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DERIVATIVES AND REACTIONS OF GLUTACONALDEHYDE—IX

SUBSTITUTION REACTIONS IN THE GLUTACONALDEHYDE ANION. ASSIGNMENT OF STRUCTURE OF A FREE GLUTACONALDEHYDE

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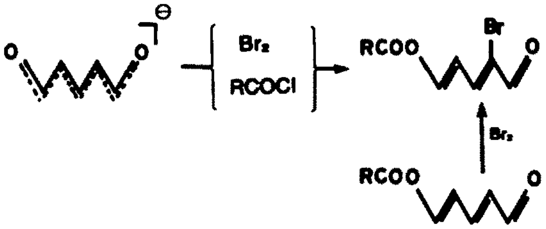
Abstract—Substitution in the glutaconaldehyde anion takes place at C 2 or 4, demonstrated by deuterium exchange and by preparation of the mono- and dichloro or bromo and the monoiodo glutaconaldehyde sodium salts and their respective enol esters. The stable 2-iodoglutaconaldehyde was suggested to have the *all-trans* structure of 2-iodo-5-hydroxy-*trans*-2, *trans*-4-pentadienal. The preparations from the monochloro and bromo glutaconaldehyde anions of 3-halogenopyridines and thiopene-2-carboxaldehyde have been reinvestigated.

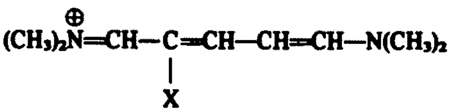
In previous papers[1] we have reported the reactions of the glutaconaldehyde anion. In the second paper[2] of this series, substitution in the glutaconaldehyde moiety in the form of the glutaconaldehyde anion or the benzoyl enol ester with bromine was found to be regiospecific taking place at carbon-2.



A survey of the early literature[3] on this subject confirmed the need for a systematic study of the substitution reactions with the halogens as well as an investigation of the structure and spectra of the previously[4] reported iodoglutaconaldehyde. In 1889 Hantzsch described a salt supposed to be a sodium salt of the 2- or 4- chloro substituted glutaconaldehyde anion, the main evidence was that reaction with ammonium acetate produced 3-chloropyridine, and with hydrogen sulphide thiophene-2-carboxaldehyde was produced. This salt as a benzoyl enol ester was mentioned in other papers[6] until Baumgarten[4] prepared the mono chloro, bromo and iodo substituted glutaconaldehyde enol esters and suggested that substitution to have taken place at carbon-4, again from the reaction with ammonia which gave rise to the 3-halogeno pyridines.

Becher[2] *et al.* then demonstrated that for X=Br, the correct structure of the enol ester was 2 - bromo - 5 - hydroxy - *trans* - 2, *trans* - 4 - pentadienal benzoate. The glutaconaldehyde anion can be regarded as a member of the series of dyes called oxonoles, as such these compounds have been the subject of theoretical calculations.[7] The CNDO/2 calculation carried out[8] for the glutaconaldehyde anion or a corresponding enol ester predicts electrophilic substitution to take place at carbon-2 or carbon-4.

In the cyanine series Kuchera and Arnold[9] showed that the simple cyanine

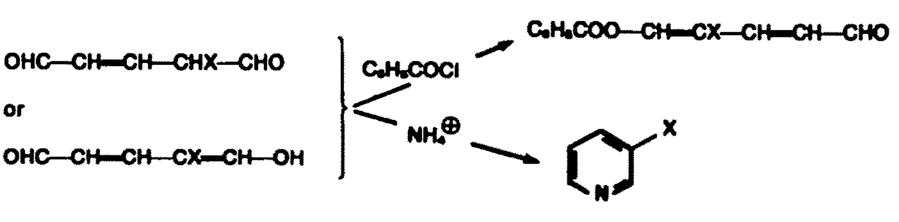


$$(CH_3)_2\overset{\oplus}{N}=CH-\underset{\displaystyle X}{\underset{|}{C}}=CH-CH=CH-N(CH_3)_2$$

was electrophilic substituted at carbon-2. The substitution reactions at carbon-2 of the related malonaldehyde are well investigated.[10]

RESULTS AND DISCUSSION

Halogenation of the glutaconaldehyde anion. The reaction of the glutaconaldehyde and chlorine, bromine or iodine was carried out at low temperature in water. The resulting acidic solutions of the halogenated glutaconaldehydes were extracted with ether. To the dried and concentrated ether phase was then added methanolic sodium hydroxide, whereupon the precipitated sodium salts were collected (Scheme 1). By this method it was possible to prepare the stable sodium salts of the mono halogenated glutaconaldehyde ions† as well as, in the case of chlorine and bomine also the di halogenated derivatives. In the case of iodine no di halogenated product could be obtained, probably due to steric hin-



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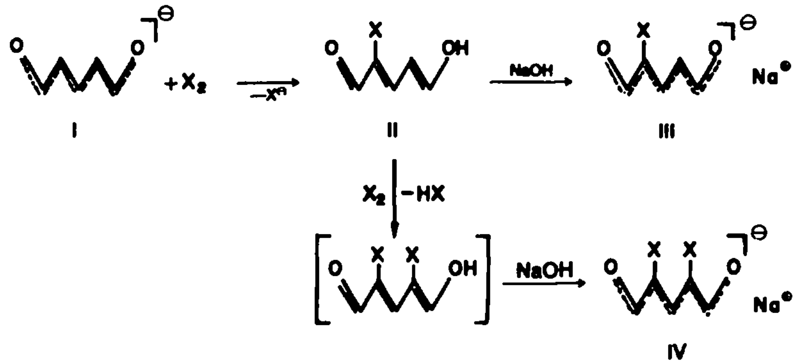
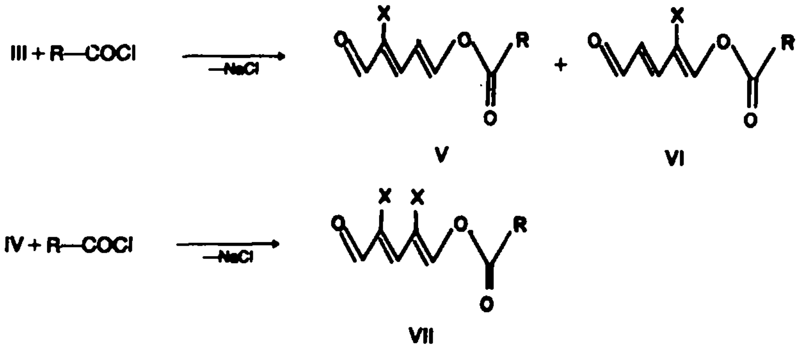
†The sodium salt IIIa has been mentioned by Sarel and Rivlin,[22] however, they only reported the UV spectrum and no structural proof.



Compound	X	R	Compound	X	R
II	J	-	V c, VI c	J	$-OCH_2CH_3$
III a	Cl	-	V d	Cl	$-C_6H_5$
III b	Br	-	V e	Br	$-C_6H_5$
III c	J	-	V f	J	$-C_6H_5$
IV a	Br	-	VII a	Cl	$-HCH_2CH_3$
IV b	Cl	-	VII b	Br	$-OCH_2CH_3$
V a, VI a	Cl	$-OCH_2CH_3$	VII c	Cl	$-C_6H_5$
V b, VI b	Br	$-OCH_2CH_3$	VII d	Br	$-C_6H_5$



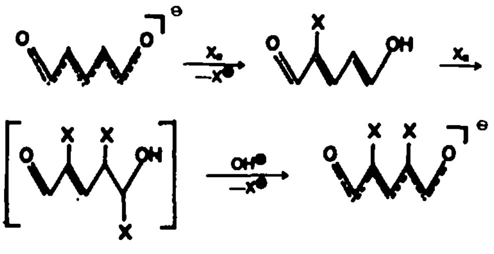
Scheme 1.

drance, as well as the reductive effect of HJ, formed during the reaction.

Subsequent benzoylation of the sodium salts III and IV gave in all cases the expected esters V and VII, thus the benzoylation in pyridine is regiospecific and yields only[a] the 2-halogen substituted isomer V, in accordance with the results obtained previously.[2] However, when the acylation was carried out with the less reactive ethyl chloroformate in DMF, a mixture of the two isomers V and VI was obtained in each case, with the ratio V:VI = 3:1,[b] measured by ^1H NMR. The mixtures of isomers could not be separated by repeated crystallization or by preparative layer chromatography, as was the case[2] for the similar mixture of the 2- and 4-Me substituted glutaconaldehyde benzoylester.

Assignment of the *all-trans* structure to all products described in Scheme 1 followed from the ^1H NMR spectra and the UV spectra, (log ε are of the same order of magnitude both in the substituted and the unsubsituated derivatives), Tables 1, 2 and 3. In the case of the sodium salts, IIIa and IIIb when compared with the salts IVa and IVb respectively (Tables 1 and 2) a characteristic change can be seen in the shift value for carbon 1 reflecting the change in the delocalization in the anion.

The substitution by halogen in the mono halogenated products is supposed to take place via an addition elimination mechanism such as:



An indication in this direction was found in an experiment where the bromination was carried out in a con-

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[a] No trace of an isomer was seen, TLC and ^1H NMR spectra.

[b] The exact values are: Va:VIa = 3.5:1; Vb:VIb = 3.3:1; Vc:VIc = 3.0:1.

Table 1. ^{1}H NMR parameters[a]

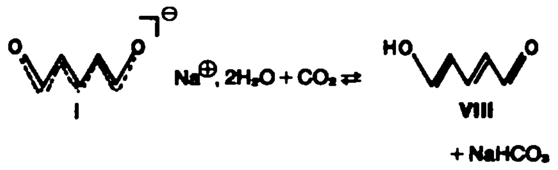
Compound	Protons at carbon no. C 1	C 3	C 4	C 5	Other protons
II	8.53 (s)	7.91 (d) J=10.5	5.97 (d,d) J=10.5;11.7	7.85 (d) J=11.7	5 (OH)
IIIa	8.52 (s)	8.84 (d) J=8.8	5.33 (d,d) J=12.6;8.8	7.25 (d) J=12.8	
IIIb	8.52 (s)	8.91 (d) J=8.8	5.39 (d,d) J=12.8;8.8	7.47 (d) J=12.6	
IIIc	8.15 (s)	9.06 (d) J=8.1	5.50 (d,d) J=8.1;12.6	7.40 (d) J=12.6	
IVa	8.70 (s)	7.67 (s)		8.70 (s)	
IVb	8.68 (s)	7.23 (s)		8.68 (s)	
Va	9.39 (s)	7.76 (d) J=12.0	6.61 (d,d) J=12.0;11.6	7.22 (d) J=11.6	4.35 (J=7.1) (q)-CH$_2$- 1.38 (J=7.1) (t)-CH$_3$
Vb	9.27 (s)	7.83 (d) J=12.4	6.63 (d,d) J=12.4;11.2	7.50 (d) J=11.2	4.37 (J=7.0) (q)-CH$_2$- 1.40 (J=7.0) (t)-CH$_3$
Vc	8.72 (s)	7.53 (d) J=11.0	6.62 (d,d) J=11.0;12.2	7.86 (d) J=12.2	4.36 (J=7.1) (q)-CH$_2$- 1.40 (J=7.1) (t)-CH$_3$
Vd	9.43 (s)	7.30 (d) J=11.6*	6.70 (d,d) J=11.8;12.0*	6.20 (d) J=12.0*	8.3 - 7.5 (m) - ϕ
Ve	9.25 (s)	7.55 (d)	6.78 J=12.0;10.5	8.20 J=12	8.25 - 7.5 (m) - ϕ
Vf	8.79 (s)	8.05 (d) J=11.0*	6.81 (d,d) J=11.0;12.0*	8.46 (d) J=12.0*	
VIIa	9.37 (s)	8.38 (s)		7.10 (s)	4.39 (J=7.1) (q)-CH$_2$- 1.41 (J=7.1) (t)-CH$_3$
VIIb	9.18 (s)	8.57 (s)		7.45 (s)	4.34 (J=7.0) (q)-CH$_2$- 1.40 (J=7.01)(t) CH$_3$
VIIc	9.30 (s)	7.12 (s)		8.70 (s)	8.15 - 7.6 (m) - ϕ
VIId	9.20	7.50		8.98	8.15 - 7.6 (m) - ϕ

[a] IIIa–IVb on DMSO-d$_6$; II, V$_a$–VIId in CDCl$_3$
J in Hz

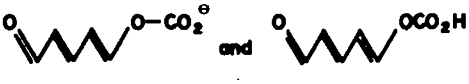
*These values were measured from the corresponding pentadeuteriobenzoyl esters (R = C_6D_5).

centrated solution of sodium chloride. No chloro substitution took place in the resulting product.

The free glutaconaldehyde enol form. Due to the instability of the free enol form of glutaconaldehyde only the UV spectra have been reported. However, a dilute solution of this aldehyde can be prepared. Schwarzenbach and Lutz[12] noted that solutions of glutaconaldehyde sodium salt should be protected from carbon dioxide, as the free glutaconaldehyde enol form is a relatively strong acid[12]; pK$_a$ = 5.75. We used this fact to prepare a methanol solution of glutaconaldehyde by addition of solid carbon dioxide to a solution of the sodium salt:



A relatively concentrated solution is stable† for 30 min at −70°. However, when this experiment is repeated with a very dilute solution at room temperature in ethanol (6 × 10^{-6} mol/l.) the reaction is reversible as seen from the UV-spectra. Fig. 1. The formation of the enol form of glutaconaldehyde VIII with a λ_{max} = 305 nm (4.55), takes place by simple protonation of the anion due to the large excess of CO$_2$, when the reaction is followed with UV it is seen that the reaction is nearly reversible with isobestic points in the UV spectrum. Thus no intermediate is seen, and the λ_{max} = 304 nm (4.55) is the same as reported by Grigorewa[24] for a solution of the anion treated with hydrochloric acid. Furthermore carbonate esters or anions



are not present as the absorption of the known enol-

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†The soln slowly darkens.

Table 2. ^{13}C NMR chemical shifts[a]

Compound	Carbon number C 1	C 2	C 3	C 4	C 5	$\overset{O}{\parallel}$ -C-O-	Other
II	183.55	92.22	156.00	111.69	166.79		
IIIa	185.69	106.69	153.08	106.10	175.10		
IIIb	185.89	98.56	154.38	108.18	175.69		
IIIc	186.01	76.73	157.95	112.02	178.15		
IVa	179.71	96.35	150.09	96.71	179.71		
IVb	178.74	106.10	146.58	106.10	178.74		
Vd	184.91	133.26	141.64	110.59	147.23	162.56	127.67 C_ω, 130.47 C_o 128.91 C_m. 134.56 C_p
Ve	185.37	126.24	145.15	112.80	147.68	162.44	127.61 C_ω, 130.40 C_o 128.84 C_m, 134.56 C_p
Vf	187.23	108.44	148.07	116.50	151.39	162.18	127.28 C_ω, 130.21 C_o 128.65 C_m, 134.56 C_p
VIIa	185.23	131.96	139.11	112.80	143.46	151.13	66.34-CH_2- 14.10-CH_3
VIIb	185.63	125.01	144.50	100.84	144.50	151.26	66.34-CH_2- 14.10-CH_3
VIIc	185.23	130.40	139.37	113.83	142.23	161.66	127.28 C_ω, 130.68 C_o 128.91 C_m, 134.76 C_p
VIId	185.69	124.81	143.33	102.07	144.82	161.66	127.28 C_ω, 130.66 C_o 128.97 C_m, 134.76 C_p

[a] IIIa – IVb in DMSO-d_6; II, Vd – VIId in $CDCl_3$, shifts in ppm.

[b] Assigned on the basis of the reported values for the 3-Me and 3-OMe derivatives, see ref. 13.

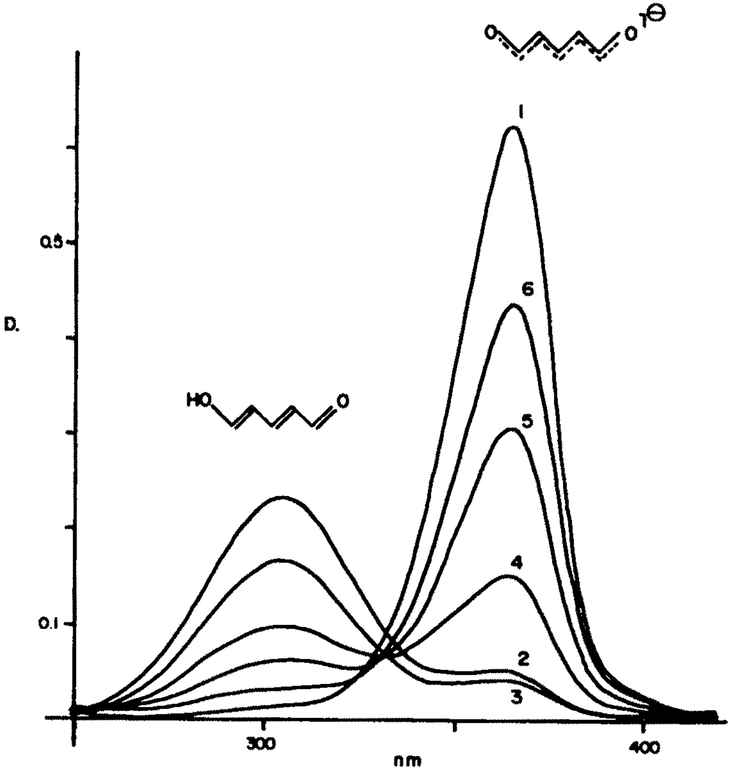
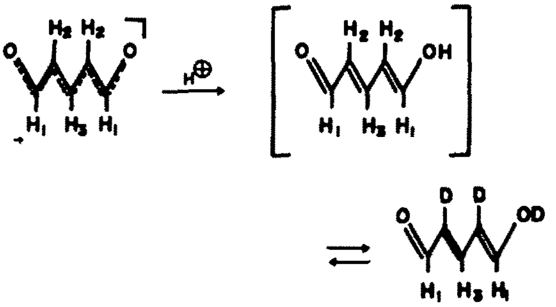


Fig. 1. UV spectra of glutaconaldehyde sodium salt dihydrate (I) in abs ethanol, (1) before addition of CO_2, (2) just after addition of CO_2, (3) 1 hr after, (4) 2 hr after, (5) 3 hr after, (6) 4 hr after. 20°, 6×10^{-4} mol/L of I.

esters:

are 276 and 274 nm respectively (4.53 and 4.57).[23]

^1H NMR of the CO_2 saturated CD_3OD solution showed that a rapid exchange reaction takes place.

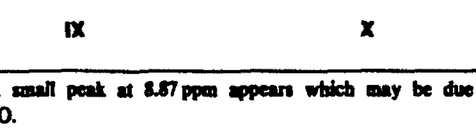


which gives rise to ^1H NMR spectra with sharp singlets at $\delta = 7.98$ and $\delta = 6.88$ ppm due to H_1 and H_3 while the splitting as well as the peaks due to H_2 at 5.14 disappears.† ^{13}C NMR confirms that we do have the same compound, here three broad peaks are seen at 183.8 ppm. (C-1 and C-5), 162.4 (C-3) and 114.0 (C-2 and C-4). The values for C-1, C-5 and C-3 are identical with the values reported for the anion,[13] but different from the value of 106.8 ppm reported for C-2 and C-4.

A rapid exchange reaction at C-2 and C-4 was seen from attempt to prepare the perdeuterated salt in which $H_2O/NaOH$ was used in the ring opening step, starting with perdeuterated pyridine according to Stanoiu and Balaban.[14]

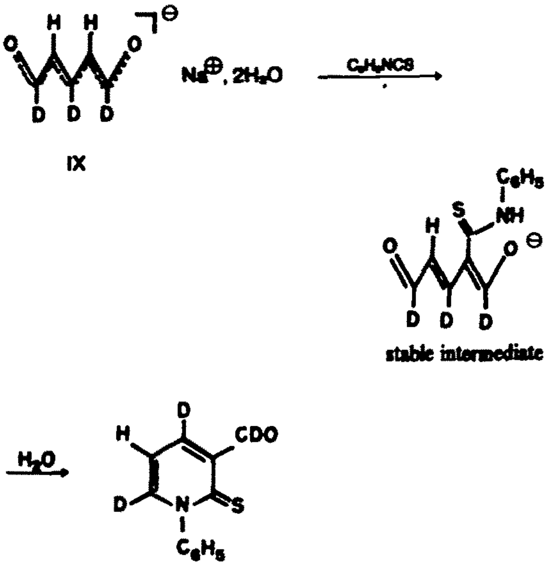
IX

We found, from IR and ^1H NMR that the deuterium at C-2 and C-4 had been completely exchanged with hydrogen. By repeated crystallization in D_2O the perdeuterated salt was obtained.



IX X

Further confirmation concerning the position of the D atoms in the glutaconaldehyde anion was obtained from the reaction of the trideuterated salt and phenyl isothiocyanate.



XI

The pyridinethione obtained in this reactions had hydrogen at C-5 (^1H NMR) and was fully deuterated at C-4, C-6 and in the formyl group, in agreement with the structure of the previously identified stable intermediate[25] and hence also in agreement with the position of the deuterium in the starting material.

In order to get information on a more stable free glutaconaldehyde we turned our attention to the iodo substituted glutaconaldehyde for which Baumgarten[4] reported a m.p. and an analysis. A reliable synthesis was worked out (Experimental). The spectroscopic data obtained showed the structure assigned by Baumgarten to be incorrect, the correct structure was the depicted one (II) with the iodine at C-2.

II

IIIc

The ^1H NMR spectrum of 2 - iodo - 5 - hydroxy - *trans* - 2, *trans* - 4 - pentadienal(II) together with the spectrum of the corresponding anion (IIIc) are shown in Fig. 2.

These spectra indicated both compounds to have the *all-trans* structure with the shift for the H-3 and H-5 protons in II nearly identical in contrast to the same values for the anion IIIc in which H-5 is much more deshielded. The –OH proton in the free enol II was hidden under the peak due to H_2O.

Heterocycles from the anions III. We reinvestigated the synthesis described by Hantzsch[5] and later by Baumgarten;[4] that 3-halogenopyridines could be obtained from the salts IIIa and IIIb.

The old synthesis of thiophene - 2 - carboxaldehyde in undisclosed yield reported by Hantzsch[5] has later been mentioned,[26] but never with any confirmation of the

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†A small peak at 8.87 ppm appears which may be due to –CHO.

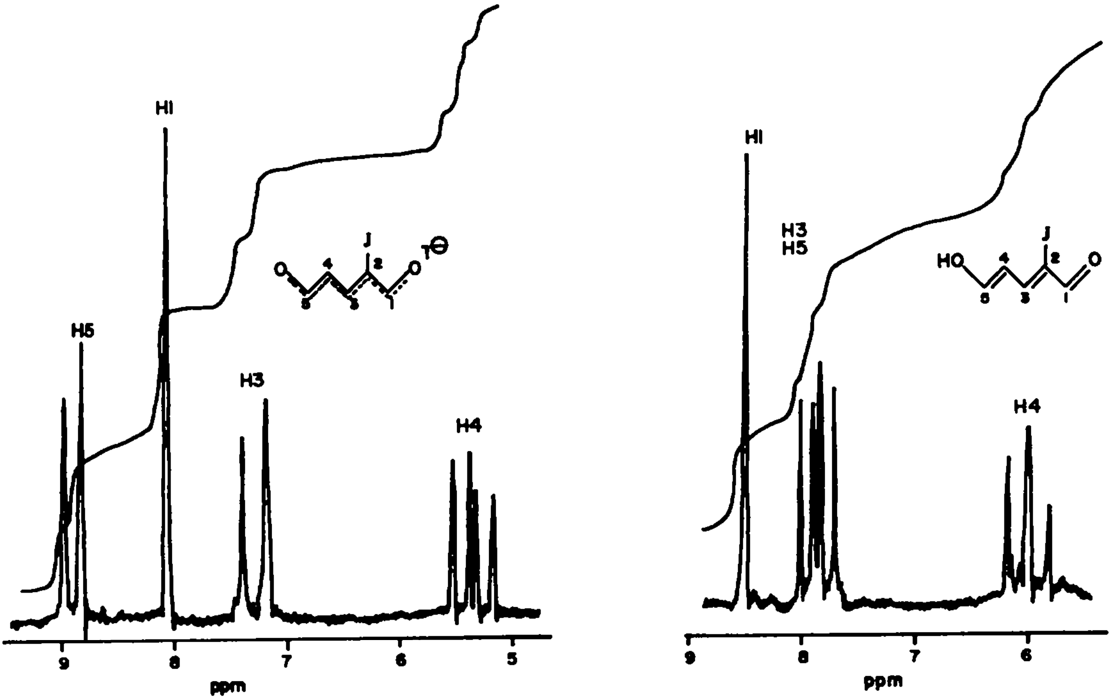

Fig. 2. ^{1}H NMR spectra of II and IIIc in DMSO-d_6.

Table 3.

Compound	yield %	m.p. °C	UV absorption in 96 % EtOH	
			λ_{max}	log ε
II	59	88-90	370,0 225.0	4.77 3.79
IIIa	16	d>100	372.0 237.5 222sh	4.68 3.43
IIIb	70	d>100	369 235 218	4.64 2.46
IIIc	31	d>100	367.5 231.0	4.69 3.70
IVa	39	d>100	379.0 237.0 221sh	4.55 3.38
IVb	25	d>100	379.0 237.5 215sh	4.62 3.57
Ve	56	127-128 b		
Vf	58	131-141 c	317 250	4.35 4.15
Vd	55	126-128 b	368.8 298.8 238.8	3.18 4.51 3.97
Va, VIa	20	91-94 a	370.0 285.5	3.25 4.44
Vb, VIb	39	88.5-90 a	289.0 367.5	4.29 3.18
Vc, VIc	69	74-78 a	307.5 287sh 250	4.15 3.94
VIIa	41	84-85 a	378 292.5	2.61 4.28
VIIb	52	78.5-79.5 a	378.3 301.2	3.30 4.15
VIIc	66	114-116 b	380.0 305 238	3.73 4.28 3.98
VIId	65	98-100 b	378 310.6 240	3.08 4.18 4.03

Recrystallized from, a: cyclohexane

b: toluene

c: methylcyclohexane

10%

IIIa X = Cl
IIIb X = Br

17–31%

yield, and with some confusion concerning the structure of the starting material.

The salt IIIa have been described by Zincke,[18] Ince[19] and Dieckmann.[20] Dieckmann[20] concludes that it is the sodium salt of chloro glutaconaldehyde which give rise to thiophene - 2 - carboxaldehyde, and finally Dieckmann[21] prepared and reported the m.p. 127° for a benzoyl derivative of the salt IIIa, this has been fully confirmed by us, compound Vd. The correct structure of some isomers described by Hantzsch have been assigned by Moye and Steinhell[16] and by Burgstahler *et al.*[17] On the basis of our experiments it can be concluded that the correct reaction scheme for the preparation of thiophene - 2 - carboxaldehyde and the 3-halogeno pyridines is the one shown above.

EXPERIMENTAL

Microanalyses were carried out at the microanalytical Department of the University of Copenhagen by Mr. P. Hansen. Instrumentation. IR: Perkin Elmer 457. UV: Beckman ACTA III. ^{1}H NMR: Jeol JNM-PMX 60, ^{13}C NMR: Jeol FX 60. M.p. Buchi apparatus (uncorrected).

The sodium salt of 2-chloro-5-hydroxy-trans-2, trans-4-pentadienal (IIIa). The Na salt of I, (3.11 g, 0.02 moles) was stirred in water (100 ml, 0°). Liquid Cl_2 collected in a freezing trap, (0.8 ml) was allowed to evaporate in the course of 3 min into the glutaconaldehyde soln. The orange-yellow mixture was stirred for 5 min until the smell of Cl_2 disappeared and it was then extracted with ether (2 × 200 ml). The yellow ether phase was dried with Na_2SO_4 and concentrated (100 ml) *in vacuo*. The ether phase then was cooled on an icebath and under vigorous stirring NaOH in MeOH was slowly added (16 ml; 0.5 M), the pH of the mixture rose from 3.5 to 9.6. The light brown Na-salt, which precipitated was collected and washed with dry ether, yield (0.81 g). The crude product was purified by reflux for 3 hr in MeOH with activated carbon (1 g of salt/20 ml of MeOH). The mixture was filtered hot and on addition of dry ether (200 ml/20 ml of filtrate) to the filtrate, the Na-salt precipitated,† as the trihydrate.

The sodium salt of 2 - *bromo* - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienal* (IIIb). The Na-salt of glutaconaldehyde (6.24 g ~ 0.04 moles) was dissolved in water (200 ml, 0°) and Br_2 (1.7 ml ~ 0.033 moles) was added under vigorous stirring. The red-orange mixture was stirred for 5 min and then extracted with ether (4 × 300 ml). The yellow ether phase was treated as described for IIIa. The brown crude product (dihydrate) which was pure enough for most purposes could be purified as described for IIIa.

2 - *Iodo* - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienal* (II). The K-salt of glutaconaldehyde (1.36 g, 0.01 mole) was dissolved in icewater (25 ml). Under vigorous stirring a soln of I_2 (2 g) and KI (16 g) in 25 ml water was slowly added. The temp. was kept at 0° by occasional addition of crushed ice. The resulting orange suspension was quickly extracted with ether (2 × 125 ml). The cooled extract was treated with activated carbon, dried (Na_2SO_4) and filtered. The yellow-orange filtrate was concentrated *in vacuo* with the temp. below 5°, this gave orange crystals m.p. 88–90°. Baumgarten[4] reported m.p. 89°. Unstable ($\tau_{1/2} < 10$ min at 20°).

The sodium salt of 2 - *Iodo* - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienal* (IIIc). A soln of II from 1.36 g glutaconaldehyde potassium salt in ether was treated as described for IIIa. The brown crude product was dissolved in MeOH (25 ml/g) activated carbon was added and the mixture was stirred at 40° for 5 min and then filtered. On addition of dry ether to the yellow filtrate (100 ml ether/25 ml filtrate) the light yellow Na-salt precipitated, as the monohydrate yield 1.3 g.

The sodium salt of 2,4 - *dibromo* - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienal* (IVa). The Na-salt of glutaconaldehyde (3.12 g ~ 0.02 moles) was stirred in 100 ml icewater and Br_2 (1.8 ml) was added. The nearly colourless soln was stirred 30 min at 0°, and then extracted with ether (3 × 200 ml). The combined light yellow ether phase was dried with Na_2SO_4 filtered and concentrated *in vacuo* (50 ml). To the ether soln NaOH in MeOH (1 M) was added under vigorous stirring and cooling in an icebath until the pH of the suspension remained at 9. The yellow Na-salt was collected and dried *in vacuo* at room temp. The almost pure compound could be further purified by heating under reflux in MeOH with activated carbon for 5 min followed by reprecipitation with dry ether.

The sodium salt of 2,4 - *dichloro* - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienal* (IVb). Cl_2 (about 2 ml of fluid Cl_2 at −34.6°) was slowly added to a well stirred soln of glutaconaldehyde sodium salt (3.12 g = 0.02 moles) in water (100 ml, 0°) until the colour of the soln turned pale yellow. After stirring for 2 min the soln was extracted with ether (3 × 100 ml). The ether extract was treated as described for compound IVa. This gave the title compound as the dihydrate.

General procedure for the preparation of the halogen substituted O-*ethoxy carbonyl* - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienal*. Va, b, c, VIa, b, c, VIIa, b. 0.005 moles of chloroformic acid ethyl ester was mixed with 0.005 moles of the halogenated salt in 20 ml of DMF under stirring and cooling. After 10 min the mixture was added to 200 ml icewater. A light brown ppt of the O-ethoxy carbonyl compound was isolated.

Recrystallization of the crude product from cyclohexane gave unstable colourless needles. (Can be stored in the freezer at −20° for 2 weeks).

Analyses: Va, VIa (Found: C, 46.75: H, 4.52: Cl, 17.25. $C_8H_9O_4Cl$ requires: 46.96; H, 4.43; Cl, 17.33%). Vb, VIb (Found: C, 38.85: H, 3.50: Br, 32.45. $C_8H_9O_4Br$ requires: C, 38.58: H, 3.64; Br, 32.09%). Vc, VIc (Found: C, 32.45: H, 3.09: J, 42.85. $C_8H_9O_4J$ requires: C, 32.45; H, 3.06; J, 42.86%). VIIa (Found: C, 40.35: H, 3.38; Cl, 29.92. $C_8H_8O_4Cl_2$ requires: C, 40.19; H, 3.37; Cl, 29.65%). VIIb (Found: C, 29.35: H, 2.35: J, 48.60. $C_8H_8O_4Br_2$ requires: C, 29.30; H, 2.46: Br, 48.73%).

General procedure for the preparation of the 2- or 4-halogen substituted O - *benzoxy* - 5 - *hydroxy* - trans - 2, trans - 4 - *pentadienals*. Vd, e, f, VIIc and VIId

0.005 moles of benzoyl chloride was added to 0.005 moles of the halogenated Na-salt in 20 ml pyridine under vigorous stirring and cooling in an icebath. After 15 min the mixture was poured into 200 ml icewater under stirring and after 0.5 hr the resulting brown ppt was filtered off and dried *in vacuo* ($CaCl_2$). The crude product could be recrystallized from methylcyclohexane or toluene, or it could be sublimed *in vacuo* at temps near the m.p.

Analyses: Vd (Found: C, 60.85; H, 3.65; Cl, 14.78. $C_{12}H_9O_3Cl$ requires: C, 60.90; H, 3.83; Cl, 14.98%). Vf (Found: C, 43.90; H, 2.69; J, 38.80. $C_{12}H_9O_3J$ requires: C, 43.92; H, 2.77; J, 38.68%), VIIc (Found: C, 53.10; 2.93; J, 26.26. $C_{12}H_8O_3Cl_2$ requires: C,

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†These glutaconaldehyde salts usually contains small amounts of inorganic material.

53.17; H, 2.98; Cl, 26.15%). VIId (Found: C, 40.15; H, 2.29; Br, 43.78. $C_{12}H_6O_3Br_2$ requires: C, 40.04; H, 2.24; Br, 44.39%).

The compounds are unstable colourless needles. (Can be stored in the freezer at −20° for 2 weeks).

1 - *Phenyl* - 3 - *deuterioformyl* - 2(1H) - 4,6 - *dideuteriopyridinethione* (XI). This was prepared as described,[23] 1,3,5 - trideuterioglutaconaldehyde sodium salt dihydrate (0.47 g) in dry DMSO (3 ml) was stirred with phenylisothiocyanate (0.36 ml) for 2 hr at room temp., addition of water (6 ml) and isolation yielded 0.46 g (70%) of XI, m.p. 179–80° (toluene).

Analyses: C, 65.90; "H", 4.23; N, 6.39. $C_{12}H_6D_3NOS$ requires: C, 55.06; "H", 4.12; N, 6.42%. ^1H NMR (DMSO-d_6) 6.98 (s, 1 H), 7.52 (m, 5 H).

Preparation of thiophene - 2 - *carboxaldehyde*. Excess H_2S gas was slowly added to a well stirred soln of IIIb in water (1 g/30 ml). The brown soln which became turbid after a few minutes was slowly heated to 40° and after 10 min the temp. was raised to the b.p. (94–96°) under constant addition of H_2S. The 25 ml of milky condensate, collected during the distillation was extracted with 25 ml ether. Drying (Na_2SO_4) and evaporation *in vacuo* yielded 0.05 g (10%) of a brown oil identified as thiopene - 2 - carboxaldehyde by comparison (tlc and IR) with an authentic sample.

3-*Bromopyridine*. Compound IIIb (300 mg) dissolved in water (10 ml) and saturated with ammonium-hydrogen phosphate (20 ml) was steam distilled (20 ml collected). The distillate was extracted with ether, work up gave 3-bromopyridine 40 mg (17%) identical with an authentic sample (IR and tlc).

3-*Chloropyridine* was prepared as above, IIIa (300 mg) yielded 3-chloropyridine 60 mg (31%) identical with an authentic sample (IR and tlc).

Methanol solution of glutaconaldehyde. To a soln of I (0.1 g) in MeOH (2 ml) an excess of solid CO_2 was added. The cold soln was filtered as quickly as possible. This solution of VIII was stable for *ca.* 30 min at −70°.

1,3,5-*Trideuterioglutaconaldehyde sodium salt dihydrate* (IX). This was prepared according to Balaban;[14] pyridine-d_5 (7 g) with HSO_3Cl (2.44 ml) in $CHCl_3$ (40 ml) gave 4.3 g (62%) of pyridinium - d_5 - 1 - sulfonate, 4.3 g of this complex with $NaOH/H_2O$ gave 2.8 g (41%) of the sodium salt. ^1H NMR (DMSO-d_6) 5.20 s (H-2 and H-4).

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