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Microwave-Assisted Rapid Preparation of Substituted Carbazole-9-acetic and Propionic Acids and their Absorption and Fluorescence Spectra

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Summary. A rapid one-pot synthesis of substituted carbazole-9-acetic and -propionic acids under microwave irradiation is described. N-Alkylation and hydrolysis was carried out in *DMF* without catalyst. The absorption and fluorescence spectroscopic characteristics of the title compounds are discussed.

Keywords. Microwaves; Carbazole-9-acetic acid; Carbazole-9-propionic acid; UV/Vis spectroscopy; Fluorescence spectroscopy.

Introduction

Numerous carbazole derivatives isolated from higher plants, microorganisms, and marine sources as well as their synthetic analogues exhibit significant biological activities, such as anticonvulsant [1], antimicrobial [2], antiviral [3], antiinflammatory [4], and analgesic [5] effects. Some copolymers containing carbazole chromophores express high excitation energy transport efficiency, and their photophysical processes have been the subject of many investigations [6]. Among these carbazole derivatives, carbazole-9-acetic and -propionic acids are important intermediates. However, conventional synthetic methodology involves multi-step, time-consuming procedures and results in low ultimate yields [7, 8]. Typically, 9*H*-carbazole-9-acetic acid has been prepared by condensing dry potassium carbazole, which was obtained by fusing 9*H*-carbazole and potassium hydroxide, with ethyl chloroacetate, followed by saponification with sodium hydroxide [9]. 9*H*-Carbazole-9-β-propionic acid has been prepared by acidic hydrolysis of 9*H*-carbazole-β-propionitrile [10]. Due to limitations in synthetic methods, an alternate approach to these compounds is desirable. Fortunately, microwave irradiation of liquid and solid samples has turned out to be a very helpful method for organic and inorganic synthesis, and its application in organic chemistry has

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received much attention in recent years. Some papers have reported on N-alkylation of heterocyclic compounds, including 9*H*-carbazole, under microwave irradiation [11–13]. The reaction has been carried out in the absence of a solvent and on solid supports such as silica gel or activated carbon with or without catalysts [14, 15]. Irradiation with microwaves for several minutes has resulted in higher yields. In order to reduce the reaction time, we investigated the rapid preparation of some substituted carbazole-9-acetic and -propionic acids under microwave irradiation. Because carbazolyl chromophores are good electron donors and possess outstanding electrical and photoelectrical properties, the absorption and fluorescence spectra of these compounds are also discussed.

Results and Discussion

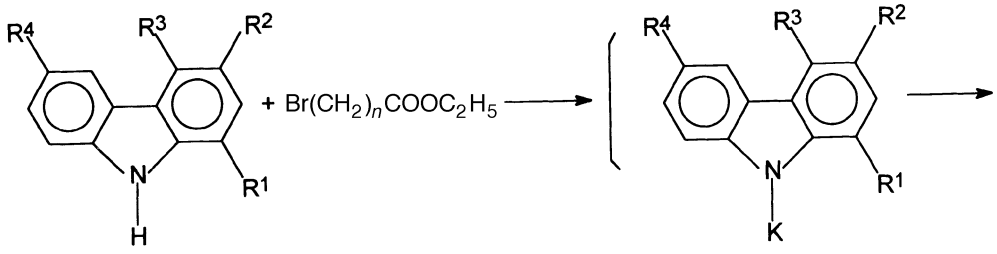
Synthesis of substituted carbazole-9-acetic and -Propionic acids

The starting material, 1.4-dimethyl-carbazole (**1a**), was prepared according to Ref. [16] and was obtained in satisfactory yields. A mixture of 1.4-dimethyl-carbazole with bromoacetic or -propionic esters and potassium hydroxide in *DMF* was irradiated in an open vessel in a domestic microwave oven for 6 minutes and treated with water and hydrochloric acid to afford 1.4-dimethyl-carbazole-9-acetic or -propionic acids **5a**,**b**. The halogenocarbazoles **1b–e** synthesized according to Refs. [17–19]. Their reactions with bromoesters were carried out as stated above (Scheme 1).

A series of experiments were carried out under a variety of conditions for the purpose of optimizing the yields. The effects of microwave power and irradiation time are shown in Tables 1 and 2. The results show that the yields are influenced heavily both by irradiation time and power When the vicinal positions of the N-H bond are substituted (*e.g.* **1a**, **1d**), longer irradiation times at 375 W were required to give good yields. A further increase of the irradiation time at this power resulted in more tar as well as in lower yield. At 225 W, the yield was lower owing to the reduced reactivity of substituted carbazoles, whereas microwave powers above 525 W led to more tar. The required range of mole ratio of KOH to substituted carbazole was found to be 3–5.

Reactions under dry conditions on silica gel, alumina, or activativted carbon as the support failed because the esters **4a–f** could not be hydrolyzed this way. For the microwave-assisted wet reaction, the choice of solvent was crucial. Whereas polar organic compounds can be heated *via* dipole rotation under microwave irradiation, nonpolar organic compounds are transparent to microwaves. Therefore, solvents of high polarity are optimal for liquid phase microwave-assisted reactions [20]; *DMF* was found to be optimal (Table 1 and Table 2). It was also found the the perfect reaction vessel is a round-bottom oven flask due to its large remaining empty space relative to the volume of the reaction mixture. Certainly, superheating should be avoided by shortening the irradiation time.

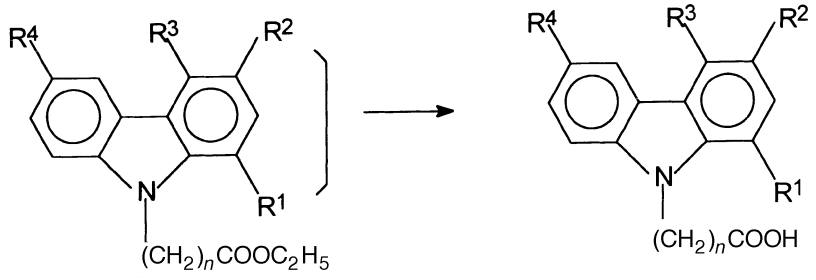
In conclusion, the reactivity of compounds **1a–e** was found to depend to a large extent on the reaction medium, the microwave power, the irradiation time, the position of the substituted group on the carbazole, and the ratio of the starting materials.



	R^1	R^2	R^3	R^4
1a	CH_3	H	CH_3	H
1b	H	Cl	H	Cl
1c	H	Br	H	Br
1d	Br	Br	H	Br
1e	H	I	H	H

	n
2a	1
2b	2

	R^1	R^2	R^3	R^4
3a	CH_3	H	CH_3	H
3b	CH_3	H	CH_3	H
3c	H	Cl	H	Cl
3d	H	Br	H	Br
3e	Br	Br	H	Br
3f	H	I	H	H



	R^1	R^2	R^3	R^4	n
4a	CH_3	H	CH_3	H	1
4b	CH_3	H	CH_3	H	2
4c	H	Cl	H	Cl	1
4d	H	Br	H	Br	1
4e	Br	Br	H	Br	2
4f	H	I	H	H	1

	R^1	R^2	R^3	R^4	n
5a	CH_3	H	CH_3	H	1
5b	CH_3	H	CH_3	H	2
5c	H	Cl	H	Cl	1
5d	H	Br	H	Br	1
5e	Br	Br	H	Br	2
5f	H	I	H	H	1

Scheme 1

Absorption and fluorescence spectra of substituted carbazole-9-acetic and -propionic acids

The absorption spectra of 1,4-dimethyl-carbazole-9-propionic acid (**5b**) and 3,6-dibromo-carbazole-9-acetic acid (**5d**) in MeCN are shown in Fig. 1, the electronic absorption characteristics of the whole series in Table 3. The first band at long wavelength, which henceforth will be designated $^1L_b \leftarrow {}^1A$ according to *Platt* notation [21], showed considerable vibrational structure [22]. The bands at about 290 and 260 nm are due to the $^1L_a \leftarrow {}^1A$ and $^1B_a \leftarrow {}^1A$ transitions, respectively

Table 1. Effect of irradiation time on yields (%)

	2 min	4 min	6 min	8 min	10 min	12 min
5a	32.4	73.1	85.2	78.6	57.3	
5b	28.8	70.5	83.1	72.9	53.2	
5e	10.2	37.4	59.8	78.5	63.9	22.4
5f	65.3	85.8	54.2			
	1 min	3 min	5 min	7 min	9 min	
5c	30.4	66.3	81.0	72.7	38.3	
5d	28.5	60.3	78.6	63.8	34.2	

Table 2. Effect of microwave power on yields (%)

	225 W	300 W	375 W	450 W	525 W
5a	75.2	82.4	85.2	80.7	65.8
5b	71.7	79.3	83.1	77.5	61.6
5c	64.8	75.9	81.0	71.3	53.2
5d	56.7	68.5	78.6	70.7	51.3
5e	32.4	58.8	78.5	51.4	18.3
5f	67.3	77.8	85.8	71.2	56.9

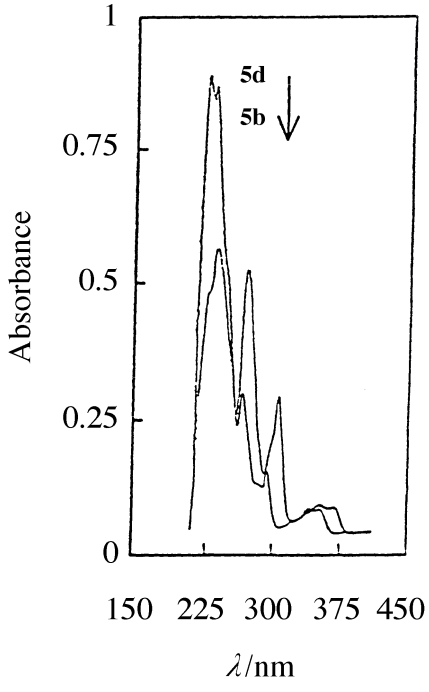


Fig. 1. Absorption spectra of **5b** and **5d** in MeCN; concentration: 1×10^{-5} mol/dm^3

Table 3. Electronic absorption and fluorescence spectra of **5a–f** in MeCN

	$^1L_b \leftarrow {}^1A$ λ_{max}/nm (logε)	$^1L_a \leftarrow {}^1A$ λ_{max}/nm (logε)	$^1B_a \leftarrow {}^1A$ λ_{max}/nm (logε)	$^1C_a \leftarrow {}^1A$ λ_{max}/nm (logε)	Fluorescence λ_{max}/nm Excitation	Emission	*Stokes* shift (cm^{-1})	Quantum yield
5a	338 323 (3.74) (3.72)	287 (4.19)	262 (4.26)	242 (4.70)	287	350	1200	1.0
5b	342 325 (3.72) (3.69)	287 (4.11)	262 (4.30)	242 (4.66)	287	353	1200	1.0
5c	352 337 (3.71) (3.72)	299 (4.41)	264 (4.55)	238 230 (4.87) (4.87)	296	357	1100	0.15
5d	352 337 (3.59) (3.63)	299 (4.33)	266 (4.45)	239 231 (4.81) (4.80)	299	365	1750	0.12
5e	355 (3.25)	300 (4.02)	267 (4.37)	239 231 (4.67) (4.60)	299	368	1700	0.04
5f	345 332 (3.54) (3.58)	296 (4.20)	264 (4.39)	239 (4.65)	300	356	1550	0.21

[23, 24]. The other bands at low wavelengths are assigned to $^1C_a \leftarrow {}^1A$ [21, 25]. Table 3 shows that the substituent causes the ^1L_b, ^1L_a, and ^1C_a bands to shift bathochromically. The higher the number of the halogen atoms attached to the carbazole, the larger the red shift. In contrast to the ^1L_a, ^1B_a, and ^1C_a bands, the influence of the substituent on the red shift of the ^1L_b band of carbazole is large. The spectra of disubstituted carbazole-9-acids visually resemble that of carbazole; however, they differ dramatically from those of the tribromo analogues, especially in their ^1B_a and ^1C_a bands. This is due to the change of the electronic structure of the π-orbital of the heterocyclic ring with increasing number of bromine atoms.

Since the lowest absorption transition of these compounds is the $^1L_b \leftarrow {}^1A$ transition, that leading to fluorescence is also a $^1L_b \leftarrow {}^1A$ transition. The fluorescence characteristics of the whole series are given in Table 3. The flurescence spectra of 1,4-dimethyl-carbazole-9-propionic acid (**5b**) and 3,6-dibromo-carbazole-9-acetic acid (**5d**) are shown in Fig. 2 as representative examples. The substituents on the carbazole ring produce a bathochromic displacement in the fluorescence spectra. The small *Stokes* shifts infers that these compounds stay planar in the ground state and first excited state [26]. From the quantum yields (Table 3) it was found that the intensity of the fluorescence of halogen substituted carbazole-9-acids, like **5d**, is weaker than for **5a** as expected, which is due to the heavy-atom effects of the halogen atoms, causing drastic enhancement of singlet-triplet intersystem crossing and resulting in weak fluorescence and intense phosphorescence [27].

The fluorescence spectra of **5b** at *pH* values from 1 to 10 is shown in Fig. 3. **5b** is a weak acid, and the change of the *pH* value of the solution intensively influences the fluorescence. The acid and its conjugate base both exhibit fluorescence, and the intensity of the latter is larger than that of the former without an emission band shift. Similar spectra were obtained for other substituted carbazole-9-acids.

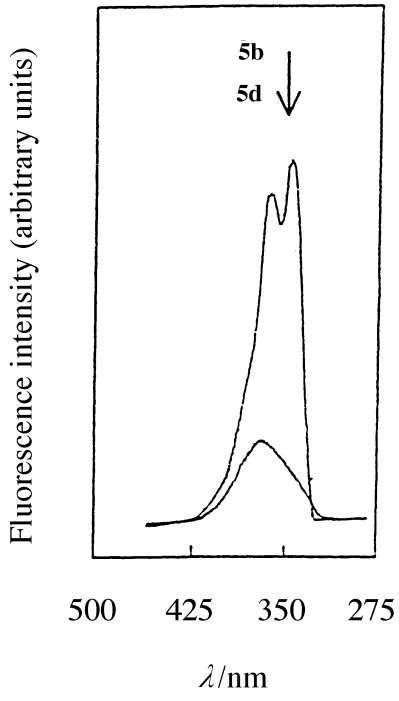


Fig. 2. Fluorescence spectra of **5b** and **5d** in MeCN; excitation wavelength: **5b**, 287 nm (slit = 1), **5d**, 299 nm (slit = 5); concentration: $1\times$ mol/dm^3

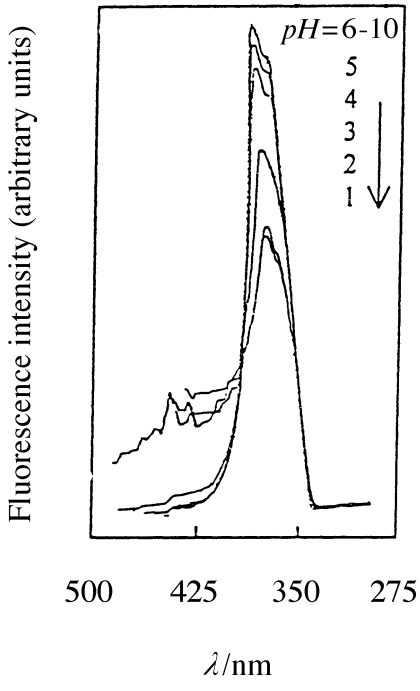


Fig. 3. Fluorescence spectra of **5b** at $pH = 1$ to 10

Experimental

^{1}H NMR and ^{13}C NMR measurements were performed on a Bruker 400 MHz NMR spectrometer in CD_3COCD_3. Chemical shifts are reported as ppm (δ) relative to *TMS*. IR spectra were recorded on a Bruker IFS 120HR instrument in KBr discs. Mass spectra were obtained on a VG7070E mass spectrometer. C,H,N microanalyses were obtained using a Carlo-Erba 1106 instrument; the experimental results were in good agreement with the calculated ones. Absorption and fluorescence spectra were recorded on hitachi 330 and hitachi 650-10S spectrophotometers. Melting points were determined on a PHMK micro-melting-point apparatus and are uncorrected. Microwave irradiations were carried out in a domestic microwave oven Galanz WP750B (2450 MHz). Measurements of fluorescence quantum efficiencies were performed according to the method of *Parker* [28] by comparison with carbazole as the standard ($\phi = 1.0$) in acetonitrile.

General procedure for the preparation of substituted carbazole-9-aceticand propionic acids (**5a–f**)

A mixture of (0.012 mol substituted carbazole (**1a–e**), 0.072 mol KOH, and 0.015 mol bromoester **2a–b** in 50 cm^3 *DMF* was heated in a domestic microwave oven in an open round-bottomed flask (for appropriate times and powers see Tables 1 and 2). Water was added, and the filtrate was acidified by adding 6 mol/dm^3 HCl until the precipitate separated entirely. The precipitate was filtered, washed with H_2O, and dried in vacuum. The crude product was purified by recrystallization from $CHCl_3$ and ethanol (90:10) to give the desired product.

1,4-Dimethyl-carbazole-9-acetic acid (**5a**; $C_{16}H_{15}NO_2$)

M.p.: 165–166°C (Ref. [16]: 164–166°C); IR (KBr): $\nu = 3050$ (m), 2970 (m), 1703 (s), 1611 (w), 1585 (w), 1460 (s), 1323 (m), 1219 (s), 931 (m) cm^{-1}; ^{1}H NMR (400 MHz, δ, CD_3COCD_3): 2.74 (3H, s, -CH_3), 2.81 (3H, s, -CH_3), 5.40 (2H, s, N-CH_2-), 6.86–8.22 (6H, aromatic protons) ppm; ^{13}C NMR (100 MHz δ, CD_3COCD_3): 19.6, 20.9, 46.9, 109.4, 118.4 120.2, 121.9, 123.1, 123.1, 124.4, 125.8, 129.6, 131.7, 140.5, 142.5, 171.1 ppm; MS: *m/z* (%) = 253 (41).

1,4-Dimethyl-carbazole-9-propionic acid (**5b**; $C_{17}H_{17}NO_2$)

M.p.: 175–177°C; IR (KBr): $\nu = 3017$ (m), 2919 (m), 1706 (s), 1610 (w), 1583 (w), 1463 (m), 1390 (m), 1322 (w), 1229 (m), 941 (w) cm^{-1}; ^{1}H NMR (400 MHz, δ, CD_3COCD_3): 2.75–2.95 (8H, -CH_2-, -CH_3-CH_3), 4.91 (2H, t, $J = 8.0$ Hz, N-CH_2-), 6.88–8.25 (6H, aromatic protons) ppm; ^{13}C NMR (100 MHz, δ, CD_3COCD_3): 20.0, 20.9, 34.9, 40.9, 109.6, 118.2, 119.9, 121.7, 122.9, 123.1, 124.5, 125.8, 129.6, 131.6, 139.3, 141.4, 172.6 ppm; MS: *m/z* (%) = 267 (43).

3,6-Dichloro-carbazole-9-acetic acid (**5c**; $C_{14}H_9NO_2Cl_2$)

M.p.: 224–225°C; IR (KBr): $\nu = 3041$(m), 2925 (m), 1712 (s), 1601 (s), 1479 (s), 1445 (m), 1445 (m), 1414 (m), 1289 (w), 1244 (m), 869 (w) cm^{-1}; ^{1}H NMR (400 MHz, δ, CD_3COCD_3): 5.24 (2H, s, N-CH_2-), 7.50–8.24 (6H, aromatic protons) ppm; ^{13}C NMR (100 MHz, δ, CD_3COCD_3): 44.7, 111.5, 121.0, 124.0, 125.5, 140.6, 169.6, MS: *m/z* (%) = 293(37).

3,6-Dibromo-carbazole-9-acetic acid (**5d**; $C_{14}H_9NO_2Br_2$)

M.p.: 245–246°C (Ref: [30]: 243–247°C): IR (KBr): $\nu = 3075$(m), 2933 (m), 1712 (s), 1595 (w), 1475 (s), 1438 (m), 1415 (m), 1249 (s), 1211 (m), 876 (m) cm^{-1}; ^{1}H NMR (400 MHz, δ, CD_3COCD_3): 5.24 (2H, s, N-CH_2-), 7.58–8.38 (6H, aromatic protons) ppm; ^{13}C NMR (100 MHz, δ, CD_3COCD_3): 44.7, 112.0, 112.9, 124.1, 124.5, 140.8, 169.5 ppm; MS: *m/z* (%) = 383(32).

1,3,6-Tribromo-carbazole-9-propionic acid (**5e**; $C_{15}H_{10}NO_2Br_3$)

M.p.: 185–186°C; IR (KBr): $\nu = 3042$(m), 2942 (m), 1716(s), 1716 (s), 1591 (w), 1471 (s), 1435 (m), 1393 (m), 1289 (m), 1239 (m), 866 (m) cm^{-1}; ^1H NMR (400 MHz, δ, CD_3COCD_3): 2.06 (2H, t, $J = 8.0$ Hz, -CH_2-), 4.72 (2H, t, $J = 8.0$ Hz, N-CH_2-), 6.64–8.37 (5H, aromatic protons) ppm; ^{13}C NMR (100 MHz, δ, CD_3COCD_3): 32.8, 38.6, 104.2, 110.8, 112.6, 114.2, 123.2, 123.4, 123.4, 123.9, 129.3, 129.3, 133.7, 139.8, 175.3 ppm; MS: *m/z* (%) = 475(14).

3-Iodo-carbazole-9-acetic acid (**5f**; $C_{14}H_{10}NO_2I$)

M.p.: 162–164°C (Ref. [29]: 162–163°C); IR (KBr): $\nu = 3044$(m), 2925(m), 1709 (s), 1623 (w), 1593 (w), 1475 (m), 1408 (m), 1362 (m), 1275 (m), 897 (w) cm^{-1}; ^1H NMR (400 MHz, δ, CD_3COCD_3): 5.22 (2H, s, N-CH_2-) 7.38–8.25 (7H, aromatic protons) ppm; ^{13}C NMR (100 MHz δ, CD_3COCD_3): 44.5, 82.1, 109.9, 112.1, 120.6, 121.2, 122.4, 126.3, 127.3, 129.7, 134.6, 140.6, 141.6, 169.8 ppm; MS: *m/z* (%) = 351 (89).

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References

[1] Shoeb A, Anwer F, Kapil S, Popil S (1973) J Med Chem **16**: 425
[2] Sakano K, Ishimaru K, Nakamura S (1980) J Antibiotics **33**: 683
[3] Tepasker MR, Gloer JB, Wicklow DT, Dowd PF (1989) J Org Chem **54**: 4743
[4] Ramlingam T, Sattur PB (1987) Indian J Pharm **26B**: 1204
[5] Purohit M, Srivastava SK (1991) Indian J Pharm Sci **53**: 162
[6] Yoshio W, Shinzaburo I, Masahide Y (1993) J Phys Chem **97**: 11164
[7] Yoshihhsa W, Takeaki MT, Masato, Kazuo Y (1974) Yukagaku **23**:304
[8] Masashi K, Takashi K (1993) Eur Pat Appl **EP557993**
[9] Reinhard S (1924) Ber Chem Ges **57B**: 1527
[10] Smith AS, Peter, Tung-yin Y (1952) J Am Chem Soc **74**: 1096
[11] Ding JC, Gu HG, Wen JZ, Lin CZ (1994) Synth Commun **3**: 301
[12] Abramovitch RA, Shin Q, Bogdal D (1995) Synth Commun **1**: 1
[13] Bogdal D, Pielichowski J, Jaskot K (1997) Synth Commun **9**: 1553
[14] Villemin D, Labiad B, Ouhilal Y (1989) Chem Ind (London) 607
[15] Baghurst DR, P Mingos DM (1990) J Organomet Chem **384**: 57
[16] Dalton LK, Demerac S, Elmes BC, W Loder J, Swan JM (1967) Aust J Chem **20**: 2715
[17] Mazzara G, Lamberit-Zanardi M (1896) Gazz Chim Ital **26**: 239
[18] Pielichowski J, Kyziol J (1974) Monatsh Chem **105**: 1036
[19] Stanley HT (1926) J Chem Soc Part I 546
[20] Bose AK, Manhas MS, Shah M (1991) J Org Chem **56**: 6968
[21] Mann DE, Platt JR (1949) J Chem Phys **17**: 481
[22] Campillo AL, Martinaud M (1975) Chem Phys Lett **33**: 26
[23] Johnson GE (1974) J Phys Chem **78**: 1512
[24] Kadiri A, Fadouach M, Benali B, Boucetta A (1994) Spectrochim Acta **50A**: 851
[25] Klevens HB, Platt JR (1949) J Chem Phys **17**: 470
[26] Berlman IB (1970) J Phys Chem **74**: 3085
[27] Biswas M, Das SK (1982) Polymer **23**: 1713

[28] Parker CA, Ress WT (1960) Analyst **85**: 587
[29] Yogendwra S (1994) Indian J Chem 799
[30] Szulc Z, Mlochowski J, Palus J (1988) J Prakt Chemie **330**: 1023

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