] in quantitative yield. Treatment of **2b** with oxalic acid dichloride and subsequently with diazomethane results in the formation of diazoketone **3**. Adding dirhodium tetraacetate[11] and an excess of dimethyl acetylene dicarboxylate (DMAD) to a solution of **3** in toluene and allowing the mixture to stir at 110 °C for 1.5 h revealed the generation of at least three products. Compound **5** was obtained in 59% yield. The structure of **5** (as compared to **8**, *vide infra*) can be proved by ^{13}C NMR spectroscopy. For C-8a there is a signal at δ = 154.45; δ(C-3a) appears at 129.75 ppm. The corresponding values for **8** are found at δ(C-8a) = 175.97 ppm and δ(C-3a) = 110.21 ppm. Additionally, two 2:1 adducts (from a reaction of **4** and **5**) could be isolated in 7 and 3% yield, respectively. In principle, six stereo(regio)isomers are possible (Scheme 4). According to the heteronuclear multiple bond correlation (HMBC) spectra structures **15**–**17** can be excluded. Molecular model and semiempirical quantum chemical calculations (AM1, PM3) show quite clearly that in **13** the two halves of the molecule are highly congested (see Fig. 1) and it appears that only structures **12** and **14** seem to be possible candidates for these 2:1-adducts. But as there are double sets of signals in the NMR spectra (^1H, ^{13}C) the detailed structures of these adducts remain unclear.

The pyryliumolates **7a,b,c** (Scheme 2) were generated using a similar method as that reported for **4**. Selective esterification of **2c**[13] yields the monoesters **2d–f**,[14] which were transformed into the diazo compounds **6a–c** using the methodology described above. Generation of **7a** in the presence of DMAD gives **8** in 68% yield. Again a 2:1 adduct (from the reaction of **7a** and **8**) could be isolated, albeit in low yield (2%). The structure [six isomers (Scheme 5, **18**–**23**) are conceivable] remains unclear. As in the benzo series[1] pyryliumolate **7b,c** can undergo intramolecular cycloadditions.

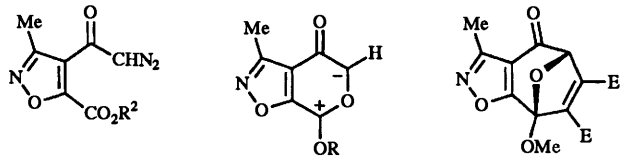


Scheme 2

Transition metal [$Rh_2(OAc)_4$] catalysed decomposition of **6b** in boiling toluene gives the tetracyclic adduct **9** in yields up to 84%.

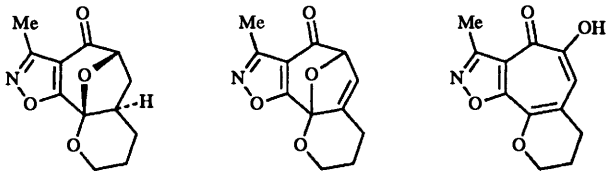
It is of interest to note that only one isomer has been isolated from the reaction mixture. Its structure has been proved unequivocally by ^1H NMR and COSY measurements. The stereochemistry at C-6a could be determined by coupling constant analysis. As shown in Fig. 2, the ^1H NMR signal of 6a-H is split by one small (J = 4.6 Hz) and three larger (J = 10.3, 9.3 and 14.6 Hz) couplings. In case of an *endo*-adduct one would expect substantially smaller J values.

Using **6c** as starting material the cycloadduct **10** could be obtained, albeit in somewhat lower yield (45%). Earlier



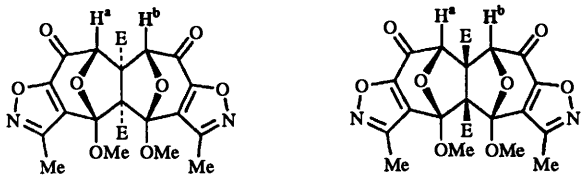
6a, b, c 7a, b, c 8 E = CO_2Me

a R = Me
b R = pentenyl
c R = pentynyl

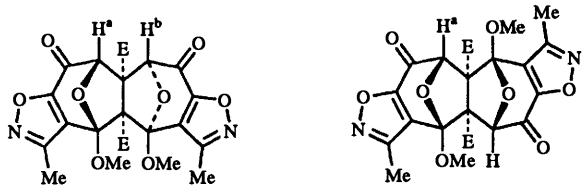


9 10 11

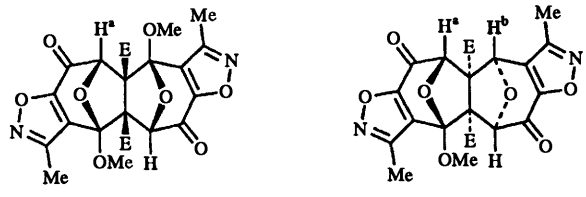
Scheme 3



12 13



14 15



16 17

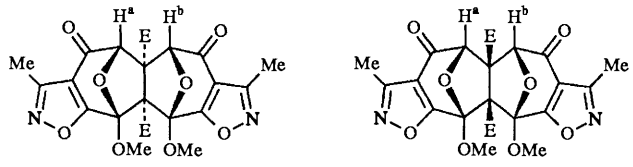
Scheme 4

experiments have shown that tetracyclic compounds of this type may serve as starting material for the preparation of annulated tropolones.[1] In strict analogy to this reaction the acid-catalysed ring opening of **10** gives compound **11** as yellow crystals in 95% yield. This route seems to offer a convenient entry into the field of heteroannulated tropolones.

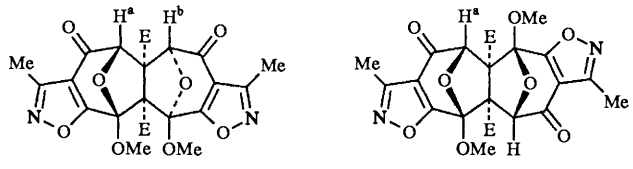
Computational studies

The 2:1 adducts (12–23)

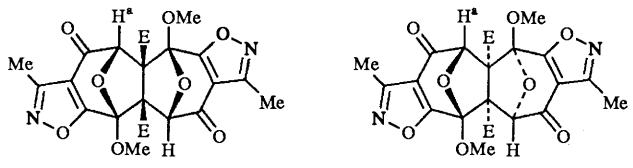
As has been pointed out above the reaction of **5** (Scheme 2) with a second molecule of **4** may give rise to six possible stereo(regio)isomers (Scheme 4). We have investigated the structures and energies (heats of formation, $\Delta_f H°$) by semiempirical quantum chemical methods (AM1, PM3).[15–17] Some results are given in Table 1. According to expectations there are two different types of 2:1 adducts. Whereas compounds **12**, **14**, **15** and **17** are less hindered ($\Delta_f H° \simeq -215$ kcal mol^{-1} [AM1]) the all-*cis* adducts (**13**, **16**) are more hindered (see Fig. 1) with a substantially lower heat of



18 19



20 21



22 23

Scheme 5

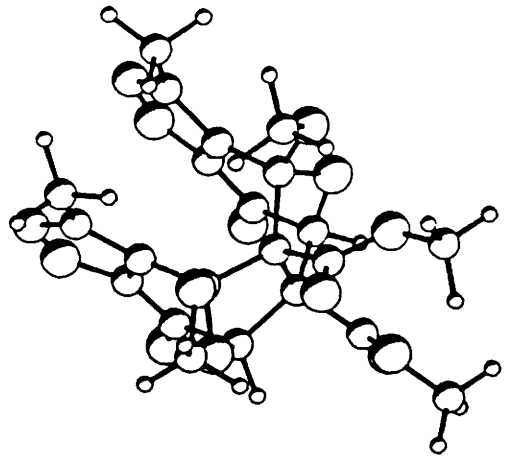
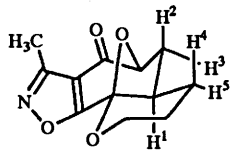


Fig. 1 PLUTO plot of **13** (AM1 optimized structure)



9

H^2	H^3	H^4	H^5
10.3	9.3	14.6	4.6

Fig. 2 Coupling constants in **9** between H^1 and H^2–H^5 (values in Hz, measured in $CDCl_3$)

formation ($\Delta_f H° \simeq -198$ kcal mol^{-1} [AM1]). Similar results are obtained for the 2:1 adducts which are formed from **7a** and **8** (Scheme 5). Whether the formation of the 2:1 adducts is controlled thermodynamically remains unclear.

The 5-hydroxycyclohepta[1,2-*d*]isoxazole-4(7*H*)-one–4-hydroxycyclohepta[1,2-*d*]isoxazole-5(6*H*)-one equilibrium

As already reported for benzannulated pyryliumolates[1] and also observed in the isoxazole series treatment of **10** with strong acids yields an annulated tropolone **11**. It is of interest whether an equilibrium between **11** and a tautomer resulting from a H-shift from the hydroxy group to the carbonyl group can be

expected. Although there is no experimental evidence for such an equilibrium a computational study has been undertaken in order to gain insight into the energy difference between these two tautomers, especially in comparison with their benzanalogues.

In order to simplify the computational effort the calculations were performed for model compounds (**24**, **25**). On the *semiempirical* level (AM1, PM3) one obtains $\Delta\Delta_fH° = \Delta_fH°(\mathbf{24}) - \Delta_fH°(\mathbf{25}) = 5.1$ (5.5) kcal mol^{-1} (Table 2) which according to expectations is less than the corresponding values for **26** and **27** ($\Delta\Delta_fH° = 14.9$ (17.5) kcal mol^{-1}). On the *ab initio* level (MP2/6-31G*//6-31G* + ZPE) values of $\Delta\Delta E$ (**25**–**24**) = 8.5 kcal mol^{-1} and $\Delta\Delta E$ (**27**–**26**) = 10.3 kcal mol^{-1} were obtained. A density-functional theory[18] study using Becke's exchange[19] with Lee, Yang and Parr[20] correlation functional (BLYP) in a 6-31G* basis reduce the former value to $\Delta\Delta E$ (**25**–**24**) = 5.1 kcal mol^{-1}.

Selected bond lengths for **24** and **25** are given in Table 3. Interestingly, the results of *ab initio* calculations on the RHF/6-31G* level show C=O distances, which may be too short. An *ab initio* treatment of tropolone (RHF/6-31G*) yields a similar result. One obtains r(C=O) = 1.212 Å, which is at variance with an X-ray study of this molecule.[21,22]

The transition state energy for the tautomerisation **24** ⇌ **25** is obtained as 29.7 kcal mol^{-1} (AM1). The geometry of the transition state is shown in Fig. 3. According to this computational model the molecule is essentially planar. The hydrogen atom H-9a is positioned nearly symmetrically between O-9 and O-10 [r(O-9–H-9a) = 1.311 Å; r(O-10–H-9a) = 1.278 Å] in agreement with results on similar systems.

Experimental

All mps were determined on a Dr Tottoli melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR 1600 spectrophotometer. NMR spectra: Bruker AM 300 (300 MHz: FT ^{1}H NMR; 74.76 MHz: ^{13}C NMR); Bruker AC 200 (200 MHz: FT ^{1}H NMR; 50.31 MHz: ^{13}C NMR); Varian EM 360 (60 MHz, ^{1}H NMR), internally referenced on Me_4Si ($CDCl_3$) or DMSO ([$^2H_6$]DMSO). *J* values are given in Hz. UV spectra: Zeiss DMR 10 spectrophotometer; mass spectra: Finnigan MAT 8230 mass spectrometer by using 70 eV ionisation potential (EI) or the chemical ionisation (CI) (isobutane) method. Radial chromatography was carried out with a Harrison-Research Chromatotron on silica gel PF_{245} (Merck, Darmstadt).

Table 1 Calculated heats of formation ($\Delta_fH°$ in kcal mol^{-1})[a] for compounds **12**–**23** (AM1)[b]

Compound	$\Delta_fH°$	Compound	$\Delta_fH°$
12	−214.0	**18**	−220.8
13	−198.4	**19**	−209.7
14	−213.9	**20**	−214.3
15	−216.4	**21**	−225.7
16	−198.5	**22**	−213.4
17	−214.7	**23**	−224.3

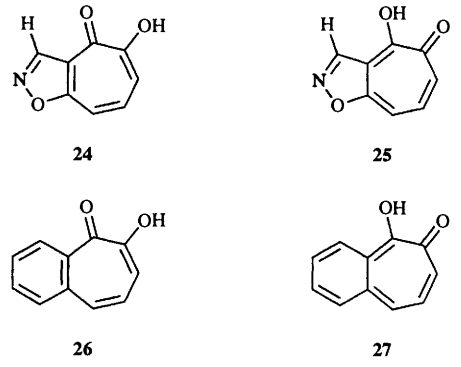
[a] 1 cal = 4.184 J. [b] All stationary points have been characterized as minima on the potential hypersurface by calculation and diagonalization of the Hessian matrix.

Materials

Toluene and ether were distilled over metal sodium. Acetone, dichloromethane and pentane were distilled from phosphorous pentoxide. Pent-4-enol and pent-4-ynol were prepared from tetrahydrofurfurylchloride[23] by treatment with metal sodium in ether[24] or sodium amide in ammonia.[23] Dimethyl 3-methylisoxazole-4,5-dicarboxylate **2a** was obtained from reaction of DMAD with acetonitrile oxide.[9] All other chemicals were used in the commercially available quality (Aldrich).

3-Methyl-4-methoxycarbonylisoxazole-5-carboxylic acid 2b

A solution of 238 mg (4.2 mmol) potassium hydroxide in 5 ml



Scheme 6

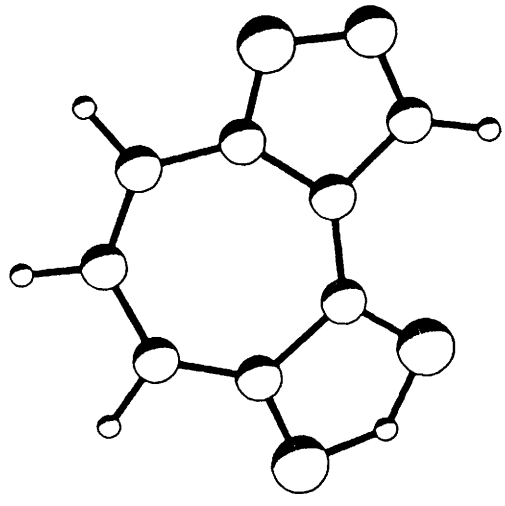


Fig. 3 PLUTO plot of the transition state **24** ⇌ **25** (AM1 optimized structure)

Table 2 Results of semiempirical (AM1, PM3), *ab initio* (RHF/6-31G*, MP2/6-31G*//6-31G*) and density-functional theory (BLYP/6-31G*) studies on **24**–**27**

Method	Compound **24**	**25**	**26**	**27**	TS[b]
AM1[a]	−1.5	+3.7	−16.9	−2.0	29.7[c]
PM3[a]	−11.4	−5.9	−19.3	−1.8	—
RHF/6-31G*	−584.819 51[d]	−584.802 59	−570.916 04	−570.889 72	—
RHF/6-31G* + ZPE	0.0	10.2[e]	0.0	16.2[f]	—
MP2/6-31G*//6-31G*	−586.513 44[d]	−586.499 19	−572.650 74	−572.633 79	—
MP2/6-31G*//6-31G* + ZPE[g]	0.0	8.5[e]	0.0	10.3	—
BLYP/6-31G*	−588.074 81	−588.066 73[h]	—	—	—

[a] Values in kcal mol^{-1}. [b] Transition state. [c] Transition state for the equilibrium **24** ⇌ **25**. [d] Values in hartree (e.u.). [e] *E* (**24**) = 0.0. [f] *E* (**26**) = 0.0. [g] Zero point vibrational energy from RHF/6-31G* calculations. [h] ΔE (**25** − **24**) = 5.1 kcal mol^{-1}.

Table 3 Calculated bond length of compounds **24** and **25** (values in Å)

	AM1[a]	PM3[a]	RHF/6-31G*[b]	BLYP/6-31G*
r (a–b) (**24**)	1.247	1.232	1.209	1.264
r (c–d) (**24**)	1.376	1.364	1.330	1.348
r (b–e) (**24**)	2.107	1.934	1.964	1.803
r (d–e) (**24**)	0.975	0.963	0.956	1.013
r (a–b) (**25**)	1.369	1.353	1.914	1.333
r (c–d) (**25**)	1.251	1.236	1.216	1.274
r (b–e) (**25**)	0.978	0.967	0.962	1.036
r (d–e) (**25**)	2.100	1.900	1.908	1.695

[a] Values for tropolone.[22] [b] Values for tropolone: r (a–b) = 1.212 Å, r (c–d) = 1.331 Å, r (b–e) = 1.939 Å, r (d–e) = 0.956 Å.

methanol was added dropwise to an ice-cold solution of 400 mg (2 mmol) **2a** in 10 ml methanol. After stirring for 1 h the precipitate was filtered off, washed with methanol and ether, suspended in dichloromethane and acidified with 30 ml 1 M sulfuric acid. The organic phase was washed with water, dried over Na_2SO_4 and evaporated. The residue was recrystallized from pentane–ether to provide 336 mg (91%) of **2b** as colourless crystals; mp 89–91 °C; ν_{max}(KBr)/cm^{-1} 2961, 2300–3500, 1752, 1638, 1599, 1196, 1130 and 762; λ_{max}(EtOH)/nm 220 (log ε 3.84); δ_H(60 MHz, $CDCl_3$) 2.52 (3 H, s, CH_3), 4.09 (3 H, s, OCH_3) and 13.29 (1 H, s, OH); δ_C(50 MHz, $CDCl_3$) 12.37 (q, CH_3), 54.68 (q, OCH_3), 112.56 (s, 4-C), 153.82 (s, 3-C), 160.44 (s, 5-C), 163.39 (s, COOH) and 166.35 (s, CO, ester); *m/z* (CI) 371 (dimer + H$^+$), 186 (M + H$^+$), 185 (M$^+$) and 101.

3-Methylisoxazole-4,5-dicarboxylic acid 2c

A suspension of 16.0 g (80 mmol) of diester **2a** in 100 ml 2 M sodium hydroxide solution was refluxed for 3 h. The clear solution was treated with 100 g ice, acidified with 2 M hydrochloric acid and evaporated *in vacuo*. The residue was extracted with ether, the combined extracts dried over Na_2SO_4 and evaporated. The residue was recrystallized from ether–pentane to provide 14.0 g (99%) of colourless crystals; mp 175–179 °C (decomp.); ν_{max}(KBr)/cm^{-1} 3500–2200, 1700, 1627, 1407, 1267 and 1209; δ_H(200 MHz, [$^2H_6$]DMSO) 2.39 (3 H, s, CH_3), 10.5–11.0 (1 H, br, OH); δ_C(50 MHz, [$^2H_6$]DMSO) 11.26 (q, CH_3), 114.37 (s, 4-C), 158.33 (s, 3-C), 160.44, 162.42 and 162.58 (3 s, 5-C, 2 COOH); *m/z* (CI) 172 (M + H$^+$) (Found: 172.0246; $C_6H_5NO_5$: 172.0245) and 153 (M − H_2O^+).

Methyl 5-diazoacetyl-3-methylisoxazole-4-carboxylate 3

A solution of 270 mg (1.46 mmol) monoester **2b** in 2 ml oxalic acid dichloride was refluxed for 30 min. After removal of the excess of oxalic acid dichloride the residue was taken up with 20 ml of ether and added dropwise to an excess of ethereal diazomethane. After 10 min the mixture was treated with 2 g silica gel and then filtered through a short column of silica gel. After evaporation of the ether the solid residue was recrystallized from ether–pentane to provide 281 mg (92%) yellow crystals; mp 81–83.5 °C; ν_{max}(KBr)/cm^{-1} 3121, 2111, 1731, 1644 and 854; λ_{max}(EtOH)/nm 216 (log ε 3.92), 249 (3.91) and 302 (4.06); δ_H(60 MHz, $CDCl_3$) 2.41 (3 H, s, CH_3), 3.82 (3 H, s, OCH_3) and 6.17 (1 H, br, CHN_2); δ_C(50 MHz, $CDCl_3$) 11.44 (q, CH_3), 52.62 (q, OCH_3), 58.54 (d, CHN_2), 112.48 (s, 4-C), 160.48 (s, 3-C), 161.51 (s, 5-C), 165.50 (s, CO, ester) and 173.61 (s, CO, ketone); *m/z* (CI) 210 (M + H$^+$).

Reaction of pyryliumolate 4 (formed *in situ* from diazoester 3) with DMAD

Dirhodium tetraacetate (10 mg) was added under nitrogen to a solution of 404 mg (2.85 mmol) DMAD and 85 mg (0.41 mmol) **3** in 100 ml toluene. After refluxing for 90 min the mixture was concentrated to 2 ml and 20 ml of ether were added. The precipitate was filtered off and washed with ether yielding 6 mg (3%) of a 2:1 adduct as colourless crystalline powder (dichloromethane–pentane); mp 203–205 °C; ν_{max}(KBr)/cm^{-1} 2995, 1719, 1654, 1296, 1027 and 927; λ_{max}(EtOH)/nm 209 (4.04) and 250 (sh, 3.53); δ_H(300 MHz, $CDCl_3$) 2.42, 2.45 (6 H, 2 s, 2 CH_3), 3.47, 3.56, 3.78, 3.87 (12 H, 4 s, 4 OCH_3), 4.99 and 5.23 (2 H, 2 s, 2 CH); δ_C(75 MHz, $CDCl_3$) 10.25, 10.28 (2 q, CH_3), 51.35, 52.28, 52.76, 52.86 (4 q, 4 OCH_3), 78.00 (d, 10-C), 85.74 (d, 11-C), 110.64 (s, 4-C), 119.07 (s, 4a-C), 119.72 (s, 10a-C), 132.22 (s, 12a-C), 135.31 (s, 8a-C), 150.44 (s, 5a-C), 155.61 (s, 3a-C), 155.83 (s, 3-C), 160.32 (s, 6-C), 162.36 (s, CO, ester), 162.88 (s, CO, ester) and 179.90 (s, C-9), 185.59 (s, C-12); a signal for 5-C could not be detected; *m/z* (CI) 505 (M + H$^+$).

The filtrate was evaporated and the residue was subjected to radial chromatography on silica gel with pentane–ether (3:1) to provide 78 mg (59%) dimethyl 7,8-dihydro-4,7-epoxy-4-methoxy-3-methyl-8-oxo-4*H*-cyclohepta[*d*]isoxazole-5,6-dicarboxylate **5** as colourless rhombic crystals (ether–pentane); mp 83–84.5 °C; ν_{max}(KBr)/cm^{-1} 2963, 1758, 1739, 1722, 1593, 1020 and 946; δ_H(300 MHz, $CDCl_3$) 2.46 (3 H, s, CH_3), 3.61, 3.83, 3.91 (9 H, 3 s, 3 OCH_3) and 5.50 (1 H, s, 8-H); δ_C(75 MHz, $CDCl_3$) 10.14 (q, CH_3), 53.00 (q, 2 OCH_3, ester), 53.12 (q, OCH_3, ketal), 85.66 (d, 7-C), 111.06 (s, 4-C), 129.75 (s, 8a-C), 138.06 (s, 5-C), 147.63 (s, 6-C), 154.45 (s, 3a-C), 156.19 (s, 3-C), 160.31, 162.20 (2 s, CO, ester) and 180.06 (s, CO, ketone); *m/z* (EI) 323 (M$^+$) (Found: 323.0640; $C_{14}H_{13}NO_8$: 323.0641). A further 14 mg (7%) of a 2:1 product could be isolated; colourless crystals (ether–pentane), mp 189–191 °C; ν_{max}(KBr)/cm^{-1} 2958, 1728, 1654, 1607, 1297 and 915; δ_H(200 MHz, $CDCl_3$) 2.37, 2.45 (6 H, 2 s, 2 CH_3), 3.50, 3.73, 3.80, 3.84 (12 H, 4 s, 4 OCH_3), 5.12 and 5.48 (2 H, 2 s, 2 CH); δ_C(75 MHz, $CDCl_3$) 10.16, 10.35 (2 q, 2 CH_3), 51.03 (2 q, 2 OCH_3), 52.69, 52.91 (2 q, 2 OCH_3), 81.78 (d, 5-C), 86.56 (d, 11-C), 110.30 (s, 4-C), 120.24 (s, 4a-C), 120.65 (s, 10a-C), 130.22 (s, 12a-C), 134.70 (s, 5a-C), 150.25 (s, 9a-C), 155.32 (s, 3a-C), 155.65 (s, 3-C), 159.65 (s, 9-C), 160.37, 161.56 (2 s, 2 CO, ester), 162.13 (s, 6-C) and 178.33 (s, C-11); *m/z* (CI) 505 (M + H$^+$), 324.

Formation of 4-diazoacetyl-3-methyl-5-carboxylates 6

General procedure. To a suspension of 342 mg (2 mmol) of diacid **2c**, 2 mmol of pent-4-enol (171 mg), pent-4-ynol (170 mg) or methanol (64 mg) and 20 ml dichloromethane was added a solution of 412 mg (2 mmol) DCC in 10 ml dichloromethane at rt. The mixture was stirred for 20 h and the precipitate (DCU) was filtered off. After removal of the solvent the residue was taken up with acetone, filtered and evaporated to dryness. This last step was repeated once. The residue, a colourless oil, was treated with 2 ml oxalic acid dichloride; a vigorous evolution of gases took place. After stirring for further 20 h the excess of oxalic acid dichloride was removed under reduced pressure. The crude acid chloride was taken up with ether and was added to an excess of an ethereal diazomethane solution. The mixture was stored at rt for 1 h, treated with 2 g of silica gel, stirred for 2 min and filtered through a short column of silica gel. After removal of the ether the residue was purified by radial chromatography on silica gel with pentane–ether (9:1, pent-4-enol) or pentane–ether (3:1).

Methyl 4-diazoacetyl-3-methylisoxazole-5-carboxylate 6a. 105 mg (25%) yellowish crystals from pentane–ether, mp 56–58 °C; ν_{max}(KBr)/cm^{-1} 3106, 2117, 1733, 1609 and 1578; λ_{max}(EtOH)/nm 235 (log ε 4.22) and 293 (3.98); δ_H(300 MHz, $CDCl_3$) 2.41 (3 H, s, CH_3), 3.92 (3 H, s, OCH_3) and 6.30 (1 H, br, CHN_2); δ_C(75 MHz, $CDCl_3$) 11.44 (q, CH_3), 53.39 (q, OCH_3), 59.08 (d, CHN_2), 121.42 (s, 4-C), 156.45 (s, 3-C), 157.59 (s, 5-C), 160.91 (s, CO, ester) and 179.16 (s, CO, ketone); *m/z* 241 (M$^+$ + isobutane − N_2).

Pent-4-enyl 4-diazoacetyl-3-methylisoxazole-5-carboxylate 6b. 181 mg (34%) yellow oil; ν_{max}(neat)/cm^{-1} 3123, 2109, 1732, 1621 and 1287; λ_{max}(EtOH)/nm 235 (log ε 4.23) and 292 (3.98); δ_H(300 MHz, $CDCl_3$) 1.85–1.99 (2 H, m, 2′-H), 2.22 (2 H, dddt, *J* 7.6, 7.0, 6.7 and 1.5, 3′-H), 2.50 (3 H, s, CH_3), 4.42 (2 H, t, *J*

6.7, 1'-H), 4.97 (1 H, ddt, *J* 7.6, 2.0 and 1.5, 5'-H, *trans*), 5.04 (1 H, ddt, *J* 17.0, 2.0 and 2.0, 5'-H, *cis*), 5.84 (1 H, ddt, *J* 17.0, 10.3 and 6.7, 4'-H) and 6.48 (1 H, br, CHN_2); δ_C(75 MHz, $CDCl_3$) 11.40 (q, CH_3), 27.54 (t, 3'-C), 29.80 (t, 4'-C), 59.02 (d, CHN_2), 66.30 (t, 1'-C), 115.81 (d, 4'-C), 121.18 (s, 4-C), 136.75 (t, 5'-C), 156.73 (s, 5-C), 157.18 (s, 3-C), 160.83 (s, COO) and 179.26 (s, CO, ketone); *m/z* 264 ($M + H^+$).

Pent-4-ynyl 4-diazoacetyl-3-methylisoxazole-5-carboxylate 6c. 212 mg (41%) yellow oil; ν_{max}(neat)/cm^{-1} 3113, 2147, 2109, 1720, 1608, 1579 and 1106; several signals of impurities could be observed in the NMR spectra. The crude product was used for further reaction.

Reaction of pyryliumolate 7a (formed *in situ* from diazoester 6a) with DMAD

A solution of 49 mg (0.24 mmol) diazoketone **6a** in 50 ml toluene was added dropwise to a refluxing solution of 10 mg dirhodium tetraacetate and 270 mg (1.9 mmol) DMAD in 50 ml toluene. After additional refluxing for 2 h the solvent was distilled off and the residue was taken up with ether, filtered through a short column of silica gel and evaporated. The residue was subjected to radial chromatography on silica gel with pentane–ether (3:1) to provide the desired main product dimethyl 5,8-dihydro-5,8-epoxy-8-methoxy-3-methyl-4-oxo-4*H*-cyclohepta[*d*]isoxazole-6,7-dicarboxylate **8** (68%); colourless needles (ether–pentane), mp 111–112 °C; ν_{max}(KBr)/cm^{-1} 2961, 1735, 1730, 1713, 1655, 1256 and 969; δ_H(300 MHz, $CDCl_3$) 2.45 (3 H, s, CH_3), 3.69, 3.83, 3.88 (9 H, 3 s, 3 OCH_3) and 5.40 (1 H, s, 5-H); δ_C(75 MHz, $CDCl_3$) 10.23 (q, CH_3), 53.06, 53.17, 53.82 (3 q, 3 OCH_3), 86.91 (d, 5-C), 107.69 (s, 8-C), 110.21 (s, 3a-C), 140.60 (s, 6-C), 145.25 (s, 7-C), 157.57 (s, 3-C), 160.36, 162.54 (2 s, 2 CO, ester), 175.97 (s, 8a-C) and 187.15 (s, 4-C); *m/z* 323 (M^+), 283. As a minor product a 2:1 adduct could be isolated; 2 mg (2%) colourless crystals (ether–pentane), mp 189–190 °C; ν_{max}(KBr)/cm^{-1} 1740 (CO), 1721 (CO), 1674, 1654, 1308, 1283, 1042 and 890; λ_{max}(EtOH)/nm 233 (log ε 2.50, sh); δ_H(200 MHz, $CDCl_3$) 2.37 (3 H, s, CH_3), 3.99 (3 H, s, OCH_3), 6.85 (1 H, s, CH); *m/z* (CI) 421, 283, 282, the M^+ peak was not observed.

General procedure for decomposition of diazocompound 6

A solution of 0.5–1 mmol diazo compound **6** in 150 ml toluene was added dropwise to a refluxing solution of 10 mg dirhodium tetraacetate in 50 ml of toluene under a nitrogen atmosphere over a period of 3 h. After additional refluxing for 1 h the solvent was evaporated and the residue was taken up with ether and filtrated through a short column of silica gel. After evaporation of ether the residue was purified by radial chromatography on silica gel with pentane–ether (3:1).

5,10a-Epoxy-5,6,6a,7,8,9-hexahydro-3-methyl-4*H*,10a*H*-pyrano[3,4-*b*]cyclohepta[1,2-*d*]isoxazol-4-one 9

Diazo compound **6b** (139 mg, 0.53 mmol) was decomposed following the general procedure. Recrystallisation from ether gave 104 mg (84%) colourless tetragonal crystals, mp 118–119 °C; ν_{max}(KBr)/cm^{-1} 2959, 2899, 1709, 1599 and 895; δ_H(300 MHz, $CDCl_3$) 1.55 (1 H, dddd, *J* 13.4, 12.5, 10.6 and 3.7, 7α-H), 1.69 (1 H, dddddd, *J* 13.9, 3.7, 2.5, 2.0, 0.5 and 0.5, 8α-H), 1.83 (1 H, ddddd, *J* 13.9, 13.4, 12.0, 4.5 and 3.0, 8β-H), 1.97 (1 H, ddd, *J* 13.9, 7.9 and 2.2, 6α-H), 2.12 (1 H, ddddd, *J* 12.5, 6.8, 3.7, 3.0 and 1.9, 7β-H), 2.14 (1 H, ddd, *J* 13.9, 8.9 and 2.1, 6β-H), 2.19 (1 H, dddddd, *J* 10.6, 7.9, 6.8, 2.1, 0.5 and 0.5, 6a-H), 2.47 (3 H, s, CH_3), 3.97 (1 H, ddd, *J* 12.0, 11.0 and 2.5, 9α-H), 4.08 (1 H, dddd, *J* 11.0, 4.5, 2.0 and 0.5, 9β-H), 4.65 (1 H, ddd, *J* 8.9, 2.2 and 0.5, 5-H); δ_C(50 MHz, $CDCl_3$) 10.37 (q, CH_3), 22.89 (t, 8-C), 28.78 (t, 7-C), 33.53 (t, 6-C), 35.31 (d, 6a-C), 63.22 (t, 9-C), 78.91 (d, 5-C), 103.29 (s, 10a-C), 112.16 (s, 3a-C), 157.25 (s, 3-C), 179.08 (s, 10b-C) and 192.25 (s, 4-C); *m/z* 235 (M^+) (Found: 235.0839; $C_{12}H_{13}NO_4$: 235.0845).

5,10a-Epoxy-3-methyl-5,7,8,9-tetrahydro-4*H*,10a*H*-pyrano[3,4-*b*]cyclohepta[1,2-*d*]isoxazol-4-one 10

Diazo compound **6c** (261 mg, 1 mmol) was decomposed following the general procedure. Recrystallisation from ether–pentane gave 106 mg (45%) as colourless tetragonal prisms, mp 80–83 °C; ν_{max}(KBr)/cm^{-1} 1700, 1465, 1065 and 926; δ_H(300 MHz, $CDCl_3$) 1.90 (1 H, ddddd, *J* 14.0, 8.9, 7.1, 7.1 and 4.4, 8α-H), 2.05 (1 H, ddddd, *J* 14.0, 7.7, 6.3, 4.3 and 4.3, 8β-H), 2.38 (1 H, ddddd, *J* 16.4, 9.2, 7.6, 2.9 and 1.6, 7α-H), 2.43 (3 H, s, CH_3), 2.78 (1 H, ddddd, *J* 16.4, 6.3, 4.2, 0.8 and 0.8, 7β-H), 4.21 (1 H, dddd, *J* 12.0, 6.4, 4.7 and 0.8, 9α-H), 4.25 (1 H, ddd, *J* 12.0, 6.9 and 4.3, 9β-H), 5.04 (1 H, dd, *J* 2.6 and 1.6, 5-H), 6.17 (1 H, *J* 2.9 and 2.6, 6-H); δ_C(75 MHz; $CDCl_3$) 10.27 (q, CH_3), 21.72 (t, 8-C), 22.98 (t, 7-C), 65.29 (t, 9-C), 87.37 (d, 5-C), 106.37 (s, 10a-C), 108.08 (s, 3a-C), 125.07 (d, 6-C), 146.12 (s, 6a-C), 157.69 (s, 3-C), 179.75 (s, 10b-C) and 190.77 (s, 4-C); *m/z* 233 (M^+) (Found: 233.0686; $C_{12}H_{11}NO_4$: 233.0688).

8,9-Dihydro-5-hydroxy-3-methyl-4*H*,7*H*-pyrano[3,4-*b*]cyclohepta[1,2-*d*]isoxazol-4-one 11

To a solution of 15.0 mg (0.64 mmol) **10** in 3 ml dichloromethane was added hydrobromic acid (48 wt %; 0.5 ml). The colour of the solution changed rapidly from colourless to orange–red. After addition of 2 ml of ether the precipitate was filtered off and washed with 10 ml ether. The washing solution was concentrated to 1 ml, diluted with 5 ml of water and extracted with 5 ml dichloromethane. After drying over Na_2SO_4 most of the solvent was evaporated and 2 ml of pentane were added to the residue. The combined precipitates gave 14.2 mg (95%) yellow crystals, mp 217–218 °C; ν_{max}(KBr)/cm^{-1} 3247, 1616, 1565, 1523, 1252 and 1070; λ_{max}(EtOH)/nm 231 (log ε 3.96), 245 (sh, 3.91), 331 (sh, 3.54), 352 (3.73) and 389 (3.38); δ_H(300 MHz, [$^2H_6$]DMSO) 1.96–2.04 (2 H, m, 8-H), 2.62 (3 H, s, CH_3), 2.79–2.83 (2 H, m, 7-H), 3.98 (br, OH + H_2O), 4.28–4.31 (2 H, m, 9-H) and 6.91 (1 H, s, 6-H); δ_C(75 MHz, [$^2H_6$]DMSO) 12.36 (q, CH_3), 20.88 (t, 7-C), 28.11 (t, 8-C), 66.12 (t, 9-C), 116.15 (d, 6-C), 117.03 (s, 3a-C), 122.76 (s, 6a-C), 141.57 (s, 10a-C), 155.21 (s, 5-C), 160.53 (s, 3-C), 161.72 (s, 10b-C) and 171.50 (s, 4-C); *m/z* 233 (M^+) (Found: 233.0688; $C_{12}H_{11}NO_4$: 233.0688).

Acknowledgements

The continuous support of our work by the Fonds der Chemischen Industrie is gratefully acknowledged.

References

1 Pyryliumolates I: C. Plüg and W. Friedrichsen, *Tetrahedron Lett.*, 1992, **33**, 7509.

2 (*a*) E. Ciganek, *Org. React.*, 1984, **32**, 1; (*b*) A. G. Fallis, *Can. J. Chem.*, 1984, **62**, 183; (*c*) D. Craig, *Chem. Soc. Rev.*, 1987, **16**, 187; (*d*) W. R. Roush, in *Comprehensive Organic Synthesis*, eds. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 1, p. 513.

3 (*a*) B. A. Keay and R. Rodrigo, *J. Am. Chem. Soc.*, 1982, **104**, 4725; (*b*) B.-M. König and W. Friedrichsen, *Tetrahedron Lett.*, 1987, **28**, 4279; (*c*) W. Friedrichsen, B.-M. König, K. Hildebrandt and T. Debaerdemaeker, *Heterocycles*, 1986, **24**, 297; (*d*) K. Hildebrandt, T. Debaerdemaeker and W. Friedrichsen, *Tetrahedron Lett.*, 1988, **29**, 2045; (*e*) L. Aβmann, T. Debaerdemaeker and W. Friedrichsen, *Tetrahedron Lett.*, 1991, **32**, 1161; (*f*) J. Nagel, W. Friedrichsen and T. Debaerdemaeker, *Z. Naturforsch., Teil B*, 1993, **48**, 213.

4 (*a*) W. Friedrichsen, *Adv. Heterocycl. Chem.*, 1980, **26**, 135; (*b*) R. Rodrigo, *Tetrahedron*, 1988, **44**, 2093; (*c*) B. Rickborn, in *Adv. Theoretically Interset. Molecules*, ed. R. P. Thummel, 1989, JAI Press, Greenwich, Conn., 1989, vol. 1, p. 1; (*d*) W. Friedrichsen, in *Houben-Weyl, Methoden der Organischen Chemie*, ed. R. Kreher, Thieme Verlag, Stuttgart, 1994, vol. E6b1, p. 163.

5 Pyryliumolates can be generated by a variety of methods.[6] One of the earliest hints seems to be the observation by Weitz and Scheffer,[6a] that on heating a solution of 2,3-diphenylindenone epoxide generates a red colour. These authors did not give an explanation for this phenomenon.

6 (*a*) E. Weitz and A. Scheffer, *Ber. Dtsch. Chem. Ges.*, 1921, **54**, 2327;

(*b*) E. F. Ullman and W. A. Henderson, *J. Am. Chem. Soc.*, 1966, **88**, 4942; (*c*) K. Ueda, T. Ibata and M. Takebayashi, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 2779; (*d*) W. Friedrichsen, W. Seidel and T. Debaerdemaeker, *J. Heterocycl. Chem.*, 1983, **20**, 1621; (*e*) K. S. Feldman, *Tetrahedron Lett.*, 1983, **29**, 5585; (*f*) V. M. Zolin, N. D. Dmitrieva, Y. E. Gerasimenko and A. V. Zubkov, *Khim. Geterotsikl. Soedin.*, 1984, 167 (*Chem. Abstr.*, 1984, **101**, 6338); (*g*) A. Padwa, S. P. Carter and H. J. Nimmesgern, *J. Org. Chem.*, 1986, **51**, 1157; (*h*) P. G. Sammes, *Gazz. Chim. Ital.*, 1986, **116**, 109; (*i*) A. Padwa, S. P. Carter, H. J. Nimmesgern and P. D. Stull, *J. Am. Chem. Soc.*, 1988, **110**, 2894; (*j*) A. R. Katritzky and N. Dennis, *Chem. Rev.*, 1989, **89**, 827; (*k*) A. Lupi, M. Patomia and F. Arcamone, *Gazz. Chim. Ital.*, 1990, **120**, 277; (*l*) P. A. Wender and J. L. Mascarenas, *J. Org. Chem.*, 1991, **56**, 6267; (*m*) A. Padwa and K. E. Krumpe, *Tetrahedron*, 1992, **48**, 5385; (*n*) B. J. McBride and M. E. Garst, *Tetrahedron*, 1993, **49**, 2839; (*o*) A. Padwa, *J. Chin. Chem. Soc.*, 1993, **40**, 97; (*p*) K. Matsumoto, Y. Ikemi, M. Toda, A. Kakehi, T. Uchida and J. W. Lown, *Tetrahedron Lett.*, 1995, **36**, 3011; (*q*) K. Matsumoto, Y. Ikemi, A. Kakehi, A. Shigihara and J. W. Lown, *Tetrahedron Lett.*, 1995, **36**, 5295.

7 The methodology used in our work and by others has been elaborated in an impressive series of papers by T. Ibata and co-workers.[8]

8 (*a*) K. Ueda, T. Ibata and M. Takebayashi, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 2779; (*b*) T. Ibata, T. Motoyama and M. Hamaguchi, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 2298; (*c*) T. Ibata, *Chem. Lett.*, 1976, 233; (*d*) T. Ibata and K. Jitsuhiro, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 3582; (*e*) T. Ibata, K. Jitsuhiro and Y. Tsubokura, *Bull. Chem. Soc. Jpn.*, 1981, **54**, 240; (*f*) T. Ibata and J. Toyoda, *Chem. Lett.*, 1983, 1453–1456; (*g*) H. Tamur, T. Ibata and K. Ogawa, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 926; (*h*) J. Toyoda, T. Ibata, H. Tamura, K. Ogawa, T. Nishino and M. Takebayashi, *Bull. Chem. Soc. Jpn.*, 1985, **58**, 2212; (*i*) T. Ibata, H. Nakamo and H. Tamura, *Bull. Chem. Soc. Jpn.*, 1986, **59**, 2489; (*j*) T. Ibata, J. Toyoda, M. Sawada, Y. Takai and T. Tanaka, *J. Chem. Soc., Chem. Commun.*, 1986, 1266; (*k*) T. Ibata, J. Tojoda, M. Sawada, Y. Takai and T. Tonaka, *Tetrahedron Lett.*, 1988, **29**, 317; (*l*) T. Ibata, H. Nakamo and H. Tamura, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 1362.

9 E. Kaji, K. Horada and S. Zen, *Chem. Pharm. Bull.*, 1978, **28**, 3254.

10 The course of the reaction can be delineated from the ^{13}C NMR spectrum of **5** (*vide infra*).

11 Nitrogen extrusion from diazo compounds can be accomplished by a variety of catalysts.[12] For the reactions described in this paper dirhodium tetraacetate was found to be superior over others.

12 (*a*) M. Regitz and G. Maas, *Diazo Compounds*, Academic Press, Orlando, 1986; (*b*) G. Maas, *Top. Curr. Chem.*, 1987, **137**, 75.

13 A. Nikatschalo, Diploma Thesis, University of Kiel, 1990.

14 Compound **2d** has been mentioned in the patent literature: Eur. Pat. Appl. EP 418,667 (V. Maywald, W. Freund, G. Hamprecht, T. Kuekenhoehner, P. Plath, B. Wuerzer and K. O. Westphalen) (*Chem. Abstr.*, 1991, **115**, 92250).

15 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.

16 (*a*) J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 209; (*b*) J. J. P. Stewart, *J. Comput. Chem.*, 1989, **10**, 221.

17 Reviews: (*a*) J. J. P. Stewart, in *Reviews in Computational Chemistry*, eds. K. B. Lipkowitz and D. B. Boyd, VCH Publishers, New York, 1990; (*b*) M. C. Zerner, in *Reviews in Computational Chemistry*, eds. K. B. Lipkowitz and D. B. Boyd, vol. 2, VCH Publishers, New York, 1991.

18 (*a*) See *e.g.*, R. G. Parr and W. Yang, *Density-Functional Theory of Atoms and Molecules*, Oxford University Press, Oxford, 1989; (*b*) T. Ziegler, *Chem. Rev.*, 1991, **91**, 651; (*c*) J. Baker, M. Muir and J. Andzelm, *J. Chem. Phys.*, 1995, **102**, 2063; (*d*) B. Jursic and Z. Zdaravkovski, *J. Chem. Soc., Perkin Trans. 2*, 1995, 1223.

19 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 1372.

20 C. Lee, W. Yang and R. G. Parr, *Phys. Rev.*, 1988, **37B**, 785.

21 H. Shimanouchi and Y. Sasada, *Acta Crystallogr., Sect. B*, 1973, **29**, 81.

22 For semiempirical studies of compounds with OH–O groups see: M. A. Rios and J. Rodriguez, *J. Comput. Chem.*, 1992, **13**, 860.

23 L. A. Brooks and H. R. Snyder, *Org. Synth., Coll. Vol.*, 1955, **3**, 698.

24 G. Eglinton, E. H. R. Jones and M. C. Whiting, *J. Chem. Soc.*, 1952, 2873.

Paper 5/06403A
Received 28*th September* 1995
Accepted 22*nd November* 1995