Diaryldiacyloxyspirosulfuranes. Part 4.[1] A Kinetic Study on the Mechanism of Hydrolysis

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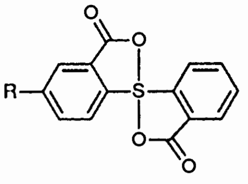
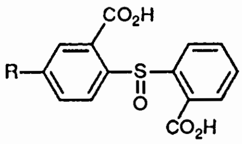
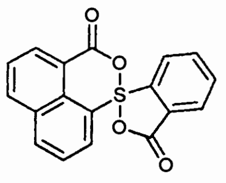
Kinetics of the hydrolysis of diaryldiacyloxyspirosulfuranes leading to sulfoxides have been studied under pseudo-first-order conditions in dioxane–water mixtures. It has been found that high solvent polarities and ionic strengths increase the reaction rate. The reaction is also promoted by electron-donating substituents (ρ −0.52). Strong acids have a catalytic effect on the reaction in which case the substituent effect is more pronounced (ρ −1.55). In neutral medium the deuterium solvent isotope effect is k_{H_2O}/k_{D_2O} 1.66, while in acidic medium the ratio of catalytic constants is found to be 0.56. The rate of the reaction is greatly increased with the increasing size of the spiroring (from 5 to 7) in the sulfurane. Kinetic data suggest a dissociative reaction mechanism.

Diaryldiacyloxyspirosulfuranes, known since 1971, are relatively stable compounds,[2] as they are only slightly sensitive to moisture in crystalline form, but hydrolyse in aqueous organic solvent mixtures. The extreme stability of sulfuranes with spirocyclic five-membered rings, as compared to the acyclic compounds, has also been observed and explained with the so-called 'five-membered ring effect' (for a review see ref. 3). On the other hand, *ab initio* computations[4] performed on SH_2F_2 and SH_2Cl_2 models suggested that in hypervalent systems of 10-S-4 type small distortions of the equatorial or axial bond angles do not play any important role in terms of energy, and so the bond system of sulfuranes should be rather flexible. Previous experiments carried out by Kapovits *et al.*[5] demonstrated that the hydrolysis of diaryldiacyloxyspirosulfuranes **1a–e** yields quantitatively bis(2-carboxyaryl) sulfoxides **2a–e**.


1a–e


2a–e

	a	b	c	d	e
R =	H	NO_2	Cl	OMe	NMe_2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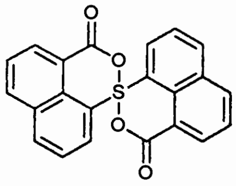
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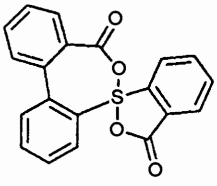
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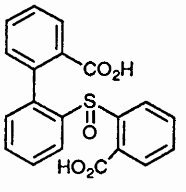
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^{18}O-Tracer experiments proved that the water molecule attacks the sulfur atom when **1a** undergoes hydrolysis. Martin and Balthazor,[6] investigating the kinetics of the hydrolysis of chlorosulfuranes in the presence of bases, proposed an associative nucleophilic displacement mechanism including an octahedral sulfur anion transition state.

In this paper we report on the kinetics of the hydrolysis of sulfuranes **1a–e** and **3–5** including the study of the medium, substituent, deuterium isotope and ring size effect and the acid catalysis. We also performed ^{18}O-tracer experiments in the case of sulfuranes **1b**, **1e** and **5** in order to decide how the nature of substituents or other structural factors affect the centre where the attack of water molecule takes place.

Results and Discussion

Kinetic Equation.—The rates of hydrolysis of spirosulfuranes were measured by a UV-spectrophotometric method in dioxane–water mixtures under the conditions given in the experimental section. The reaction followed pseudo-first-order kinetics as water was used in great excess compared to the sulfuranes, so its concentration could be considered as constant. Rate eqn. (1) was found to be valid until 3–5 half-lives.

$$\text{rate} = k\,[\text{sulfurane}] \qquad (1)$$

The partial order of water and the second-order rate constants could not be calculated from the pseudo-first-order rate constants (k) as the rate of the reaction was strongly affected by the medium effect on changing the concentration of water.

Medium Effect in the Hydrolysis of **1a**.—The rate of the sulfurane hydrolysis is markedly increased with increasing water content of the solvent (Table 1).

Good linear correlations were obtained between log k and the empirical solvent polarity parameters Y,[7] Z,[8] and E_T[9] [eqns. (2)–(4)].

$$\log k = -18.43 + 0.1941\,Z \quad (r\,0.9906) \qquad (2)$$

$$\log k = -2.237 + 0.6461\,Y \quad (r\,0.9994) \qquad (3)$$

$$\log k = -22.33 + 0.3391\,E_T \quad (r\,0.9991) \qquad (4)$$

Table 1 Rate constants (k) for the hydrolysis of spirosulfurane **1a** in different water–dioxane mixtures at 25 °C, and parameters of the solvent polarity E_T, Z[8], and Y[7]

H_2O (% v/v)	$k/10^{-3}\ s^{-1}$	$E_T{}^a$/kcal mol^{-1}	Z/kcal mol^{-1}	Y
10	0.2714	55.4	76.7	−2.030
15	0.7862	56.6	79.2	−1.338^b
20	1.644	57.6	80.2	−0.833
25	3.235	58.5	81.7	−0.390^b
30	5.853	59.3	83.8	0.013

[a] See Experimental section. [b] Calculated from empirical equations given in ref. 7.

Table 2 Rate constants (k) for the hydrolysis of spirosulfuranes **1a–e** in 80:20 (v/v) dioxane–water at 25 °C, and parameters k_o and k_{cat} related to eqn. (8) for p-toluenesulfonic acid

Sulfurane	$k/10^{-3}\ s^{-1}$	$k_o/10^{-3}\ s^{-1}$	k_{cat}/dm^3 mol^{-1} s^{-1}	r
1a^a	1.644	1.745	4.18	0.9991
1a^b	0.992	1.020	7.43	0.9995
1b^c	0.935	(1.039)	(0.162)	0.7020
1c	2.018	1.773	1.64	0.9991
1d	4.154	4.201	13.99	0.9997
1e	6.24	5.48	46.1	0.9981

[a] In reactions catalysed by nitric acid k_o 1.64 × 10^{-3} s^{-1} and k_{cat} 3.36 dm^3 mol^{-1} s^{-1} (r 0.9999) were obtained. [b] Determined in 80:20 (v/v) dioxane–D_2O. [c] The experimental error is higher for values given in parentheses.

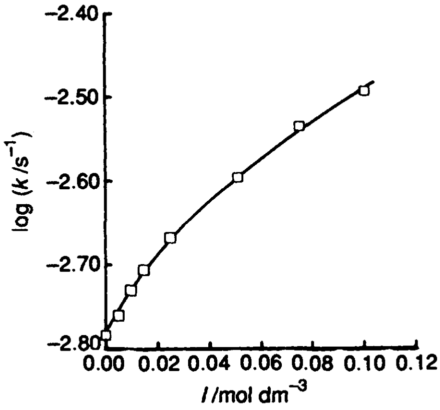


Fig. 1 Effect of the ionic strength (I) on the rate constant (k) for the hydrolysis of spirosulfurane **1a** in 80:20 (v/v) dioxane–water at 25 °C: electrolyte, $LiClO_4$

Since the reaction discussed occurs between neutral molecules, the increase in reactivity with the increasing ionizing power of the solvent indicates that the polarity of the transition state is higher than that of the ground state. Ionization takes place with the splitting of the S–O bonds during the hydrolysis of sulfuranes.

The increase in the ionic strength of the medium increased the rate of the reaction, too, even at low concentrations of the added salt (Fig. 1). The log k *versus* I plot is not linear (especially at low ionic strengths) showing some similarity to the 'special electrolyte effect' of the S_N1 reactions which proceed through an ion pair intermediate.[10]

Substituent Effects.—The hydrolysis of spirosulfuranes is retarded by electron-withdrawing substituents, and promoted by electron-donating ones.

The correlations of the rate constants (Table 2) with the substituent constants σ and σ^+ (*cf.* ref. 11), as well as with σ_I and σ_R (*cf.* ref. 12) were tested using the Hammett (5, 6) and the dual parameter Taft (7) equations, respectively.

$$\log k = \log k_o + \rho\sigma \quad (5)$$

$$\log k = \log k_o + \rho^+\sigma^+ \quad (6)$$

$$\log k = \log k_o + \rho_I\sigma_I + \rho_R\sigma_R \quad (7)$$

While eqn. (5) gave an acceptable correlation (ρ −0.524, r 0.9542), in the case of eqns. (6) and (7) the correlation proved to be better (ρ^+ −0.335, r 0.9780, and ρ_I −0.189, ρ_R −0.729, r 0.9988, respectively). In all three cases small, negative ρ values were obtained. The high correlation coefficient found for eqn. (7) might be partly associated with the increase in the number of parameters.

Acid Catalysis.—The hydrolysis of spirosulfuranes was catalysed by strong acids (Table 2). p-Toluenesulfonic acid (pK_a −6.5) which can be highly ionized in dilute solution even in a solvent mixture containing only 20% v/v of water in dioxane, showed a measurable catalytic effect. A linear relationship was found between the rate of hydrolysis and the concentration of p-toluenesulfonic acid, taken equal to $[H_3O^+]$. Catalytic constants were calculated from eqn. (8).

$$k = k_o + k_{cat}[\text{acid}] \quad (8)$$

The catalytic effect was smaller by only 20% when the reaction was carried out in the presence of nitric acid, although HNO_3 is much weaker (pK_a −1.4) than p-TsOH (Table 2). The results prove that H_3O^+ ions take part in the reaction.

The substituent effect in the acid catalysis was evaluated from the Hammett eqn. (5) using the k_{cat} catalytic constants (Table 2) and the σ substituent constants. The reaction constant ρ −1.55 (r 0.998) obtained indicated that the acid catalysed reaction was also promoted by electron-donating substituents. In sulfurane **1e** the NMe_2 group is a weak base as it has a strong electron-withdrawing sulfuranyl group in the *para* position, and therefore it can be protonated only to a very small amount in a solvent containing 10^{-3} mol dm^{-3} of p-toluenesulfonic acid. This is supported by the identity of the UV-absorption of compound **1e** both in acidic and in neutral solutions, and by the observed high reactivity. In the protonated form the UV bands of **1e** should show a blue shift and in this case the compound should react as slowly as the nitro-substituted derivative, because the substituent constants of the two groups are nearly the same.

Deuterium Isotope Effect.—The solvent isotope effect for the hydrolysis of spirosulfurane **1a** was studied in dioxane containing 20% v/v of H_2O or D_2O. The non-catalysed reaction gave k_{H_2O}/k_{D_2O} 1.66, while in the hydrolysis catalysed by p-TsOH for the catalytic constants an inverse isotope effect k_{H_2O}/k_{D_2O} 0.56 was obtained (*cf.* Table 2).

Ring Size Effect.—For the elucidation of the ring size effect on the stability, the rate of hydrolysis of spirosulfuranes **3–5**[1] was studied. As these compounds hydrolyse rapidly, kinetic measurements were carried out at low water concentrations, and rate constants were correlated with the E_T values determined by us for the solvent mixtures used (Table 3).

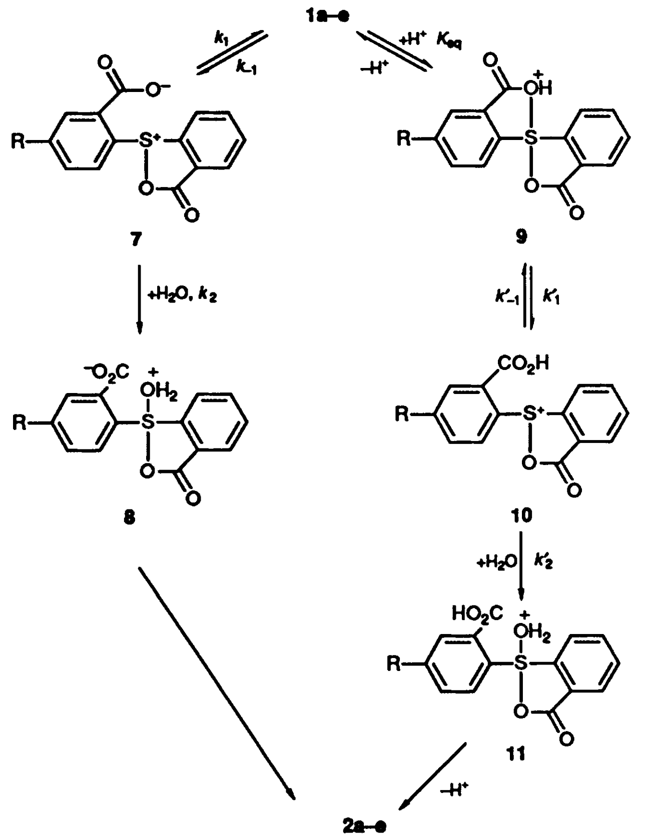
Similarly to the case of **1a**, linear correlations were found between log k and E_T for sulfuranes **3** and **4** [eqns. (9) and (10)].

$$\log k_3 = -13.097 + 0.2034\,E_T\,(r\ 0.9986) \quad (9)$$

$$\log k_4 = -11.274 + 0.1701\,E_T\,(r\ 0.9991) \quad (10)$$

Table 3 Rate constants (k) for the hydrolysis of spirosulfuranes **3**, **4** and **5** at 25 °C in water–dioxane mixtures, and corresponding E_T parameters

H_2O (% v/v)	$k/10^{-3}$ s^{-1} **3**	**4**	**5**	E_T/kcal mol^{-1}
2.5	1.07	1.57	63	49.7
5.0	3.60	4.50	—	52.5
7.5	8.69	8.75	—	54.3
10.0	14.56	13.49	—	55.4
12.5	21.78	20.05	—	56.1



Scheme 1

A comparison of the slopes of eqns. (4), (9) and (10) shows that the influence of the solvent polarity on the reaction rate increases in the order **4** < **3** < **1a**. In dioxane containing 10% v/v of water sulfuranes **3** and **4** hydrolyse approximately 50-times faster than **1a**. Sulfurane **5** containing a seven- and a five-membered ring is the most unstable towards hydrolysis, therefore we could measure its rate with the conventional methods only in dioxane containing 2.5% v/v of H_2O. The rate constants in Table 3 indicate that compound **5** reacts 60-times faster than **3** under these conditions.

^{18}O *Tracer Experiments.*—Sulfuranes **1b**, **1e** and **5** were hydrolysed in dioxane–$^{18}OH_2$ mixtures. In the IR spectra of the obtained sulfoxides **2b**, **2e** and **6** only the $\nu_{S=O}$ band shifted markedly as compared with that of the corresponding unlabelled compounds (see Experimental section). The ^{18}O content of labelled compounds was determined from the mass spectra of the dimethyl esters of sulfoxide dicarboxylic acids **2b**, **2e** and **6**.

Mechanism.—From the experimental data we concluded that the hydrolysis of spirosulfuranes **1a–e** starts with a fast equilibrium reaction of ring opening and ring closure. In the subsequent rate-determining slow step water attacks the sulfonium centre in the intermediate **7** leading to **8**. The sulfoxides **2a–e** are formed in fast proton transfers (Scheme 1).

Since the carboxylate group in the zwitterion **7** is in a favourable position to initiate an intramolecular nucleophilic attack at the sulfonium centre, the recyclisation leading to the original five-membered spiroring is more likely. That is why the average lifetime of the sulfonium ion **7** is very short, and the intermediate is transformed mostly into spirosulfurane. Using the steady-state approximation for **7**, the condition $k_{-1} \gg k_2[H_2O]$ leads to the rate eqn. (11), where [S] is the sulfurane concentration.

$$\text{rate} = \frac{k_1 k_2}{k_{-1}}[H_2O][S] = k\,[S] \qquad (11)$$

High solvent polarities or ionic strengths stabilize the zwitterion intermediate **7**, increasing its average lifetime (k_{-1} decreases). Thus the rate of hydrolysis also increases because water molecules will have a greater chance to attack the sulfonium centre (k_2 and k will increase, too).

All these facts are supported by the linear free energy relationships observed between the reaction rates and the ionizing power of the solvent [eqns. (2)–(4)] and the non-linear dependence of log k on the ionic strength at low salt concentrations (Fig. 1). Reaction constants are composed of three terms: $\rho = \rho_1 - \rho_{-1} + \rho_2$ corresponding to the rate constants in eqn. (11). It can be expected that (i) ρ_1 will be negative owing to the formation of the sulfonium centre, (ii) ρ_2 and ρ_{-1} related with nucleophilic substitutions will be positive, and (iii) the summation of the three terms will result in a negative ρ constant of small absolute value. According to the mechanism presented in Scheme 1, only a secondary isotope effect is to be taken into account. This effect can be estimated on the basis of eqn. (12) using the isotopic fractionation factors.[13]

$$\frac{k_{H_2O}}{k_{D_2O}} = \left[\frac{k^H}{k^D}\right]_{sec} = \left[\frac{\varphi^2_{OL}}{\varphi^2_{OL^+}}\right]^x = 1.66 \qquad (12)$$

Substituting φ_{OL} 1 and φ_{OL^+} 0.69 values[13] in eqn. (12), from the observed isotope effect, x 0.68 was obtained for the reaction coordinate of the transition state, which seems to be reasonable.

Sulfuranes **3–5** containing six- and seven-membered rings hydrolyse more rapidly than compounds **1a–e**. It is known that, for steric reasons, the anchimeric assistance and the sulfur–oxygen non-bonded interaction of neighbouring groups capable of forming six- or seven-membered rings is much weaker than the activity of those groups which can be closed to a five-membered ring.[14–16] The cyclisation of the zwitterion intermediates formed from **3–5** (which are analogues of **7** with different ring sizes) is much slower than in the case of compounds **1a–e**, because of the unfavourable entropy factor. Thus the chance of the attack of water molecules is greater and, consequently, the hydrolysis is faster. In accordance with these suppositions, the importance of the solvent polarity is also decreased in stabilizing the sulfonium centre, which is reflected in the smaller slopes of log k–E_T functions [eqns. (9) and (10)].

In acid-catalysed reactions the sulfurane is protonated to **9** in a fast equilibrium reaction. The next step is a ring opening which results in the formation of a sulfonium intermediate **10**. As the neutral carboxyl is a weaker nucleophile than the negatively charged carboxylate, the rate of the ring closure reaction (k_{-1}) is smaller, and the lifetime of the sulfonium ion **10** is greater than that of the zwitterion **7**. This results in a higher rate constant for the hydrolysis reaction. The reaction constant ρ calculated from the Hammett equation is of a greater negative value than

Table 4 Wavelengths of the absorption maxima for the solvatochromic band of 2,4,6-triphenyl-1-(4-hydroxyphenyl)pyridinium betaine in different water–dioxane mixtures at 25 °C

H_2O (% v/v)	λ_{max}/nm	H_2O (% v/v)	λ_{max}/nm
2.5	575.7	30.0	482.5
5.0	544.3	35.0	477.5
7.5	526.7	40.0	472.1
10.0	516.5	45.0	467.3
12.5	509.2	50.0	460.2
15.0	505.0	55.0	454.7
20.0	495.9	60.0	450.0
25.0	488.6	—	—

that found for the non-catalysed reaction. To the usual three terms of ρ is added a new term ($\rho = \rho_{eq} + \rho'_1 - \rho'_1 + \rho'_2$) arising from the protonation equilibrium which is also promoted by the electron-donating substituents. By calculating the deuterium isotope effect for the acid-catalysed reaction, both the isotope effect connected with the protonation equilibrium and the secondary isotope effect generated by the nucleophilic substitution are to be considered [eqn. (13)].[13]

$$\frac{k_{H_2O}}{k_{D_2O}} = \left[\frac{K^H}{K^D}\right]_{eq}\left[\frac{k^H}{k^D}\right]_{sec} = \left[\frac{\varphi^3_{OL^+}}{\varphi^3_{OL}}\right]\left[\frac{\varphi^2_{OL}}{\varphi^2_{OL}}\right]^x = 0.56 \quad (13)$$

Substituting the values of the isotopic fractionation factors and the observed isotope effect, x 0.72 was obtained for the reaction coordinate of the transition state, which is in agreement with the data found in the non-catalysed reaction.

Experimental

Materials.—Spirosulfuranes were prepared by known methods (see Ref. 5 for **1a–d**, Ref. 17 for **1e** and Ref. 1 for **3–5**). *p*-Toluenesulfonic acid was recrystallized from concentrated HCl solution. Spectroscopic grade abs. dioxane used in kinetic experiments was obtained from analytical grade dioxane (Reanal, Budapest) by adequate procedure.[18] Before use, traces of peroxides were removed by distillation from $LiAlH_4$.

Kinetics.—Kinetic measurements were carried out with a SPECORD 40M UV-VIS (Zeiss, Jena) spectrophotometer in dioxane–water mixtures (2.5–30% v/v of H_2O) using quartz cells of 1 cm, in the wavelength range 258–333 nm. The initial concentration of the sulfuranes was $0.5–5 \times 10^{-4}$ mol dm^{-3}. The reaction was started by mixing quickly aliquots of solutions of sulfurane in dioxane with adequate quantities of water, aqueous $LiClO_4$, *p*-toluenesulfonic acid or HNO_3 solutions, and with D_2O or solutions of *p*-toluenesulfonic acid in D_2O, as required. The effect of the ionic strength was studied in the presence of $LiClO_4$ (0.005–0.1 mol dm^{-3}), while acid catalysis was investigated using *p*-toluenesulfonic acid or HNO_3 (5×10^{-5}–1×10^{-3} mol dm^{-3}). Relative errors of the rate constants were less than ± 3%.

Determination of E_T *Values for Dioxane–Water Mixtures.*—2,4,6-Triphenyl-1-(4-hydroxyphenyl) pyridinium betaine (Aldrich, 98%) was used to indicate the polarity of the solvent mixtures. Water content of the solvent was varied in the range 2.5–30% v/v. E_T Values were calculated from the wavelengths corresponding to the solvatochromic band of the dye (Table 4) using eqn. (14).

$$E_T = hc/\lambda_{max} = 2.859 \times 10^4/\lambda_{max} \quad (14)$$

Solutions ($3–4 \times 10^{-4}$ mol dm^{-3}) were prepared immediately before use and the dye was stabilized by adding $Na_2S_2O_3$ ($1–3 \times 10^{-4}$ mol dm^{-3}). Note that λ_{max} values found by us were somewhat higher than those reported,[19] especially at lower water concentrations.

Preparation of ^{18}*O-Labelled Sulfoxides.*—^{18}O-Labelled sulfoxides **2b**, **2e** and **6** were prepared from the corresponding sulfuranes **1b**, **1e** and **5**, respectively by hydrolysis. A mixture of ^{18}O-enriched water (82.9% atom, 0.1 cm^3) and abs. dioxane (0.9 cm^3) was added to sulfuranes (*ca.* 70 mg) then the mixtures were heated in sealed tubes at 100 °C for 1 h (in each case the mixture became homogeneous). The solvent was evaporated and the product was dried in vacuum over P_2O_5. In the IR spectra of sulfoxides **2b**, **2e** and **6** (50 mg cm^{-3} in DMF, 0.04 mm cell length) the $\nu_{S=O}$ bands were shifted by ^{18}O-labelling from 1031 cm^{-1}, 1028 cm^{-1} and 1026 cm^{-1} to 1004 cm^{-1}, 996 cm^{-1} and 994 cm^{-1}, respectively. Mass spectra (recorded with MS 25-RFA instrument with direct evaporation at 260 °C) of the dimethyl esters of the ^{18}O-labelled sulfoxide dicarboxylic acids **2b** [EI *m*/*z* 365 (M^+, 2.1%), 363 (0.4), 334 (5.4), 332 (1.0)], **2e** [EI *m*/*z* 363 (M^+, 6.8%), 361 (1.4)] and **6** [CI (isobutane) *m*/*z* 397 (8.5%, M + H), 395 (2.9)], prepared with diazomethane from products obtained in hydrolysis experiments, indicated ^{18}O incorporations of 84, 83 and 75%, respectively. The lower value found for sulfoxide **6** can be explained by the partial hydrolysis of the starting sulfurane **5**, which is very sensitive to moisture.

Acknowledgements

The authors thank the Hungarian Scientific Research Foundation (OTKA, Nr. 2238) for the financial support and one of us (E. Vass) for the grants given by the 'Kemény Zsigmond' Foundation (Budapest, Hungary) and the 'Foundation for the Hungarian Science' of the Hungarian Credit Bank. The authors also thank Dr. Kálmán Újszászy for the mass spectra analyses, and Prof. Árpád Kucsman for discussions.

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Paper 3/00499F
Received 26*th January* 1993
Accepted 24*th February* 1993