

REACTIONS OF 2-FURFURYLIDENEMALONALDEHYDE WITH AROMATIC AMINES AND MELDRUM'S ACID

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2-Furfurylidene-malon-aldehyde (*II*) reacts with primary aromatic amines as an organic Lewis acid, affording 1,3-di-(N-4-X-phenylamino)-3-(2-furyl)-2-formyl-1-propenes (*IIIa–IIIj*). Condensation of these compounds with 2,2-dimethyl-1,3-dioxane-4,6-dione (*I*) gives the products *IVa–IVj*.

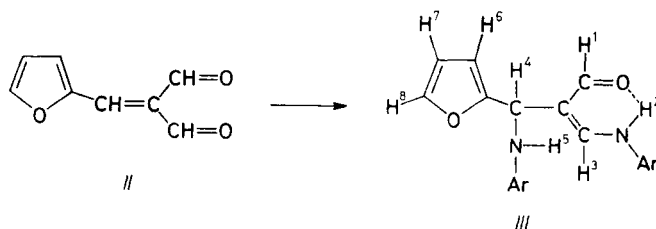
Arylmethylenemalon-aldehydes^{1–4} are organic Lewis acids with a C=C double bond, activated by two geminal, strongly electron-accepting groups. Compounds of this type, particularly methylene derivatives of 2,2-dimethyl-1,3-dioxane-4,6-dione (*I*, Meldrum's acid), have been studied in detail by Polansky and coworkers⁴. The electron-accepting properties of these organic acids are demonstrated by their reactions with nucleophiles such as tertiary bases⁵, water and alcohols^{2,6}, or salts⁷ (e.g. KCN, KN₃, KOCN etc.).

To furan derivatives of organic Lewis acid properties belong also the condensation products of 2-furaldehyde with compounds containing a methylene grouping X—CH₂—Y where the substituents X and Y are strong electron-accepting groups (CN, CHO, COOR). The effect of these groups, which strongly polarize the C=C double bond, is transmitted across the furan nucleus, activating the position 5 of the ring toward a nucleophile attack. This effect is illustrated by reactions of 2-furfurylidene-propanedinitrile and its derivatives in which one of the nitrile groups is replaced by an ester or amide group⁸.

The present work concerns the reactions of 2-furfurylidene-malon-aldehyde (*II*) with nucleophilic reagents and investigates whether the furan nucleus participates in delocalization of an activated C=C double bond. At the same time we looked for an analogy with the Stenhouse reaction (opening of the furan ring) in reactions of compound *II* with arylamines in the presence of mineral acids^{9–11}.

Under conditions of the Stenhouse reaction, compound *II* turned into unisolable resins. The reaction of compound *II* with primary aromatic amines in the absence of mineral acids led to compounds *IIIa–IIIj*. Elemental analysis together with mass spectra have shown that these products arise from one molecule of compound

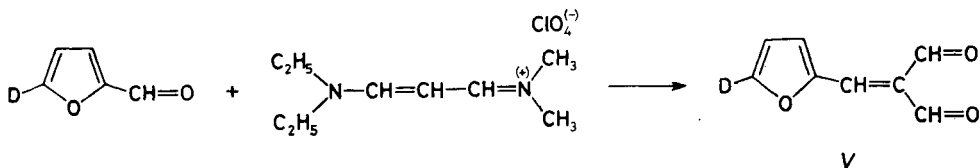
II and two molecules of the aromatic amine, one molecule of water being lost. The reaction was not influenced by the amount of the aromatic amine used. The IR and ^1H NMR spectra confirmed unequivocally the presence of an aldehyde group. On the basis of spectral characteristics of compounds *IIIa–IIIj* we assume that compound *II* reacts with aromatic amines in an addition reaction as depicted in Scheme 1.



In formulae *III* and *IV*: *a*, Ar = C₆H₅ *b*, Ar = 4-Cl-C₆H₄ *c*, Ar = 4-Br-C₆H₄
d, Ar = 4-I-C₆H₄ *e*, Ar = 4-CH₃-C₆H₄ *f*, Ar = 4-CH₃O-C₆H₄
g, Ar = 4-O₂N-C₆H₄ *h*, Ar = 4-F₃C-C₆H₄ *i*, Ar = 1-naphthyl
j, Ar = 2-naphthyl

SCHEME 1

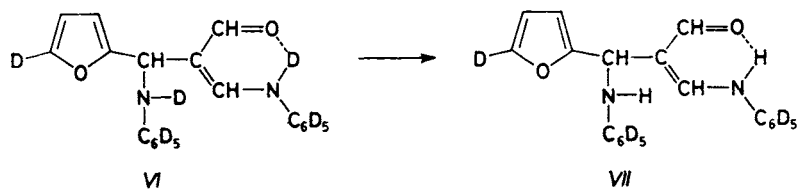
Since the complex splitting of the ^1H NMR signals made impossible an unequivocal structural assignment to compounds *IIIa–IIIj*, we synthesized 2-furfurylidene malonaldehyde in which the hydrogen atom in position 5 of the furan ring was replaced by a deuterium atom. 5- $^{[2}\text{H}]$ -2-Furaldehyde (98% isotopic purity, prepared according to ref.¹²) reacted with 3-diethylaminopropenylidene dimethyliminium perchlorate^{13,14} in a mixture of acetic acid and acetic anhydride under formation of 5- $^{[2}\text{H}]$ -2-furfurylidene malonaldehyde (*V*) (83% yield; 98% isotopic purity) (Scheme 2).



SCHEME 2

To simplify the ^1H NMR spectra as much as possible, we performed the reaction of *V* with perdeuterated amine. This reaction, in perdeuterated acetonitrile, afforded compound *VI*. Its ^1H NMR spectrum exhibited a singlet at δ 9.3 due to the aldehyde H-1 atom, doublets at δ 6.32 and δ 6.38 ($J(6, 7) = 3.8$ Hz) due to the H-6 and H-7

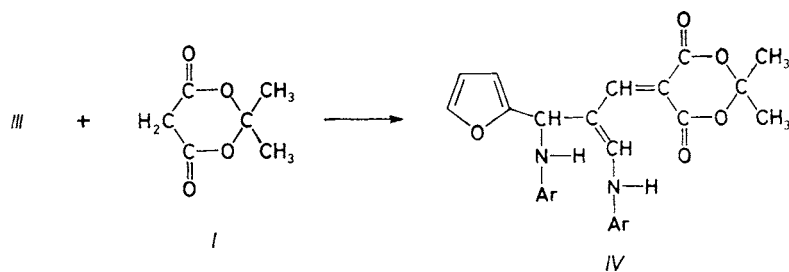
atoms of the furan nucleus and two singlets at δ 7.80 and δ 5.84 that could not be unequivocally ascribed. Treatment of compound *VI* with water replaced the N–D deuterium atom by hydrogen (Scheme 3).



SCHEME 3

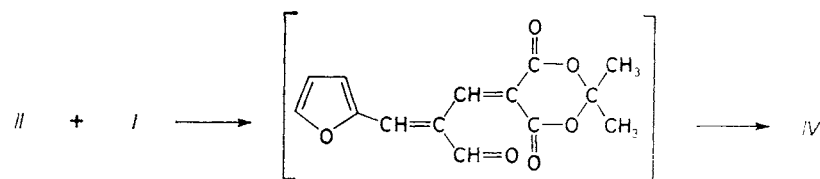
On treatment with water, the singlets at δ 7.80 and δ 5.84 in the ^1H NMR spectra of *VI* changed into doublets and we also observed doublets at δ 9.48 ($J(2,3) = 14$ Hz) and δ 4.12 ($J(4,5) = 8$ Hz), corresponding to N–H signal splitting.

The presence of the aldehyde group in compounds *IIIa–IIIj* was proven by their condensation with Meldrum's acid (*I*) leading to the products *IVa–IVj* (Scheme 4).



SCHEME 4

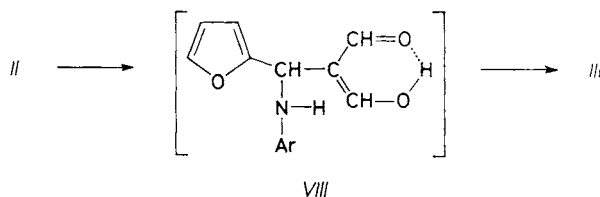
The ^1H NMR spectra of compounds *IVa–IVj* confirm that, as a result of absence of the aldehyde group (and thus absence of the intramolecular hydrogen bond) there is no splitting of the H-3 signal due to its coupling with the H-2 proton of the



SCHEME 5

N-H group. The same condensation products were also obtained by reaction of compound *II* with Meldrum's acid followed by reaction with aromatic amines (Scheme 5). In this reaction no addition of Meldrum's acid to the double bond was observed (as evidenced by the ^1H NMR spectra).

The obtained results show that the aldehyde *II*, as an organic Lewis acid, reacts with primary aromatic amines under formation of compounds *IIIa-IIIj*, the likely intermediate being the addition product *VIII* which on reaction with another molecule of the amine affords the products *III* (Scheme 6). The assumed 1,4-addition product *VIII* explains why the furan nucleus does not react further with aromatic amines¹⁵.



SCHEME 6

EXPERIMENTAL

The melting points were determined on a Boetius block and are uncorrected. IR spectra were measured on M-80 (Zeiss, Jena) and Beckman-Acculab (Beckman) spectrometers, using the KBr technique. Electronic absorption spectra were recorded on an M-40 spectrophotometer (Zeiss, Jena) in methanol, concentration $1 \cdot 10^{-4}$ mol dm⁻³ (ϵ in m² mol⁻¹). ^1H NMR spectra were taken on a Varian VXR-300 instrument (75.05 MHz) at 25°C in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Mass spectra were obtained with an AEI MS 902 S spectrometer (direct inlet, ionizing electron energy 70 eV, electron current 100 μA , ion source temperature 70–170°C).

3-Diethylaminopropenylienedimethyliminium Perchlorate

A solution of dimethylammonium perchlorate (45.3 g, 311 mmol) in dry ethanol (120 ml) was mixed with β -diethylaminoacrolein¹³ (39.4 g, 310 mmol) and refluxed for 6 h. After cooling, the separated salt was filtered and crystallized from methanol, affording 71.8 g (91%) of the title compound, m.p. 92–94°C. ^1H NMR spectrum (CD_3COCD_3): 1.28 t, 3 H (NCH_2CH_3 , $J = 7$); 1.30 t, 3 H (NCH_2CH_3 , $J = 7$); 3.20 s, 3 H (NCH_3); 3.38 s, 3 H (NCH_3); 3.64 q, 4 H ($2 \times \text{NCH}_2\text{CH}_3$, $J = 7$); 5.60 dd, 1 H (H-2, (2,1) = 11; $J(2,3) = 11$); 7.86 d, 1 H (H-1, $J(2,1) = 11$); 7.90 d, 1 H (H-3, $J(2,3) = 11$). For $\text{C}_9\text{H}_{19}\text{ClN}_2\text{O}_4$ (254.7) calculated: 42.44% C, 7.52% H, 13.91% Cl, 10.99% N; found: 42.31% C, 7.44% H, 13.58% Cl, 10.76% N.

5-[^2H]-2-Furfurylienedimalonaldehyde (*V*)

5-[^2H]-2-Furaldehyde¹² (3.88 g, 40 mmol) was added to a solution of 3-diethylaminopropenylienedimethyliminium perchlorate (10.2 g, 40 mmol) in a mixture of acetic acid (30 ml) and

acetic anhydride (30 ml). After cooling to +5°C, boron trifluoride etherate (10.5 ml) was added dropwise during 30 min and the mixture was stirred at +5°C for 2 h and at room temperature for 24 h. Dry ether (250 ml) was added and the separated product was filtered and hydrolyzed in water (1 000 ml) and dichloromethane (150 ml). The organic layer was separated and the aqueous one was twice extracted with a benzene-dichloromethane mixture (5 : 1, 250 ml). The combined organic phases were dried over anhydrous sodium sulfate and the solvents were evaporated in vacuum to give 5.02 g (83%) of yellow crystalline product, m.p. 52–55°C, which was stored as a solution in dry ether. ¹H NMR spectrum (CD₃COCD₃): 6.80 d, 1 H (H-4, *J*(3,4) = 3.8); 7.70 s, 1 H (CH=C); 7.73 d, 1 H (H-3, *J*(3,4) = 3.8); 9.95 s, 1 H (CH=O); 10.59 s, 1 H (CH=O).

TABLE I
Analytical data of compounds IIIa–IIIj

Compound	Formula (M. w.)	M.p., °C (Yield, %)	Calculated/Found		
			% C	% H	% N
IIIa	C ₂₀ H ₁₈ N ₂ O ₂ (318.4)	134–137 (95)	75.45	5.70	8.80
			75.27	5.65	8.90
IIIb ^a	C ₂₀ H ₁₆ Cl ₂ N ₂ O ₂ (387.3)	116–119 (88)	62.03	4.16	7.23
			62.31	4.31	7.50
IIIc ^b	C ₂₀ H ₁₆ Br ₂ N ₂ O ₂ (476.2)	140–143 (87)	50.45	3.39	5.88
			50.50	3.48	5.99
IIIc ^c	C ₂₀ H ₁₆ I ₂ O ₂ (570.2)	162–164 (98)	32.13	2.83	4.91
			42.01	2.71	5.08
IIIe	C ₂₂ H ₂₂ N ₂ O ₂ (346.4)	113–116 (88)	76.28	6.40	8.09
			76.38	6.32	8.43
IIIf	C ₂₂ H ₂₂ N ₂ O ₄ (378.4)	147–149 (96)	69.83	5.86	7.40
			69.73	5.71	7.58
IIIg	C ₂₀ H ₁₆ N ₄ O ₆ (408.4)	194–196 (84)	58.82	3.95	13.72
			58.73	3.94	13.41
IIIh ^d	C ₂₂ H ₁₆ F ₆ N ₂ O ₂ (454.4)	oil (92)	58.16	3.55	6.17
			58.08	3.61	6.36
IIIi	C ₂₈ H ₂₂ N ₂ O ₂ (418.5)	143–145 (93)	80.36	5.29	6.69
			80.36	5.39	6.82
IIIj	C ₂₈ H ₂₂ N ₂ O ₂ (418.5)	151–154 (89)	80.36	5.29	6.69
			80.22	5.40	6.89

^a Calculated: 18.31% Cl; found: 18.18% Cl. ^b Calculated: 33.56% Br; found: 33.38% Br. ^c Calculated: 44.51% I; found: 44.08% I. ^d Calculated: 25.09% F; found: 25.03% F.

General Procedure for Preparation of Compounds *IIIa--IIIj*

A solution of the aromatic amine (4 mmol) in acetonitrile (5 ml) was added to a solution of 2-furfurylidenealdehyde (*II*, 300 mg, 2 mmol) in acetonitrile (10 ml). After stirring at room temperature for 15 min, the separated product was filtered and purified by crystallization from tetrahydrofuran. For yields and physical constants of the products *IIIa--IIIj* see Table I. ¹H NMR spectra are given in Table III, IR and UV spectra in Table V.

General Procedure for Preparation of Compounds *IVa--IVj*

A) Meldrum's acid (*I*, 288 mg, 2 mmol) was added at 40°C to a stirred solution of compound *IIIa--IIIj* (2 mmol) in dry methanol (10 ml). The mixture was stirred at 45°C for 2 h and at

TABLE II
Analytical data of compounds *IVa--IVj*

Compound M. p., C°	Yield, %		Formula (M. w.)	Calculated/Found		
	A	B		% C	% H	% N
<i>IVa</i> 164—166	72	89	C ₂₆ H ₂₄ N ₂ O ₅ (444·5)	70·26 70·12	5·44 5·37	6·30 6·41
<i>IVb^a</i> 188—190	69	77	C ₂₆ H ₂₂ Cl ₂ N ₂ O ₅ (513·5)	60·83 60·89	4·32 4·30	5·46 5·27
<i>IVc^b</i> 186—189	70	79	C ₂₆ H ₂₂ Br ₂ N ₂ O ₅ (602·3)	51·85 51·77	3·68 3·70	4·65 4·42
<i>IVd^c</i> 203—205	68	76	C ₂₆ H ₂₂ I ₂ N ₂ O ₅ (696·3)	44·85 44·85	3·18 3·09	4·02 3·90
<i>IVe</i> 184—186	71	84	C ₂₈ H ₂₈ N ₂ O ₅ (472·5)	71·17 71·02	5·97 5·89	5·93 5·77
<i>IVf</i> 187—189	70	86	C ₂₈ H ₂₈ N ₂ O ₇ (504·5)	66·66 66·60	5·59 5·67	5·55 5·27
<i>IVg</i> 180—182	72	88	C ₂₆ H ₂₂ N ₄ O ₉ (534·5)	58·43 58·36	4·15 4·02	10·48 10·21
<i>IVh^d</i> 179—182	68	78	C ₂₈ H ₂₂ F ₆ N ₂ O ₅ (580·5)	57·94 57·86	3·82 3·90	4·83 4·93
<i>IVi</i> 147—149	69	82	C ₃₄ H ₂₈ N ₂ O ₅ (544·6)	74·99 74·89	5·18 5·09	5·14 5·29
<i>IVj</i> 157—159	73	84	C ₃₄ H ₂₈ N ₂ O ₅ (544·6)	74·99 74·88	5·18 5·10	5·14 5·30

^a Calculated: 13·81% Cl; found: 13·72% Cl. ^b Calculated: 26·53% Br; found: 26·39% Br. ^c Calculated: 36·45% I; found: 36·31% I. ^d Calculated: 19·64% F; found: 19·38% F.

TABLE III
Proton NMR data for compounds *IIIa–IIIj*

Compound	δ , ppm							
	H-1, s	H-2, d ^e	H-3, d ^e	H-4, d ^d	H-5, d ^d	H-6 and H-7, m	H-8, d ^f	Aromatic protons
<i>IIIa</i>	9.22	9.13	7.78	5.78	5.53	6.25	7.43	6.54–7.25 m, 10 H
<i>IIIb</i>	9.25	9.20	7.83	6.76	5.45	6.30	7.47	6.70–7.16 m, 8 H
<i>IIIc</i>	9.28	9.12	7.85	5.77	5.46	6.32	7.50	6.73–7.40 m, 8 H
<i>III d</i>	9.18	9.28	7.83	5.92	5.70	6.35	7.68	7.09–7.58 m, 8 H
<i>III e^a</i>	9.25	9.28	7.78	5.79	5.39	6.32	7.48	6.68–7.16 m, 8 H
<i>III f^b</i>	9.05	9.25	7.76	6.15	5.75	6.34	7.52	6.58–7.15 m, 8 H
<i>III g</i>	9.12	9.34	7.72	6.21	5.81	6.37	7.60	6.71–7.28 m, 8 H
<i>III h</i>	9.32	9.78	7.73	5.95	5.62	6.35	7.60	6.65–8.13 m, 8 H
<i>III i</i>	9.24	9.24	7.90	5.82	6.53	6.71	^c	6.94–7.74 m, 15 H
<i>III j</i>	9.30	9.56	8.01	5.98	6.61	6.80	^c	7.00–7.88 m, 15 H

^a Other signals: 2.15 s and 2.24 s, $2 \times 3 \text{ H}$ ($2 \times \text{CH}_3$). ^b Other signals: 3.35 s and 3.65 s $2 \times 3 \text{ H}$ ($2 \times \text{CH}_3\text{O}$). ^c Overlap with other aromatic proton signals. ^d $J(4,5) = 7.8\text{--}8.0 \text{ Hz}$. ^e $J(2,3) = 14 \text{ Hz}$. ^f $J(7,8) = 1.8\text{--}2.0 \text{ Hz}$.

TABLE IV
Proton NMR data for compounds *IVa*–*IVj*

Compound	δ , ppm							
	H-1, s	H-3, m	H-4, m	H-6, d ^d	H-7, m	H-8, d ^e	(CH ₃) ₂ , s	Aromatic protons
<i>IVa</i>	8.65	8.48	5.37	6.04	6.26	7.41	1.40	7.12–7.50 m, 10 H
<i>IVb</i>	8.63	8.43	5.36	6.00	6.25	7.49	1.54	7.25–7.45 m, 8 H
<i>IVc</i>	8.65	8.41	5.32	6.02	6.27	7.45	1.56	7.2–7.60 m, 8 H
<i>IVd</i>	8.69	8.46	5.35	6.08	6.29	7.49	1.58	7.32–7.68 m, 8 H
<i>IVe</i> ^a	8.55	8.39	5.35	6.02	6.25	7.40	1.54	7.01–7.25 m, 8 H
<i>IVf</i> ^b	8.45	8.30	5.26	6.01	6.25	7.40	1.53	6.92–7.17 m, 8 H
<i>IVg</i>	8.80	8.66	5.44	6.02	6.26	7.42	1.56	7.45–7.76 m, 8 H
<i>IVh</i>	8.72	8.56	5.53	6.06	6.34	7.48	1.54	7.85–7.99 m, 8 H
<i>IVi</i>	8.78	8.63	5.60	6.28	6.38	^c	1.61	7.30–7.98 m, 16 H
<i>IVj</i>	8.85	8.67	5.44	6.10	6.28	^c	1.59	7.30–7.98 m, 16 H

^a Other signals: 2.00 s and 2.22 s, $2 \times 3 \text{ H}$ ($2 \times \text{CH}_3$). ^b Other signals: 3.27 s and 3.68 s, $2 \times 3 \text{ H}$ ($2 \times \text{CH}_3\text{O}$). ^c Overlap with other aromatic proton signals. ^d $J(6,7) = 1.8\text{--}2.0 \text{ Hz}$ ^e $J(8,7) = 1.8\text{--}2.0 \text{ Hz}$.

room temperature for 1 h. The product was collected on filter and purified by crystallization from acetone-water. For yield and physical constants of the products *IVa*–*IVj* see Table II; ^1H NMR spectra are given in Table IV, IR and UV spectra in Table V.

B) A solution of 2-furfurylidene-malonaldehyde (*II*, 300 mg, 2 mmol) in dry acetonitrile (5 ml) was added to a stirred solution of Meldrum's acid (*I*, 288 mg, 2 mmol) in dry acetonitrile (10 ml). After stirring at room temperature for 2 h, the aromatic amine (4 mmol) in dry acetonitrile (3 ml) was added. The mixture was stirred for 3–8 h, the separated product was filtered and purified by crystallization from acetone-water. The products were identical with those obtained by method *A*); for yields see Table II.

Compound *VI*

A solution of perdeuterated aniline (400 mg, 4 mmol) in perdeuterated acetonitrile (2 ml) was added to a solution of dialdehyde *V* (302 mg, 2 mmol) in perdeuterated acetonitrile (10 ml).

TABLE V
IR and UV spectral data of compounds *IIIa*–*IIIj* and *IVa*–*IVj*

Compound	UV spectra				IR spectra	
	λ_{\max} nm	(log ϵ) ($\text{m}^2 \text{mol}^{-1}$)	λ_{\max} nm	(log ϵ) ($\text{m}^2 \text{mol}^{-1}$)	$\tilde{\nu}(\text{C}=\text{O})$ cm^{-1}	$\tilde{\nu}(\text{N}-\text{H})$ cm^{-1}
<i>IIIa</i>	236	(3.35)	329	(3.37)	1 631	3 301
<i>IIIb</i>	246	(3.34)	332	(3.46)	1 643	3 340
<i>IIIc</i>	251	(3.24)	332	(3.43)	1 641	3 348
<i>III d</i>	253	(3.44)	338	(3.56)	1 650	3 338
<i>IIIe</i>	238	(3.30)	332	(3.31)	1 652	3 330
<i>III f</i>	236	(3.36)	335	(3.32)	1 658	3 349
<i>III g</i>	227	(3.33)	322	(3.39)	1 643	3 350
<i>III h</i>	258	(3.38)	337	(3.44)	1 648	3 348
<i>III i</i>	275	(3.46)	346	(3.35)	1 635	3 328
<i>III j</i>	290	(3.44)	336	(3.37)	1 639	3 322
<i>IVa</i>	265	(2.70)	401	(2.87)	1 641	3 440
<i>IVb</i>	260	(2.72)	406	(2.83)	1 638	3 438
<i>IVc</i>	263	(2.62)	409	(2.73)	1 653	3 430
<i>IVd</i>	262	(2.92)	414	(2.96)	1 639	3 442
<i>IVe</i>	261	(2.72)	408	(2.90)	1 640	3 432
<i>IVf</i>	255	(2.72)	416	(2.99)	1 650	3 430
<i>IVg</i>	266	(2.58)	372	(2.88)	1 650	3 410
<i>IVh</i>	261	(2.72)	408	(2.68)	1 640	3 440
<i>IVi</i>	263	(2.72)	410	(2.68)	1 652 1 630	3 435
<i>IVj</i>	265	(2.87)	424	(2.96)	1 639 1 628 1 652	3 443

After stirring for 30 min at room temperature, the product was filtered, washed with perdeuterated methanol and dried in vacuo over molecular sieve 3A. The substance was stored under argon. Yield 590 mg (89%) of compound VI, m.p. 129–131°C. Mass spectrum, m/z : 331 M^+ , 100. 1H NMR spectrum (CD_3SOCD_3): 5.84 s, 1 H (H-4); 6.32 d, 1 H (H-6, $J(6,7) = 3.8$); 6.50 d, 1 H (H-7, $J(6,7) = 3.8$); 7.86 s, 1 H (H-3); 9.30 s, 1 H (H-1).

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