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Derivatives and Reactions of Glutacondialdehyde. VII. Reaction of the Glutacondialdehyde Anion with Heterocumulenes

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Dedicated to Professor K. A. Jensen on his 70th birthday

Organic isothiocyanates and isoselenocyanates react with the glutacondialdehyde anion (*1*) to give 1-substituted-3-formyl-2(1*H*)-pyridinethiones and -selones, respectively. ^{1}H NMR spectroscopy showed the intervention of a stable intermediate, *i.e.* the 2-(*N*-substituted-thio or selenocarbamoyl)glutacondialdehyde anions (*8*). Subsequent cyclization leading to the products only takes place in the presence of water.

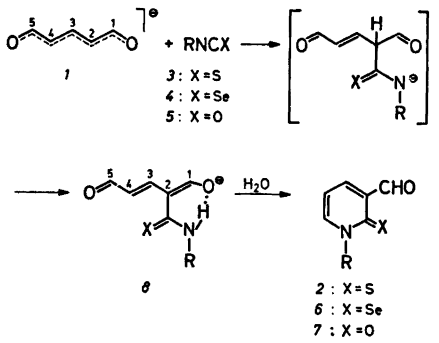
The reaction of *1* with organic isocyanates, at best, gives 1-substituted-3-formyl-2(1*H*)-pyridones in poor yield. The preparation of these compounds is most conveniently effected by desulfuration of the pyridinethiones.

The reactions of *1* can be rationalized in terms of the concept of hard and soft acids and bases.

Derivatives of glutacondialdehyde are bifunctional reagents and, as such, potential precursors for various heterocyclic compounds.[1] In connection with a current investigation [2] of the properties of the glutacondialdehyde anion (*1*) we have studied the reactions with heterocumulenes. Recently, we have shown [3] that 1-substituted-3-formyl-2(1*H*)-pyridinethiones (*2*) are formed from *1* and organic isothiocyanates (*3*). We now report on the course of this reaction and present a study of the reaction of *1* with organic isoseleno- (*4*) and isocyanates (*5*) which leads to 1-substituted-3-formyl-2(1*H*)-pyridineselones (*6*) and -ones (*7*), respectively. The last reaction is not suited for preparative work and alternative routes to *7* from the readily available compounds *2* have been included.*

* The spectroscopic properties of *2* and *6* will be reported in a separate paper.

RESULTS



Scheme 1.

Course of reaction. The time dependent ^{1}H NMR spectrum of the reaction mixture of *1* (potassium salt) and methyl isothiocyanate is shown in Fig. 1. The figure shows the disappearance of the signal from *1* and simultaneous appearance of the signal of a single new species (*8*). The same pattern was observed in the reactions of *1* with phenyl and *t*-butyl isothiocyanate and with *t*-butyl isoselenocyanate. The integral ratio of the well-separated signals from H(1)+H(5) in *8* and from H(2)+H(4) in *1* allows an estimate of the rate of the reaction. The following periods for 50 % conversion have been obtained in this way: Reagent ($t_{50\%}$ min; °C), phenyl isothiocyanate (10; 20), methyl isothiocyanate (97; 50 and 16; 80) and *t*-butyl isothiocyanate (*ca.* 3×10^3; 73). The results show that aryl isothiocyanates are more

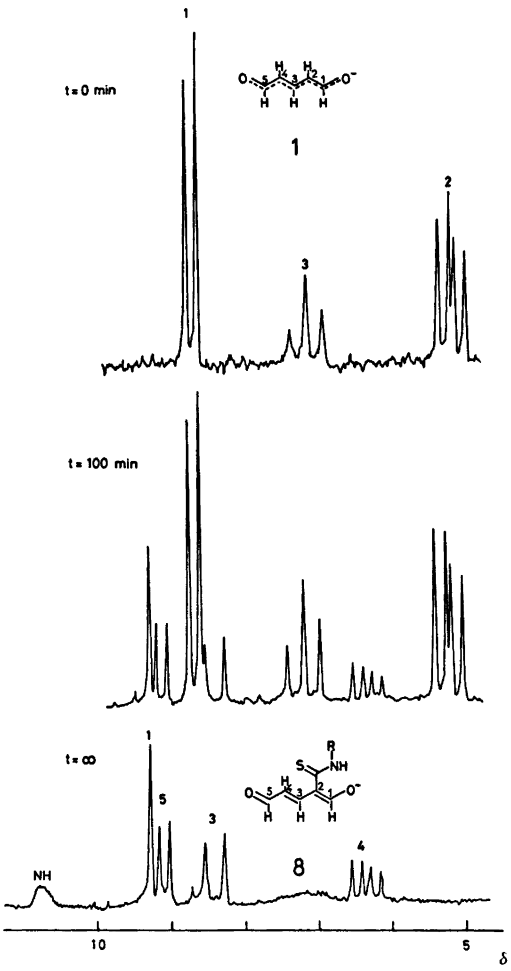


Fig. 1. ^{1}H NMR spectrum of the reaction mixture of *1* and methyl isothiocyanate (DMSO-d_6, 50 °C).

reactive than alkyl isothiocyanates and that the sterically hindered *t*-butyl isothiocyanate is the least reactive species. The same trend was qualitatively observed in the isoselenocyanate series.

Table 1 presents ^{13}C and ^{1}H chemical shifts and H–H coupling constants * for selected compounds *8*. When these values are compared to the corresponding values for the anion *1* and some of its simple derivatives, the structures of which have been established as *all-trans*,[2] this comparison strongly indicates that also the intermediate has the *all-trans* configuration *8*. Additional evidence for this structure is found in the low-field NH-signal ($\delta \sim 12$) indicating a chelated proton. Furthermore, the ^{13}C shift of C(5) is in complete agreement with values reported for α,β-unsaturated aldehydes,[6] suggesting that the formulation *8* is the most reasonable classical representation of the delocalized anion.

Solutions of *8* in dry DMSO stay unchanged for several days at room temperature. This is not surprising since the system *8* is a vinylogue of a push-pull substituted ethylene. The latter systems are reported to form stable, almost nonbasic, mono-anions.[7] However, on addition of water, solutions of *8* undergo a rapid cyclization to give the products, with the exception of the *N*-*t*-butyl derivatives.

The function of water in the cyclization step is almost certainly that of an acid-base active species. The conversion of the stable intermediate *8* into a species which can undergo cyclization requires *trans-cis* isomerization around the C(3) – C(4) bond and a tautomerization disrupting the internal interaction between electrophilic and nucleophilic centers. Proton exchange steps are probably involved in both conversions.

1-Alkyl and aryl-3-formyl-2(1H)pyridineselones (6). The yields of *6* obtained from the reaction of *1* with a series of alkyl and aryl isoselenocyanates are presented in Table 2. Neither these yields nor the reaction conditions differ appreciably from those reported previously for the analogous sulfur compounds.[3] Thus, the aryl isoselenocyanates reacted readily with *1* at room temperature whereas the reaction with alkyl isoselenocyanates required an elevated temperature (*ca.* 80 °C). As in the sulfur series the yield of the *t*-butyl derivative was anomalously low. This feature can be ascribed to a strong repulsive interaction between the bulky *t*-butyl group and the neighbouring chalcogen atom, impeding the cyclization to give *6*. In these terms it is reasonable that the yield of the selenium compound is even lower than that of its thio analogue.

The chemical properties of compounds *6* resemble those of their sulfur analogues. In

* The assignment of the ^{13}C NMR chemical shifts were based on both the decoupled and the undecoupled spectra.

Table 1. ^1H and ^{13}C chemical shifts of the intermediates *8* (DMSO-d_6).

R	H(1)[a]	H(3)	H(4)	H(5)	NH	Other H[b]
Methyl	9.30s	8.40d	6.31dd	9.15d	11.65s	2.82d CH_3
X=S		J=15	J=15, 8	J=8		J=4
Phenyl	9.31s	8.15d	6.35dd	9.20d	13.95s	7.2–7.9 m
X=S		J=15	J=15, 8	J=8		phenyl
t-Butyl	9.15s	8.43d	6.11dd	9.00d	11.80s	1.45s CH_3
X=S		J=15	J=15, 8	J=8		
t-Butyl	9.16s	8.96d	6.00dd	9.13d	12.50s	–
X=Se		J=15	J=15, 8	J=8		
R	C(1)[a]	C(2)	C(3)	C(4)	C(5)	Other C[c]
Methyl	180.8	110.1	161.9	110.5	191.4	214.5 C=S
X=S						30.6 CH_3
Phenyl	180.7	111.2	161.2	112.1	191.8	214.7 C=S
X=S						

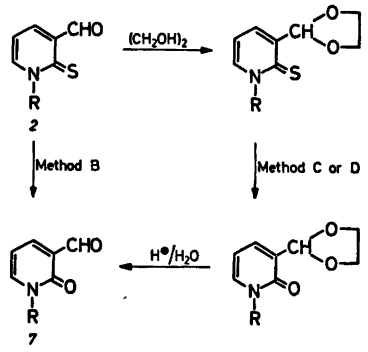
[a] The numbering of the intermediate is given in Scheme 1. [b] δ (ppm from TMS), J in Hz. [c] Hz from TMS.

particular, they are much more inert than is customary of compounds containing a formal selenocarbonyl group *i.e.* they are neither affected by dilute acid or base, nor by atmospheric oxygen at room temperature and they are thermally stable up to at least 150 °C.

1-Alkyl and aryl-3-formyl-2(1H)-pyridones (7). The reaction of *1* with aryl isocyanates afforded compounds *7* in low yields (method A, Table 3). A study of this reaction by ^1H NMR spectroscopy showed the emergence of a complex spectrum which defied analysis in terms of a single intermediate or reaction product. Thus, the low yield of *7* is caused by the fact that the isocyanates, unlike their thio- and selenoanalogues, do not react specifically at C(2) of *1*.

Alternative preparative routes to *7* from *1* *via* the readily accessible compounds *2* were studied (Table 3 and Scheme 2). We have previously prepared *7b* from the corresponding thione by reaction with mercury(II) oxide.[3] However, mercury(II) acetate is normally used [8] and better (although only fair) yields were obtained with this reagent (method B).

The oxidation with alkaline hydrogen peroxide is a general method for the conversion of thiocarbonyl to carbonyl functions.[9] Before this reagent was used in the present investigation, the aldehyde group was protected by 1,3-dioxolane formation with ethylene glycol. Compound *7b* was prepared in a good yield in this way (method C), whereas only traces of the *N*-alkyl compounds, *7c* and *7d*, were observed. Probably oxidation of the *N*-alkyl group takes place under these reaction conditions. The three compounds *7b*–*7d* were obtained in very good yields by oxidation with *m*-chloroperoxybenzoic acid (method D).



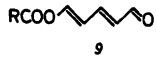
Scheme 2. Method B, $(CH_3CO_2)_2Hg$; C, H_2O_2/OH^-; D, *m*-$ClC_6H_4CO_3^+$. *Cf.* Table 3 for yields.

DISCUSSION

The reactions of ambident anions such as *1* have been subject to several mechanistic interpretations.[10] Of these, the concept of hard and soft acids and bases (HSAB), introduced by Pearson,[4] has the most general applicability. In Klopman's [5] interpretation the hard acid-hard base reactions are dominated by the electrostatic interaction and the soft acid-soft

base reactions by frontier orbital (LUMO-HOMO) interactions between the reaction partners.

The striking difference between the reaction of *1* with *3* and *4* (almost clean formation of *8*) compared with *5* (complex reaction mixture) can be rationalized in terms of the HSAB concept. In the delocalized aldehyde anion *1* the higher charge density is found at the terminal oxygen atoms, whereas the HOMO amplitude is the highest at the carbon atoms,[2,11] C(2) and C(4). Thus, the oxygen centers should be the harder and the carbon centers the softer bases. In accordance with this view acyl chlorides which are considered as relatively hard generalized acids [4] react at the oxygen atom to give the enol esters [2] *9*.



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The organic isocyanates *5* are harder acids than their thio- (*3*) and seleno (*4*) analogues. This is apparent from the application of Jørgensen's symbiotic principle [12] or by a more explicit consideration of the LUMO of these three reagents. Since this orbital is of the π^* type, the poor π-overlap between carbon and third- and higher-row elements ensures a lowered LUMO energy of the S- and Se- relative to the O-compounds. Consequently, the observations can be rationalized such that the relatively soft acids *3* and *4* react virtually exclusively at the carbon center whereas competing reaction at the oxygen center becomes important for the harder acids *5*.

The enhanced reactivity of aryl isothio- and isoselenocyanates compared with the alkyl compounds may also be explained by the Klopman approach.[5] The in-phase interaction of the XCN-group LUMO with a higher lying unoccupied orbital of the arene substructure lowers the energy of the compound LUMO thus giving a more efficient soft acid.

EXPERIMENTAL

Microanalyses were carried out by Mr. P. Hansen, Microanalytical Department of the University of Copenhagen.

Instrumentation. IR: Perkin Elmer 457. UV: Beckman ACTA III. ^{1}H NMR: Jeol JNM-PMX 60 or Varian T-60. ^{13}C NMR: Jeol X60. M.p.: Büchi apparatus (uncorrected).

1-Substituted-3-formyl-2(1H)-pyridineselones (6). 1-Aryl-3-formyl-2(1H)-pyridineselones. Aryl isoselenocyanate [13] (25 mmol) and the potassium salt of glutacondialdehyde (25 mmol) were dissolved in DMSO (100 ml). The mixture was stirred for 90 min at room temperature. Half-saturated aqueous sodium chloride (200 ml) was added and the solution was cooled to 0 °C with continued stirring. A red precipitate of *2* was isolated by filtration, washed with water and dried. The crude product was dissolved in methylene chloride-light petroleum (1:1), filtered through alumina (Woelm W 200 neutral; 5 g) and then crystallized from the same solvent mixture. 1-Alkyl-3-formyl-2(1*H*)-pyridineselones were prepared by the same procedure; however, the reaction temperature was raised to *ca.* 80 °C.

1-Substituted-3-formyl-2(1H)-pyridones (7). Method A. To *1* (potassium salt, 0.01 mol) in DMSO or DMF (50 ml) at 50 °C was added aryl isocyanate (0.01 mol). After 1 h the dark red reaction mixture was added to water (100 ml). Filtration, continuous extraction with ether (24 h) and concentration *in vacuo* of the extract yielded a crystalline crude product.

Method B. To the appropriate 3-formyl-2-(1*H*)-pyridinethione [3] (0.01 mol) in chloroform (60 ml) was added a solution of mercury(II)

Table 2. 1-Alkyl and aryl-3-formyl-2(1*H*)-pyridineselones (*6*).

R	Yield %	M.p. °C	Analyses (C, H, N and Se)
Methyl	55	148 – 150	C_7H_7NOSe
Isopropyl	47	119 – 121	$C_9H_{11}NOSe$
t-Butyl	2	65 – 68	$C_{10}H_{13}NOSe$
Cyclohexyl	27	164 – 167	$C_{12}H_{15}NOSe$
Methylbenzyl	58	106 – 107	$C_{14}H_{13}NOSe$
Phenyl	55	195 – 197	$C_{12}H_9NOSe$
p-Methoxyphenyl	67	191 – 193	$C_{13}H_{11}NOSe$
p-Chlorophenyl	24	182 – 184	$C_{12}H_8ClNOSe$
2′-Naphthyl	52	217 – 219	$C_{16}H_{11}NOSe$

Table 3. 1-Alkyl and aryl-3-formyl-2(1*H*)-pyridones (*7*).

Compound	R	Method[a] A	B	C	D	M.p. °C	Analyses (C, H and N)
7a	1'-Naphthyl	8	–	–	–	138–141[c]	$C_{16}H_{11}NO_2$
7b	Phenyl	11	46	65	75	155–157[c]	$C_{12}H_9NO_2$
7c	Methylbenzyl	–	37	0[b]	82	132–133[c]	$C_{14}H_{13}NO_2$
7d	Isopropyl	–	–	0[b]	73	115–116[c]	$C_9H_{11}NO_2$

[a] Yields (%). [b] Pure material was not isolated, but *7c* and *7d* were detected by TLC. [c] Recrystallized from methylcyclohexane or a mixture of benzene and methylcyclohexane.

acetate (0.01 mol) in glacial acetic acid (150 ml). The mixture was left for 30 days and then filtered. The filtrate was poured on a mixture of water (500 ml) and chloroform (50 ml). Further extraction with chloroform (100 ml) and concentration *in vacuo* yielded a pale yellow oil. Stirring with 4 M hydrochloric acid (50 ml) for 4 h at room temperature, extraction with chloroform and work-up gave pale yellow crystals.

Method C. To 1-phenyl-3-(2'-dioxolanyl)-2-(1*H*)-pyridinethiones (0.01 mol) in ice-cold 2 M sodium hydroxide (80 ml) was added 50 % hydrogen peroxide (40 ml). The mixture was stirred at room temperature for 21 h. Then unreacted hydrogen peroxide was destroyed by addition of sodium bisulfite. Acidification with 2 M sulfuric acid (80 ml), stirring for 1 h, extraction with chloroform and concentration *in vacuo* yielded pale yellow crystals.

Method D. To an ice-cold solution of 1-substituted-3-(2'-dioxolanyl)-2(1*H*)-pyridinethione (0.01 mol) and sodium hydroxide (0.04 mol) in ethanol (350 ml) was added *m*-chloroperoxybenzoic acid (0.04 mol). When the temperature reached 20–22 °C, the initial red-orange colour suddenly disappeared. Stirring for 1 h at room temperature, addition of a solution of sodium bisulfite, filtration, evaporation, addition of 2 M sodium hydroxide (100 ml), extraction with ethyl acetate or chloroform (2 × 100 ml) and concentration *in vacuo* yielded a pale yellow oil. Hydrochloric acid (4 M, 50 ml) was added and the mixture was stirred for 4 h at room temperature. Extraction with chloroform and concentration *in vacuo* gave pale yellow crystals.

1-Substituted-3-(2'-dioxolanyl)-2(1H)-pyridinethiones. 1-Substituted-3-formyl-2(1*H*)-pyridinethione [3] (0.04 mol), ethylene glycol (0.08 mol) and *p*-toluenesulfonic acid (0.5 g) in benzene (500 ml) were refluxed (with water separator) for 6 h. If the resulting product was not obtained analytically pure, dissolution in benzene, washing with hydrazine hydrate (*ca.* 98 %) and water removed the impurities.

1-R,S-(Methylbenzyl)-3-(2'-dioxolanyl)-2(1H)-pyridinethione. Yield 91 %. Oil, which after standing for *ca.* two months, crystallized. M.p. = 89–91 °C. Anal. $C_{16}H_{17}NSO_2$: C, H, N, S. *1-Isopropyl-3-(2'-dioxolanyl)-2(1H)-pyridinethione.* Yield 62 %. Orange crystals. M.p. = 79–82 °C. Anal. $C_{11}H_{15}NSO_2$: C, H, N, S, *1-Phenyl-3-(2'-dioxolanyl)-2(1H)pyridinethione.* Reported previously.[3]

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