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Photochemical Dimerization of Methoxy Substituted Cinnamic Acid Methyl Esters

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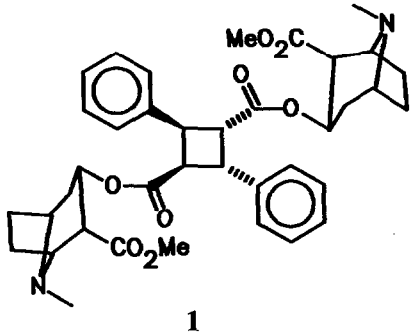
Abstract: Photochemical dimerization of methyl methoxycinnamates was studied. Dimer formation was observed both in unsensitized and in sensitized reactions. The reactions showed a high stereoselectivity.

α- and β-Truxilline **1** and **2** are alkaloid components of *Erythroxylum coca* and *Erythroxylum novogranatense*.[1] They are strong heart toxins.[2]



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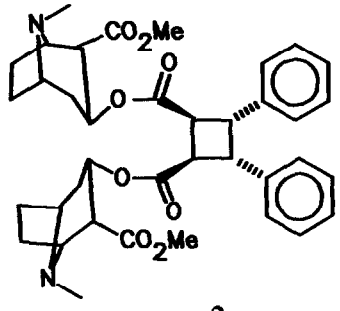

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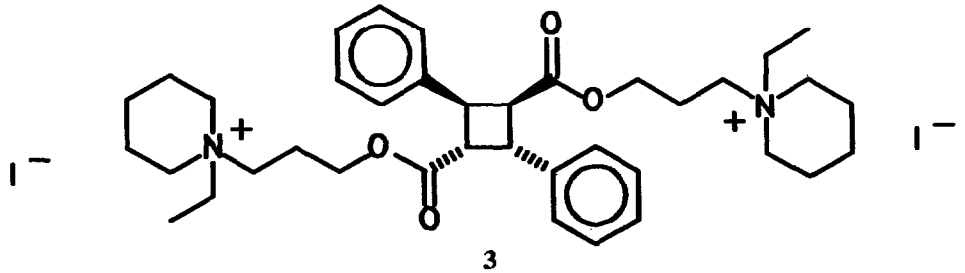

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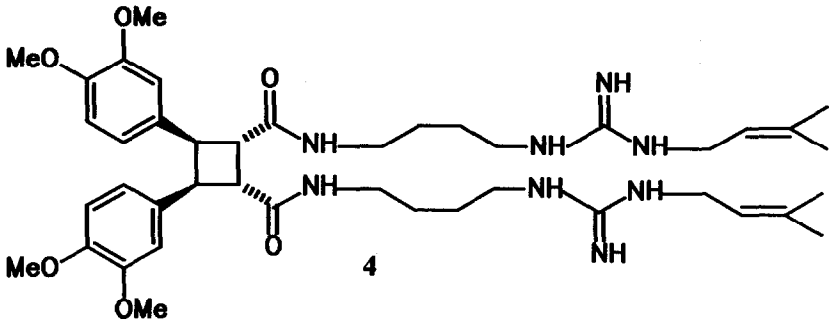

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Bis-quaternary ammonium derivatives of truxillic acid such us **3** are active antidepolarizing curare-like agents. They are able to induce tachycardia by blockade of muscarinic receptors of the heart.[3]

Dimers of *p*-coumaric and ferulic acid are present in graminaceous cell walls and are likely to be of importance in limiting wall biodegradability.[4,5]

Finally compound **4**, isolated in *Verbesina caracasana*, shows hypotensive activity.[6]

Recently we have reported a new photochemical dimerization procedure in solution of 3-(2-furyl)acrylates.[7] Unfortunately this reaction did not work using methyl cinnamate. The photochemical dimerization of cinnamic acid is a very old reaction.[8] Cinnamic acid, irradiated in solid state gave the corresponding photodimers depending on the crystal form of the starting material.[9] However, while *o*-methoxycinnamic acid furnished the corresponding dimer, *m*-methoxy- and *p*-methoxycinnamic acid did not give any dimerization product.[9] The reactivity of the esters is more complex. Cinnamate esters are able to dimerize without solvents[10] and in micellar media.[11] Irradiation in methanolic solution did not furnish any cyclodimerization product, giving instead only *E-Z* isomerization.[12] The irradiation of a dichloromethane solution in the presence of BF_3 furnished a mixture of dimeric products.[13] However the application of this methodology to methyl 3,4-dimethoxycinnamate failed.[14] 3,4-Dimethoxycinnamic derivatives can be dimerized only in the presence of cyclodextrin.[15]

On the basis of these reported data we decided to test the photochemical dimerization of methyl methoxycinnamate derivatives in acetonitrile both without and in the presence of a sensitizer.

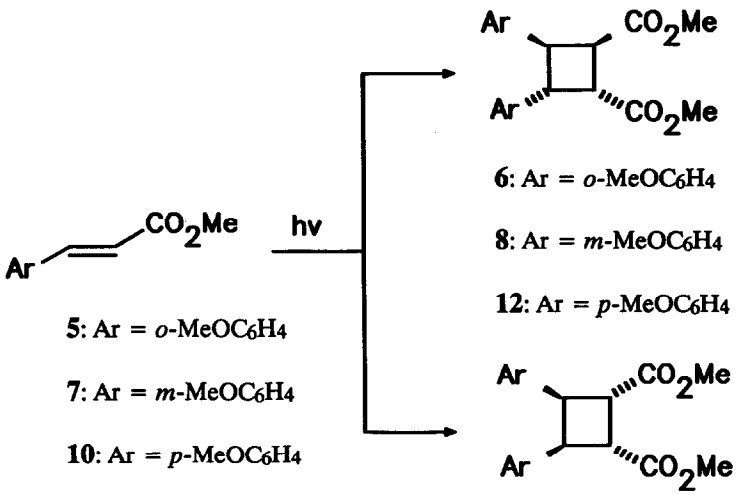
All the reactions were carried out in acetonitrile by using $1.2 - 1.3 \times 10^{-2}$ M solution of each substrate. The irradiation was performed by using a 500 W high-pressure mercury arc and a Pyrex filter. In all the experiments the irradiation was maintained for 30 hours.

First we have used *ortho*, *meta*, and *para*-methoxycinnamic acids methyl ester. The irradiation of methyl *o*-methoxycinnamate without sensitizer allowed us to obtain only 28% conversion of the starting material. At the end of the reaction the *E/Z* ratio in the cinnamate was 0.35.

The reacted material furnished 74% yield of only one dimer, the compound **6**. When the irradiation was carried out in the presence of benzophenone, while the *E/Z* ratio in **5** was 0.45, we could obtain 40% conversion and the converted material gave **6** in 83% yield. The irradiation of *meta*-methoxycinnamic acid methyl ester **7** showed a similar behaviour with an important difference: all the reactions was almost quantitative. The irradiation of **7** without the sensitizer provided a 96% conversion. The recovered starting material showed an *E/Z* ratio equal to 1. The reaction afforded **8** in 71% yield in the presence of a little amount of **9** (7%).

In the presence of benzophenone we observed 94% conversion of **7**. The starting material showed an *E/Z* ratio = 2.0, while **8** can be obtained in 81% yield in the presence of only 5% of **9**.

Para-methoxycinnamic acid methyl ester **10** did not react when irradiated without the sensitizer. We observed only *E-Z* isomerization of **10** with an *E/Z* ratio of 1.6. On the contrary, when the irradiation was performed in the presence of benzophenone, 65% conversion of **10** was observed. The *E/Z* ratio in **10** at the end of the reaction was 3 and we obtained from the converted materials an 1:1 mixture of **11** and **12**.



As regards the selectivity of the reaction better results can be obtained using *p*-nitroaniline as sensitizer. This compound was used in photodimerization reactions of ethyl cinnamate without solvent.[12] Using this sensitizer **11** can be obtained in 75% yield while **12** lowered to 18% yield; however the reaction afforded only 15% conversion of **10**; the latter result probably can be due to decomposition of the sensitizer during the irradiation.

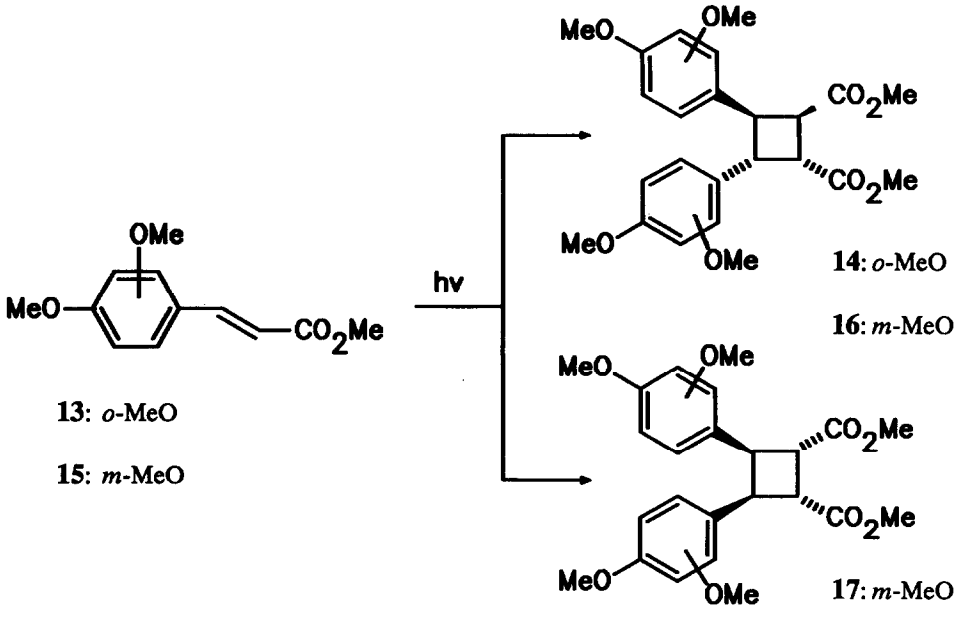
In conclusion, considering only methyl monomethoxycinnamate esters, the observed reactivity order was *meta* >*para* > *ortho*. In particular, this reactivity order is related only to sensitized reactions, because in non sensitized experiments *para* isomer did not react. Ishigami et al.[16] reported that β-truxinate dimers were obtained *via* the singlet state of the starting material while δ-truxinate dimers derived from the excited triplet state: in fact, the formation of δ-truxinate dimers was favored in sensitized reactions. Our results do not seem to be in agreement with this hypothesis. In fact, *o*-methoxycinnamate ester gave the same product both in unsensitized and in sensitized reactions. The same result was obtained using *m*-methoxy substituted derivatives. Only with *p*-methoxycinnamic acid methyl ester, using *p*-nitroaniline as sensitizer, we observed a considerable change in product distribution.

We have tested also some bisubstituted cinnamic esters. We used 2,4-dimethoxy and 3,4-dimethoxycinnamic acid methyl ester. 2,4-Dimethoxy derivative **13** showed a very low reactivity. In fact, without sensitizer 20% conversion of **13** was observed. The converted material gave **14** in 50% yield.

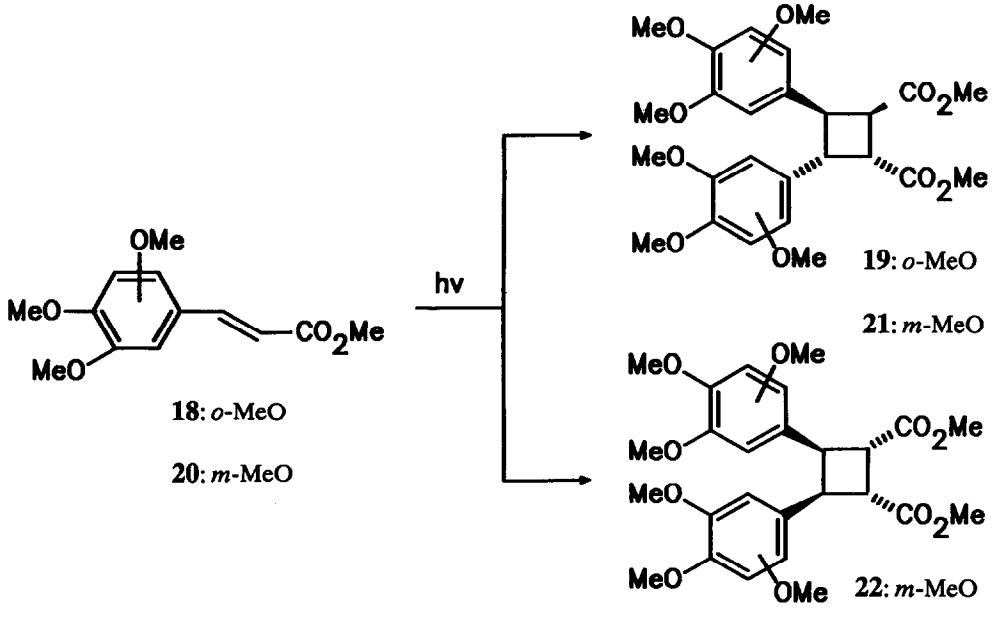
In sensitized reaction (benzophenone) the conversion failed further (14%), but the converted material gave **14** in 71% yield. 3,4-Dimethoxycinnamic acid methyl ester showed a different trend of reactivity. Without sensitizer 67% conversion of **15** was obtained, giving **16** (85%) and **17** (15%).

Using benzophenone as sensitizer, **15** gave 80% conversion, furnishing **16** and **17** in 54 and 31% yields respectively.

Finally we have tested the reactivity of two trisubstituted cinnamates, 2,4,5-trimethoxy- and 3,4,5-trimethoxycinnamic acid methyl ester. Also in this case dramatic differences in reactivity were observed changing the substitution pattern of the substrate. While methyl 2,4,5-trimethoxycinnamate **18** both in unsensitized and in sensitized reactions furnished 40% conversion giving **19** in 5 and 10% yields respectively, **20**, irradiated in the absence of benzophenone, gave 50% conversion of the starting material giving **21** and **22** in 70 and 26% yields respectively.



In sensitized reaction 100% conversion of **20** was observed giving **21** and **22** in 49 and 43% yields, The same ratio between **21** and **22** was obtained using *p*-nitroaniline as sensitizer, although also in this case lower conversion of the starting material was observed (36%).



In conclusion, we have shown that photochemical dimerization of methoxycinnamic esters can be obtained, in contrast with previous reported data. These reactions can be sensitized by benzophenone

showing in most cases an increase in selectivity. When polysubstituted cinnamate esters were used, the presence of a methoxy group in *ortho*-position inhibits the reactivity. The reason of this effect is not clear. Also using polysubstituted methoxycinnamate esters any relationship was not found between product distribution and use of a sensitizer. While methyl *p*-methoxycinnamate showed different selectivity by using *p*-nitroaniline as sensitizer, this effect did not work in **20**. Finally, all the reactions showed a high stereoselectivity allowing us to obtain only head-to-head dimers and only one or two isomeric compounds. Further studies devoted to determine photophysical properties of methoxycinnamate esters are in due course.

Experimental

^{1}H NMR spectra were recorded with a Varian Gemini 200 MHz spectrometers with $CDCl_3$ as solvent. Mass spectra were obtained with a Kratos MS-80 instrument by direct insertion at a source temperature of 150C.

Synthesis of cyclobutane derivatives - General Procedure - Cinnamate ester (1 g) was dissolved in acetonitrile (300 ml). In sensitized reactions benzophenone or *p*-nitroaniline (100 mg) were added. The solution was outgassed with nitrogen for 1 h and was then irradiated in an immersion apparatus with a 500 W high-pressure mercury arc (Helios- Italquartz) surrounded by a Pyrex water-jacket. After 30 h, removal of the solvent under reduced pressure yielded a crude product, which was chromatographed on silica gel. The products were identified in comparison with ^{1}H NMR and MS spectral data of similar compounds.[17-19] The following compounds were thus prepared.

Dimethyl t-3,c-4-di-(2-methoxyphenyl)cyclobutane-r-1,t-2-dicarboxylate 6 - ^{1}H NMR ($CDCl_3$) δ: 6.99 (m, 2 H), 6.71 (dd, 1 H, J = 8 Hz), 6.51 (d, 1 H, J = 8 Hz), 4.57 (m, 1 H), 3.98 (m, 1 H), 3.72 (s, 3 H), 3.51 (s, 3 H); MS (*m/z*): 384 (1), 240 (1), 192 (100%).

Dimethyl t-3,c-4-di-(3-methoxyphenyl)cyclobutane-r-1,t-2-dicarboxylate 8 - ^{1}H NMR ($CDCl_3$) δ: 7.03 (dd, 1 H, $J_1 = J_2 = 8$ Hz), 6.59 (dd, 1 H, $J_1 = 8$ Hz, $J_2 = 2.6$ Hz), 6.55 (d, 1 H, J = 8 Hz), 6.43 (m, 1 H), 4.34 (m, 1 H), 3.80 (m, 1 H), 3.73 (s, 3 H), 3.60 (s, 3 H); MS (*m/z*): 384 (2), 240 (1), 192 (100%).

Dimethyl t-3,t-4-di-(3-methoxyphenyl)cyclobutane-r-1,c-2-dicarboxylate 9 - ^{1}H NMR ($CDCl_3$) δ: 7.22 (m, 1 H), 6.83 (m, 3 H), 3.77 (s, 3 H), 3.72 (s, 3 H), 3.68 (m, 1 H), 3.46 (m, 1 H); MS (*m/z*): 384 (2), 240 (1), 192 (100%).

Dimethyl t-3,t-4-di-(4-methoxyphenyl)cyclobutane-r-1,c-2-dicarboxylate 11 - ^{1}H NMR ($CDCl_3$) δ: 7.18 (d, 2 H, J = 9 Hz), 6.83 (d, 2 H, J = 9 Hz), 3.76 (s, 3 H), 3.70 (s, 3 H), 3.58 (m, 1 H), 3.40 (m, 1 H); MS (*m/z*): 384 (2), 240 (1), 192 (100%).

Dimethyl t-3,c-4-di-(4-methoxyphenyl)cyclobutane-r-1,t-2-dicarboxylate 12 - ^{1}H NMR ($CDCl_3$) δ: 6.81 (d, 2 H, J = 9 Hz), 6.63 (d, 2 H, J = 9 Hz), 4.27 (m, 1 H), 3.78 (m, 1 H), 3.71 (s, 3 H), 3.68 (s, 3 H); MS (*m/z*): 384 (1), 240 (1), 192 (100%).

Dimethyl t-3,c-4-di-(2,4-dimethoxyphenyl)cyclobutane-r-1,t-2-dicarboxylate 14 - ^{1}H NMR ($CDCl_3$) δ: 6.6 - 6.1 (m, 3 H), 4.43 (m, 1 H), 3.88 (m, 1 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 3.51 (s, 3 H); MS (*m/z*): 444 (3), 300 (1), 222 (100%).

Dimethyl t-3,c-4-di-(3,4-dimethoxyphenyl)cyclobutane-r-1,t-2-dicarboxylate 16 - ^{1}H NMR ($CDCl_3$) d: 6.63 (d, 1 H, J = 8 Hz), 6.52 (dd, 1 H, J_1 = 8 Hz, J_2 = 2 Hz), 6.29 (d, 1 H, J = 2 Hz), 4.25 (m, 1 H), 3.83 (m, 1 H), 3.75 (s, 3 H), 3.71 (s, 3 H), 3.58 (s, 3 H); MS (m/z): 444 (1), 300 (1), 222 (100%).

Dimethyl t-3,t-4-di-(3,4-dimethoxyphenyl)cyclobutane-r-1,c-2-dicarboxylate 17 - ^{1}H NMR ($CDCl_3$) d: 6.80 (s, 2 H), 6.77 (s, 1 H), 3.87 (s, 3 H), 3.83 (s, 6 H), 3.57 (m, 1 H), 3.41 (m, 1 H); MS (m/z): 444 (3), 300 (2), 222 (100%).

Dimethyl t-3,c-4-di-(2,4,5-trimethoxyphenyl)cyclobutane-r-1,t-2-dicarboxylate 19 - ^{1}H NMR ($CDCl_3$) d: 6.48 (s, 1 H), 6.22 (s, 1 H), 4.46 (m, 1 H), 3.82 (m, 1 H), 3.74 (s, 3 H), 3.70 (s, 3 H), 3.64 (s, 3 H), 3.51 (s, 3 H); MS (m/z): 504 (2), 360 (1), 252 (100%).

Dimethyl t-3,c-4-di-(3,4,5-trimethoxyphenyl)cyclobutane-r-1,t-2-dicarboxylate 21 - ^{1}H NMR ($CDCl_3$) δ: 6.10 (s, 2 H), 4.26 (m, 1 H), 3.79 (m, 1 H) 3.73 (s, 3 H), 3.70 (s, 3 H), 3.63 (s, 6 H); MS (*m/z*): 504 (3), 360 (1), 252 (100%).

Dimethyl t-3,t-4-di-(3,4,5-trimethoxyphenyl)cyclobutane-r-1,c-2-dicarboxylate 22 - ^{1}H NMR ($CDCl_3$) δ: 6.47 (s, 2 H), 3.79 (s, 6 H), 3.78 (s, 3 H), 3.72 (s, 3 H), 3.56 (m, 1 H), 3.42 (m, 1 H); MS (*m/z*): 504 (2), 360 (1), 252 (100%).

REFERENCES

1 Novak, M.; Salemink, C. A.; Khan, I. *J. Ethnopharmacol.*, **1984**, *10*, 261.
2 Liebermann, C. *Chem. Ber.*, **1888**, *21*, 2342.
3 Kharkevich, D. A.; Skoldinov, A. P.; Samoilov, D. N.; Shorr, V. A. *Adv. Behav. Biol.*, **1981**, *25*, 351.
4 Ford, C. W.; Hartley, R. D. *J. Sci. Food Agric.*, **1989**, *46*, 301.
5 Hartley, R. D.; Whatley, E. R.; Harris, P. J. *Phytochemistry*, **1988**, *27*, 349.
6 Botta, M.; Corelli, F.; De Luca, C. *Proceedings of Sino-Italian Symposium on Chemistry of Natural Products*, Shanghai, 1991, p. 114.
7 D'Auria, M.; Piancatelli, G.; Vantaggi, A. *J. Chem. Soc. Perkin Trans. I*, **1990**, 2999.
8 Stobbe, H. *Chem. Ber.*, **1919**, *52*, 666.
9 a) Cohen, M. D.; Schmidt, G. M. J.; Sonntag, F. I. *J. Chem. Soc.*, **1964**, 2000; b) Schmidt, G. M. J. *J. Chem. Soc.*, **1964**, 2014; c) Bregman, J.; Osaki, K.; Schmidt, G. M. J.; Sonntag, F. I. *J. Chem. Soc.*, **1964**, 2021; d) Schmidt, G. M. J. *Pure Appl. Chem.*, **1971**, *27*, 647.
10 Egerton, P. L.; Hyde, E. M.; Trigg, J.; Payne, A.; Beynon, P.; Mijovic, M. V.; Reiser, A. *J. Am. Chem. Soc.*, **1981**, *103*, 3859; Bolt, J.; Quina, F. H.; Whitten, D. G. *Tetrahedron Lett.*, **1976**, 2595.
11 Amarouche, H.; de Bourayne, C.; Riviere, M.; Lattes, A. *C.R. Acad. Sci.*, **1984**, *298*, 121.
12 Curme, H. C.; Natale, C. C.; Kelley, D. J. *J. Phys. Chem.*, **1967**, *71*, 767.
13 Lewis, F. D.; Oxman, J. D.; Huffman, J. C. *J. Am. Chem. Soc.*, **1984**, *106*, 466; Lewis, F. D.; Quillen, S. L.; Hale, P. D.; Oxman, J. D. *J. Am. Chem. Soc.*, **1988**, *110*, 1261.
14 Botta, B.; Iacomacci, P.; Vinciguerra, V.; Delle Monache, G.; Gacs-Baitz, E.; Botta, M.; Misiti, D. *Chem. Pharm. Bull.*, **1990**, *38*, 3238.
15 Hirayama, F.; Utsuki, T.; Uekama, K. *J. Chem. Soc. Chem. Commun.*, **1991**, 887.
16 Ishigami, T.; Murata, T.; Endo, T. *Bull. Chem. Soc. Jpn*, **1976**, *49*, 3578.
17 Ben-Efraim, D. A.; Green, B. S. *Tetrahedron*, **1974**, *30*, 2357.
18 Caccamese, S.; Montaudo, G.; Prybylski, M. *Org. Mass Sprectrom.*, **1974**, *9*, 1114.
19 Caccamese, S.; Maravigna, P.; Montaudo, G.; Prybylski, M. *J. Polym. Sci., Polym. Chem. Ed.*, **1975**, *13*, 2061.