PREPARATION OF UNSYMMETRICALLY SUBSTITUTED STENHOUSE SALTS

Peter ŠAFÁŘ and Jaroslav KOVÁČ

Department of Organic Chemistry,
Slovak Technical University, 813 37 Bratislava

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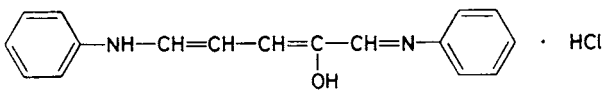
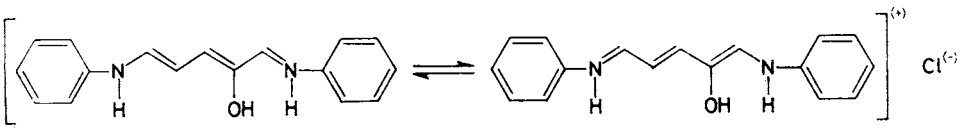
Unsymmetrically substituted Stenhouse salts *IVa*–*IVj* (iminium salts of 1-phenylmethylamino--5-(4-X-phenylamino)-2-hydroxy-2,4-pentadienal) arise by reaction of N-2-furfurylidene-N-phenylmethyliminium perchlorate (*V*) with substituted anilines. Primary and secondary aliphatic amines do not react in this way. Unsymmetrically substituted Stenhouse salts are also formed from iminium salt of 1,5-di(phenylmethylamino)-2-acetoxy-2,4-pentadienal (*IV*) by nucleophilic substitution with aromatic and aliphatic amines.

Stenhouse[1,2] has shown for the first time that mixing 1 mol-equivalent of 2-furaldehyde, 2 mol-equivalents of aromatic amine and 1 mol-equivalent of hydrochloric acid leads to a violet salt which was later assigned the structure *I* by Zincke and Mühlhausen[3]. Foley and collaborators[4] studied the mechanism of the Stenhouse reaction and suggested the resonance-stabilized pentamethinium system *II* for the final product. This system fits better the concept of the mobile proton than the classical structure suggested by Zincke and Mühlhausen. A Stenhouse salt, in which the N—H hydrogen atoms are replaced by methyl groups, was prepared by Hafner and Asmus[5]; it was also obtained by Lewis and Mulquiney[6] from 4,5-di(N-phenylmethylamino)-2-cyclopentenone by treatment with mineral acids.

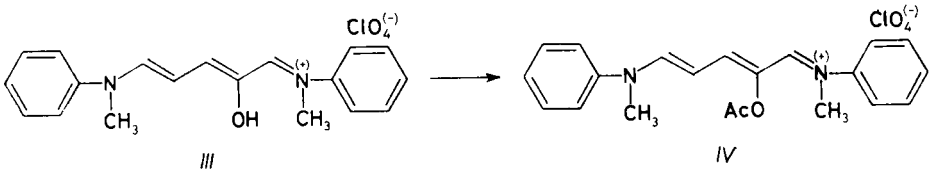


I



II

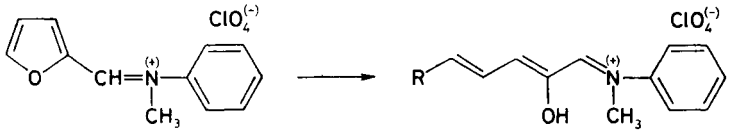
In order to study further the reactions of Stenhouse salts and to prepare unsymmetrically substituted salts of this type, we studied the reactions of the salt *III*. The attempted preparation of compound *III* by treatment of 2-furaldehyde and N-methylaniline with hydrogen bromide was unsuccessful[5]. After addition of perchloric acid, we isolated from the reaction mixture a compound identified by elemental analysis and spectra as N-2-furfurylidene-N-phenylmethyliminium perchlorate (*V*). The compound *V* arises probably by cyclization of the N-methylated Stenhouse salt *III* in the strongly acidic medium[7]. We have proven the structure *V* also by an independent synthesis consisting in condensation of 2-furaldehyde and phenylmethylammonium perchlorate in dry methanol at room temperature[8]. Under acetylation conditions, the Stenhouse salt *III* is converted into the corresponding iminium salt of 1,5-di(phenylmethylamino)-2-acetoxy-2,4-pentadienal (*IV*) (Scheme 1). This protection of the hydroxyl enables an investigation of reactions of the salt *III* with nucleophilic reagents, because the unprotected salt *III* reacts with alkaline reagents to give cyclopentenone derivatives[9–12].



III *IV*

SCHEME 1

The strong electron-accepting effect of the iminium grouping in compound *V* results in a considerable decrease of electron density in position 5 of the furan nucleus. An attack by a suitable nucleophilic reagent opens the furan ring under formation of unsymmetrically substituted Stenhouse salts *VIa* – *VIj* (Scheme 2). The reactions

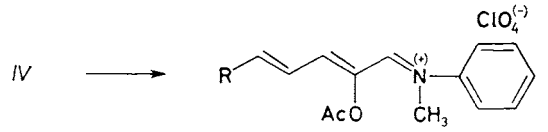


V *VI*

In formula *VI*: *a*, R = C_6H_5NH *b*, R = 4 - CH_3—C_6H_4NH
c, R = 4 - CH_3O—C_6H_4NH *d*, R = 4 - Cl—C_6H_4NH *e*, R = 4 - Br—C_6H_4NH
f, R = 4 - I—C_6H_4NH *g*, R = 4 - CF_3—C_6H_4NH *h*, R = 3 - CF_3—C_6H_4NH
i, R = 2 - CF_3—C_6H_4NH *j*, R = 4 - HOOC—C_6H_4NH

SCHEME 2

of compound *V* with aromatic amines proceed smoothly in solution as well as without any solvent. Since isolation of the arising compounds *VIa–VIj* from solution is difficult, working without solvent represents the method of choice that gives the products in high yields (Table I). Reactions with primary or secondary amines were unsuccessful. Unsymmetrically substituted Stenhouse salts are also formed by nucleophilic substitution reaction of salt *IV* with primary aromatic and secondary aliphatic amines. With primary aromatic amines, the phenylmethylamino group on the C-5 carbon atom is substituted; no substitution on the C-1 atom takes place as evidenced by ^{1}H NMR spectroscopy. The salt *IV* reacts with aromatic amines, containing electron-accepting groups, at the boiling point of the solvent (Scheme 3).

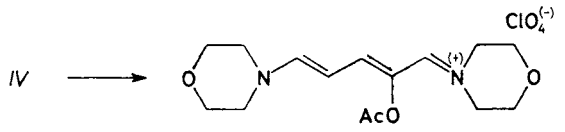


VII

In formula *VII*: *a*, R = C_6H_5NH *b*, R = 4 - CH_3—C_6H_4NH
c, R = 4 - CH_3O—C_6H_4NH *d*, R = 4 - Cl—C_6H_4NH *e*, R = 4 - Br—C_6H_4NH
f, R = 4 - I—C_6H_4NH *g*, R = 4 - CF_3—C_6H_4NH *h*, R = 4 - HOOC—C_6H_4NH
i, R = C_6H_5—N◯N— *j*, R = ◯N—

SCHEME 3

No reaction with imidazole, triazole, benzimidazole, benzotriazole and diphenylamine was observed and only the starting compound *IV* was recovered (as proven by ^{1}H NMR spectroscopy). When treated with secondary aliphatic amines of pK_B 2–4, the salt *IV* was degraded. In the case of N-phenylpiperazine and piperidine, one phenylmethylamine group was substituted whereas with morpholine both the two phenylmethylamine groups were replaced (Scheme 4). The attempted preparation of derivatives *VIIi* and *VIIj* by treatment of *V* with N-phenylpiperazine and piperidine, respectively, failed because the reagent probably added to the iminium grouping instead of reacting in position 5 of the furan ring. The same results were also obtained with derivative *VIII*.



VIII

SCHEME 4

TABLE I

Analytical data of compounds *VIa*—*VIj* and *VIIa*—*VIIj*

Compound	Formula (M. w.)	M.p., °C (Yield, %)	Calculated/Found			
			% C	% H	% N	% Cl
VIa	$C_{18}H_{19}ClN_2O_5$	97—99	57·07	5·06	7·39	9·35
	(378·8)	(81)	56·83	4·93	7·20	9·12
VIb	$C_{19}H_{21}ClN_2O_5$	102—104	58·09	5·39	7·13	9·02
	(392·8)	(82)	57·09	5·09	7·01	8·87
VIc	$C_{19}H_{21}ClN_2O_6$	111—114	55·82	5·17	6·85	8·67
	(408·8)	(92)	55·91	5·03	6·90	8·41
VId	$C_{18}H_{18}Cl_2N_2O_5$	91—93	52·31	4·39	6·77	17·15
	(413·3)	(85)	52·20	4·20	6·51	16·93
VIe[a]	$C_{18}H_{18}BrClN_2O_5$	107—110	47·23	6·12	6·12	7·44
	(457·7)	(85)	47·11	3·40	5·98	7·21
VIf[b]	$C_{18}H_{18}ClIN_2O_5$	121—124	42·83	3·59	5·55	7·02
	(504·7)	(84)	42·70	3·40	5·29	6·88
VIg[c]	$C_{19}H_{18}ClF_3N_2O_5$	147—149	51·07	4·06	6·26	7·93
	(446·8)	(83)	50·93	3·94	6·03	7·75
VIh[d]	$C_{19}H_{18}ClF_3N_2O_5$	100—103	51·07	4·06	6·26	7·93
	(446·8)	(68)	50·98	3·88	5·98	7·90
VIi[e]	$C_{19}H_{18}ClF_3N_2O_5$	118—121	51·07	4·06	6·26	7·93
	(446·8)	(67)	51·34	4·01	6·11	7·81
VIj	$C_{19}H_{19}ClN_2O_7$	167—169	53·97	4·52	6·62	8·38
	(422·8)	(86)	53·82	4·39	6·41	8·12
VIIa	$C_{20}H_{21}ClN_2O_6$	204—206	57·08	5·03	6·06	8·42
	(420·8)	(92)	56·91	5·12	6·30	8·10
VIIb	$C_{21}H_{23}ClN_2O_6$	200—202	58·00	5·33	6·44	8·15
	(434·8)	(81)	57·81	5·11	6·21	7·92
VIIc	$C_{21}H_{23}ClN_2O_7$	158—161	55·94	5·14	6·21	7·86
	(450·9)	(78)	55·73	4·96	6·02	7·79
VIId	$C_{20}H_{20}Cl_2N_2O_6$	157—159	52·76	4·43	6·15	15·57
	(455·3)	(85)	52·51	4·19	5·92	15·21
VIIe[f]	$C_{20}H_{20}BrIN_2O_6$	210—213	48·06	4·03	5·60	7·09
	(499·8)	(80)	47·72	3·08	5·29	6·81
VIIf[g]	$C_{20}H_{20}ClIN_2O_6$	182—185	43·94	3·69	5·12	6·48
	(546·7)	(85)	43·67	3·54	5·01	6·22
VIIg[h]	$C_{21}H_{20}ClF_3N_2O_6$	183—186	51·49	4·13	5·72	7·25
	(488·9)	(80)	51·28	4·01	5·40	7·01

TABLE I
(*Continued*)

Compound	Formula (M. w.)	M.p., °C (Yield, %)	Calculated/Found			
			% C	% H	% N	% Cl
VIIh	$C_{21}H_{21}ClN_2O_8$ (464·8)	192–194 (72)	54·27 53·98	4·55 4·21	6·03 5·71	7·62 7·29
VIIi	$C_{24}H_{28}ClN_3O_6$ (488·9)	106–108 (74)	58·84 58·59	5·76 5·39	8·57 8·21	7·24 6·98
VIIj	$C_{19}H_{25}ClN_2O_6$ (412·8)	160–162 (82)	55·27 54·96	6·10 5·88	8·58 8·27	6·87 6·87

[a] Calculated: 17·45% Br; found: 17·62% Br. [b] Calculated:24·96% I; found: 24·73% I. [c] Calculated: 12·75% F; found: 12·43% F. [d] Calculated: 12·75% F; found: 12·49% F. [e] Calculated: 12·75% F; found: 12·45% F. [f] Calculated: 15·98% Br; found: 15·63% Br. [g] Calculated: 23·05% I; found: 22·71% I. [h] Calculated: 11·65% F; found: 11·33% F.

Our present results have shown that unsymmetrically substituted Stenhouse salts can be prepared from N-2-furfurylidene-N-phenylmethyliminium perchlorate (*V*) by reaction with aromatic amines or from iminium salt of 1,5-di(phenylmethylamino)--2-acetoxy-2,4-pentadienal (*IV*) by nucleophilic substitution with primary and secondary amines.

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. IR spectra were taken on an IR-75 (Zeiss, Jena) and a Beckman–Acculab instrument (KBr technique), wavenumbers are given in cm^{-1}. UV spectra were measured on an M-40 (Zeiss, Jena) spectrometer in methanol ($c = 10^{-4}$ mol l^{-1}); λ_{max} are given in nm, ε in m^2 mol^{-1}. ^1H NMR spectra were obtained at 25°C with a Varian VXR-300 (75·05 MHz) spectrometer in hexadeuteriodimethyl sulfoxide with tetramethylsilane as internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants in Hz.

Acetylation of Stenhouse Salt *III*

Stenhouse salt *III* (4·71 g, 12 mmol) was added during 5 min into a mixture of acetic anhydride (15 ml) and pyridine (1·5 ml). After stirring at room temperature for 2 h, dry ether (50 ml) was added dropwise and the mixture was stirred for further 2 h. The separated product was collected and crystallized from methanol; yield 5·16 g (99%) of compound *IV*, m.p. 134–135°C. IR spectrum: 1 780 (C=O); 1 600, 1 575 (C=C). UV spectrum, λ_{max} (log ε): 246 (2·92); 300 (2·49); 384 (2·96). ^1H NMR spectrum: 1·56 s, 3 H (CH_3CO); 3·55 s, 3 H (CH_3); 3·62 s, 3 H (CH_3); 5·91 dd, 1 H (H-4, $J(3, 4) = 12·0$; $J(4, 5) = 12·0$); 7·25–7·62 m, 10 H (2 × phenyl); 7·66 d,

1 H (H-3, $J(3, 4)$ = 12·0); 8·02 s, 1 H (H-1); 8·32 d, 1 H (H-5, $J(4, 5)$ = 12·0). For $C_{21}H_{23}ClN_2O_6$ (434·9) calculated: 58·00% C, 5·33% H, 8·15% Cl, 6·44% N; found: 57·88% C, 5·13% H, 8·26% Cl, 6·56% N.

N-2-Furfurylidene-N-phenylmethyliminium Perchlorate (*V*)

A) A solution of 2-furaldehyde (2·07 ml, 25 mmol) in methanol (5 ml) was added to a vigorously stirred solution of N-phenylmethylammonium perchlorate (5·19 g, 25 mmol) in methanol (20 ml). After stirring for 2 h the separated product was collected and crystallized from methanol; yield 4·86 g (68%) of compound *V*, m.p. 185—187°C. IR spectrum: 1 655 (C=N). UV spectrum, λ_{max} (log ε): 248 (2·19). ^{1}H NMR spectrum: 2·88 s, 3 H (CH_3); 6·70 dd, 1 H (H-4, $J(4, 5)$ = 0·7); 7·45 s, 5 H (phenyl); 7·36 d, 1 H (H-3, $J(3, 4)$ = 2·0); 8·03 d, 1 H, (H-5, $J(5, 4)$ = 2·0); 9·56 s,

TABLE II

^{1}H NMR spectral data for compounds *VIa*—*VIj* and *VIIa*—*VIIj*

Compound	δ, ppm						
	H-1, m	H-3, d	H-4, m	H-5, d	N-H, m	CH_3, s	Aromatic protons
VIa	8·06	7·28[h]	6·43	8·10[h]	11·25	3·50	7·0—7·6 m, 10 H
VIb[a]	8·22	7·48[g]	6·63	8·25[g]	11·38	3·70	7·3—7·8 m, 9 H
VIc[b]	8·08	7·31[g]	6·59	8·23[g]	11·30	3·59	7·1—7·7 m, 9 H
VId	8·23	7·33[h]	6·43	8·18[h]	11·25	3·65	7·4—7·7 m, 9 H
VIe	8·03	7·30[g]	6·55	8·18[g]	11·00	3·56	7·4—7·8 m, 9 H
VIf	8·06	7·35[h]	6·48	8·21[h]	11·87	3·60	7·5—7·9 m, 9 H
VIg	8·08	7·42[h]	6·60	8·35[h]	11·10	3·63	7·3—7·6 m, 9 H
VIh	8·10	7·80[g]	6·63	8·23[g]	11·08	3·65	7·5—7·9 m, 9 H
VIi	8·14	7·72[h]	6·65	8·27[h]	11·03	3·67	7·3—7·5 m, 9 H
VIj	8·05	7·37[g]	6·65	8·30[g]	11·08	3·63	7·5—7·9 m, 9 H
VIIa	8·75	7·65[h]	6·03	8·53[h]	11·00	3·63	7·0—7·2 m, 10 H
VIIb[c]	8·45	7·72[g]	5·91	8·36[g]	11·13	3·65	7·6—7·7 m, 9 H
VII[d]	8·32	7·63[h]	6·00	8·35[h]	11·08	3·65	7·3—7·6 m, 9 H
VIId	8·42	7·73[h]	6·10	8·45[h]	11·00	3·69	7·4—7·7 m, 9 H
VIIe	8·45	[i]	6·08	8·70[g]	11·13	3·68	7·3—7·8 m, 10 H
VIIf	8·50	7·93[h]	6·20	8·55[h]	10·88	3·73	7·4—7·8 m, 9 H
VIIg	8·38	7·63[g]	6·03	8·41[g]	11·30	3·64	7·2—7·8 m, 9 H
VIIh	8·40	[i]	6·13	8·46[h]	11·21	3·65	7·3—7·9 m, 10 H
VIIi[e]	7·50	6·58[g]	5·98	7·73[g]	—	3·66	7·1—7·5 m, 9 H
VIIj[f]	7·65	7·61[g]	6·00	8·03[g]	—	3·80	7·4—7·5 m, 9 H

[a] Other signal: 2·43 s, 3 H (CH_3). [b] Other signal: 3·88 s, 3 H (CH_3O). [c] Other signal: 2·42 s, 3 H (CH_3). [d] Other signal: 3·89 s, 3 H (CH_3O). [e] Other signals: 3·23—3·50 m, 4 H; 3·82—3·99, 4 H. [f] Other signals: 1·06—2·68 m, 8 H. [g] Observed values $J(3, 4)$ = 12·0; $J(4, 5)$ = 12·0. [h] Observed values $J(3, 4)$ = 12·2; $J(4, 5)$ = 12·2. [i] Overlapping with other aromatic proton signals, the value cannot be determined.

1 H(CH). For $C_{12}H_{12}ClNO_5$ (285·7) calculated: 50·45% C, 4·23% H, 12·41% Cl, 4·90% N; found 50·32% C, 4·17% H, 12·21% Cl, 4·98% N.

B) A mixture of 2-furaldehyde (1·66 ml, 20 mmol), N-methylaniline (4·33 ml, 40 mmol) and methanol (20 ml) was refluxed for 45 min. After cooling to +10°C, a solution of 66% hydrobromic acid (5·2 g) in methanol (5 ml) was added, the mixture was stirred at room temperature for 20 min, cooled to +10°C and mixed with a solution of 70% perchloric acid (10 g) in methanol (5 ml). The precipitate was filtered and crystallized from methanol, affording 3·09 g (54%) of coumpound *V*, identical with the product prepared ad *A*).

Preparation of Stenhouse Salts *VIa*– *VIj*

The corresponding amine (20 mmol) was added into a 50 ml flask, containing a few drops of methanol and the salt *V* (5·71 g, 20 mmol). The mixture was kept in a stoppered flask at 40°C for 1 h and the arising green product was suspended in a mixture of dry ether (30 ml) and methanol (2 ml). After standing for 1 h, the product was filtered, washed with methanol–ether (1 : 5)

TABLE III

IR and UV spectral data of compounds *VIa*– *VIj* and *VIIa*– *VIIj*

Compound	UV spectra				IR spectra		
	λ_{max} nm	(log ε) (m^2 mol^{-1})	λ_{max} nm	(log ε) (m^2 mol^{-1})	$\tilde{\nu}$(N–H) cm^{-1}	$\tilde{\nu}$(C=N) cm^{-1}	$\tilde{\nu}$(C=O) cm^{-1}
VIa	514	(2·90)	243	(2·36)	3 255	1 658	—
VIb	513	(3·01)	252	(2·31)	3 268	1 625	—
VIc	514	(2·98)	242	(2·34)	3 276	1 654	—
VId	514	(2·70)	294	(2·32)	3 295	1 652	—
VIe	514	(2·72)	296	(2·32)	3 265	1 654	—
VIf	514	(2·66)	297	(3·01)	3 246	1 651	—
VIg	478	(2·45)	250	(2·96)	3 256	1 652	—
VIh	513	(2·45)	293	(2·28)	3 266	1 655	—
VIi	514	(2·48)	297	(2·36)	3 275	1 655	—
VIj	512	(2·51)	291	(2·58)	3 265	1 653	—
VIIa	482	(2·42)	247	(2·53)	3 280	1 685	1 760
VIIb	480	(2·35)	243	(2·69)	3 245	1 685	1 765
VIIc	476	(2·32)	246	(2·48)	3 254	1 684	1 770
VIId	472	(2·36)	249	(2·48)	3 244	1 685	1 770
VIIe	470	(3·01)	247	(2·63)	3 275	1 684	1 780
VIIf	465	(2·76)	249	(2·52)	3 265	1 684	1 770
VIIg	483	(2·50)	246	(2·71)	3 284	1 682	1 770
VIIh	486	(2·40)	251	(2·71)	3 246	1 686	1 786
VIIi	401	(3·21)	262	(2·92)	—	1 688	1 770
VIIj	418	(2·93)	259	(2·71)	—	1 687	1 770

and air-dried. Yields and analytical data of products *VIa*—*VIj* are given in Table I, spectral characteristics in Tables II and III.

Preparation of Stenhouse Salts *VIIa*—*VIIj*

A solution of the corresponding amine (20 mmol) in dry methanol (5 ml) was added at 45°C in one portion to a solution of the salt *IV* (8·70 g, 20 mmol) in dry methanol (10 ml). After stirring at room temperature for 1 h, the separated salt was filtered and purified by crystallization from methanol. Yields and analytical data of products *VIIa*—*VIIj* are given in Table I, spectral characteristics in Tables II and III.

Stenhouse Salt *VIII*

The title salt was prepared as described in the preceding experiment, using morpholine (3·5 ml, 40 mmol); yield 7·58 g (96%) of compound *VIII*, m.p. 220—221°C. IR spectrum: 1 755 (C=O); 1 684 (C=N). UV spectrum, λ_{max} (log ε): 270 (3·02); 421 (3·92). ^{1}H NMR spectrum: 2·28 s, 3 H (CH_3CO); 3·55—3·83 m, 16 H (2 × morpholine ring); 5·71 dd, 1 H (H-4, $J(3, 4) = 12·0$; $J(4, 5) = 12·0$); 7·26 d, 1 H (H-3, $J(3, 4) = 12·0$); 7·58 s, 1 H (H-1); 7·88 d, 1 H, (H-5, $J(5, 4) = 12·0$). For $C_{15}H_{23}ClN_2O_8$ (394·8) calculated: 45·64% C, 5·87% H, 8·98% Cl, 7·09% N; found 45·49% C, 5·72% H, 8·84% Cl, 7·20% N.

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