The Cyclization of Some *cis*-Alkenynoic Acids to α-Pyrones. I.

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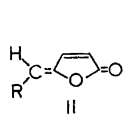
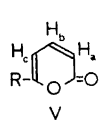
For some years now it has been well known that many *cis*-alkenynoic acids of the form $R-C\equiv C-HC=CH-COOH$ (I) readily lactonize in polar, water-containing organic solvents or in neutral or alkaline water solutions to give the unsaturated 5-membered-ring lactone (II). Thus, the acetylenic acids (I) R = *cis* $H_3C-HC=CH-C\equiv C$-(*cis,cis*-matricaria acid) (III), and (I), R = $CH_3CH_2CH_2C\equiv C$-(*cis*-lachnophyllum acid) (IV) both undergo rapid cyclization to the corresponding γ-lactones (II).[1,2] These lactones are also found in nature, and in recent years many other γ-lactones similarly related to corresponding *cis*-alkenynoic acids have been isolated.[3]

An investigation has now been carried out to see whether the acetylenic acids (III) and (IV) under suitable conditions could undergo ring closure to the C_5-atom to give the corresponding α-pyrones (V). These pyrones are of interest as possible natural and biologically active substances. In the literature such cyclizations of a few short-chain alkenynoic acids such as (I) R = CH_3[4] and R = phenyl[5] are reported, generally by warming in acid medium. For 2,5-diphenyl-pentenynoic acid use of $HgSO_4$ as catalyst for the cyclization has been reported.[6]

Sufficient *cis,cis*-matricaria ester was isolated from *Matricaria inodora* L.[7] *cis*-Lachnophyllum ester was synthesized in good yield by known methods.[8,9] The esters were hydrolysed by refluxing in a mixture of 80 % dioxane, 7 % H_2SO_4 and 13 % H_2O, and the free acids were isolated in 80–85 % yields. No tendency to α-pyrone formation was observed under these conditions. An attempt was then made to cyclize the acids by using $HgSO_4$ (30–40 mol% of the acetylenic acid) in a mixture of 1:1 volumes of acetone and 25 % sulfuric acid at room temperature.



II

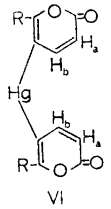


V

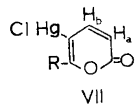
Experimental. Reaction with cis,cis-*matricaria acid.* Work-up after *ca.* 20 h reaction time gave 2 main substances and a small quantity of a third, all showing absorption in the ultraviolet region.

The least polar of these was identified as the desired α-pyrone (V), R = *cis*-$H_3C-HC=CH-C\equiv C-$, yield *ca.* 50 %, m.p. 27–28°. UV: λ_{max} 333, 254 and 247 mμ (ε = 16650, 8200 and 8200) in methanol. IR (liquid): α-pyrone: 1730, 1620, 1536 cm^{-1}. $-C\equiv C-$: 2195 cm^{-1}. NMR (in $CDCl_3$): H_a: dd, τ = 3.70, J = 9.4 + 0.9 cps. H_b: dd, τ = 2.72, J = 9.4 + 6.7 cps. H_c: dd, τ = 3.64, J = 6.7 + 0.9 cps. These values agree well with literature data.[10,11] Side-chain signals: Same as for the C_8-C_{10}-protons in the acid (III). Mass spectrum: Parent peak and base peak: *m/e* 160, other prominent peaks: M − 28 (−CO), M − 29, M − 56 and M − 57. By gas chromatography the totally hydrogenated α-pyrone was indistinguishable from authentic 5-hydroxydecanoic acid, δ-lactone (co-chromatography on a 5 % SE20-column).

Besides the α-pyrone (V) a polar main substance was isolated, identified as the Hg-containing bilactone derivative VI, R = *cis*-$H_3C-HC=CH-C\equiv C-$. Yield 23 %, m.p. 154°. UV: λ_{max} 341, 260 mμ (ε = 30 300, 18 100) in methanol. IR: α-pyrone: 1725, 1590, 1508 cm^{-1}. $-C\equiv C-$: 2185 cm^{-1} (in $CHCl_3$). NMR (in $CDCl_3$): H_a: d, τ = 3.63, J = 9.2 cps. H_b: d, τ = 2.59, J = 9.2 cps. Side chain: same signals as for the corresponding protons in III. Mass spectrum: Parent peak (^{200}Hg-isotope peak): *m/e* 518.



VI



VII

The third substance also contains Hg and has the structure VII, R = *cis*-$CH_3-HC=CH-C\equiv C-$. This compound has obviously originated from some sort of chloride impurity, most probably in the $HgSO_4$. The substance is a solid, m.p. 192,5°. Yield *ca.* 3 %. UV: λ_{max} 341, 255 mμ (ε = 15 050, 8 500) in methanol. IR: α-pyrone: 1690, 1570, 1500 cm^{-1}. $-C\equiv C-$: 2180 cm^{-1} (KBr-disc). NMR (in hexadeutero-dimethylsulfoxide): H_a: d, τ = 3.58, J = 9.3 cps. H_b: d, τ = 2.37, J = 9.3 cps. R: Signals as in acid III. Mass spectrum:

Parent peak (^{200}Hg, ^{35}Cl-peak): *m/e* 394. Observed isotopic abundances for the parent peak cluster are in fair agreement with the theoretical values.

Reaction with cis-*lachnophyllum acid.* Work-up after *ca.* 24 h reaction time gave 2 main products V and VI, a minor amount of VII; in addition small quantities of two new substances were isolated and identified.

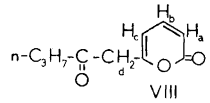
The aqueous layer contained a substance absorbing UV-light and not extractable with ether. After addition of NaCl the substance was easily extracted, apparently as a consequence of anion exchange. The isolated product was identified as VII.

The α-pyrone (V), R = $CH_3CH_2CH_2C{\equiv}C-$, is a liquid, m.p. *ca.* 10°, yield *ca.* 50 %. UV: λ_{max} 318, 225, 219 mμ (ε = 11 250, 9500, 7300) in methanol. IR (as liquid): α-pyrone: 1730, 1619, 1537 cm^{-1}. $-C{\equiv}C-$: 2230 cm^{-1}. NMR (in hexadeutero-acetone): H_a: dd, τ = 3.71, J = 9.5 + 1 cps. H_b: dd, τ = 2.53, J = 6.7 + 9.5 cps. H_c: dd, τ = 3.44, J = 6.7 + 1 cps. Propyl group in side chain: same signals as in acid IV. Mass spectrum: Parent peak: *m/e* 162, base peak *m/e* 147. Other prominent peaks: M − 28 (−CO), M − 43, M − 57.

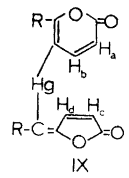
Hg-containing bilactone derivative VI, R = $CH_3CH_2CH_2C{\equiv}C-$: Yield 32 %, m.p. 159°. UV: λ_{max} 325, 250 (s), 233 mμ (ε = 20 900, 11 800, 15 800) in methanol. IR (in $CHCl_3$): α-pyrone: 1725, 1589, 1515 cm^{-1}. $-C{\equiv}C-$: 2225 cm^{-1}. NMR (in $CDCl_3$): H_a: d, τ = 3.66, J = 9.5 cps. H_b: d, τ = 2.63, J = 9.5 cps. Propyl group in side chain: Same signals as in acid IV. Mass spectrum: Parent peak (^{200}Hg-isotope): *m/e* 522. By acid hydrolysis, both VI-derivatives are converted into the corresponding α-pyrones of type V.

VII, R = $CH_3CH_2CH_2C{\equiv}C-$, was isolated in *ca.* 6 % yield, m.p. 175°. UV: λ_{max} 323, 232 mμ (ε = 10 500, 10 150) in methanol. IR (KBr-disc): α-pyrone: 1685, 1577, 1508 cm^{-1}. $-C{\equiv}C-$: 2225 cm^{-1}. NMR (in hexadeutero-acetone): H_a: d, τ = 3.67, J = 9.4 cps. H_b: d, τ = 2.35, J = 9.4 cps. R-group: Same signals as in III, V and VI. Mass spectrum: Parent peak (^{200}Hg, ^{35}Cl-isotope peak): *m/e* 396. The relative isotopic abundances observed for the parent peak cluster are in fair agreement with the calculated ones. Peak-matching performed on the lowest *m/e*-peak in the parent peak cluster agrees with the formula $^{12}C_{10}{}^{1}H_9{}^{16}O_2{}^{198}Hg{}^{35}Cl$.

One of the new products isolated is the 6-substituted α-pyrone VIII, apparently a result of Hg-catalysed water addition to the second triple bond. The substance is a liquid, yield



VIII



IX

ca. 4 %. UV: λ_{max} 299 and 219 mμ (ε = 5800, 4150) in hexane. IR (of liquid): α-pyrone: 1723, 1637, 1557 cm^{-1}. Acetylenic absorption is absent. Non-conjugated carbonyl: *ca.* 1715 cm^{-1} (overlaps with the strong α-pyrone carbonyl band). NMR ($CDCl_3$): H_a: d, τ = 3.80, J = 9.5 cps. H_b: dd, τ = 2.71, J = 9.5 + 6.5 cps. H_c: d, τ = 3.88, J = 6.5 cps. H_d: s, τ = 6.42 (2 H). Normal signals from n-propyl group. Mass spectrum: Parent peak: *m/e* 180. Base peak: *m/e* 110. Further prominent peaks: *m/e* 95, 71, 43, 28.

The structure of the second new compound has been elucidated as IX, R = n-$C_3H_7-C{\equiv}C-$. Here one of the two original acid molecules linked together with a Hg-atom has undergone ring closure to the C_4-atom, resulting in γ-lactone formation. Yield ca. 2 %. UV: λ_{max} 327.5, 231 mμ (ε = 32 500, 13 300) in methanol. IR (in $CHCl_3$): α-pyrone: 1728, 1591, 1514 cm^{-1}. Butenolide ring: 1774, 1755, 1112, 1073, 885 cm^{-1}. $-C{\equiv}C-$ 2225 and 2195 cm^{-1} (2 bands). NMR (in $CDCl_3$): H_a: d, τ = 3.67, J = 9.2 cps. H_b: τ = 2.57, d, J = 9.2 cps. H_c: d, τ = 3.75, J = 5.4 cps. H_d: d, τ = 2.57, J = 5.4 cps. R-group signals: The same as in the corresponding V and VI. Mass spectrum: Parent peak (^{200}Hg-isotope peak): *m/e* 522.

After acid hydrolysis of IX, V and a minor amount of II are isolated.

In one of the lachnophyllum acid cyclization runs, the relative concentrations of the products were followed by thin layer chromatography combined with absorbance measurements of the zone eluates. The product composition varies as follows: After 1.5 h: 7.5 % V, 78 % VI, 8.8 % IX (the rest isolated as VII). After 4 h (all the acetylenic acid IV had then reacted): 18.5 % V, 68 % VI, 7.1 % IX. After 24 h: 61 % V, 21 % VI, 1 % IX. This suggests that VI is an intermediate in the formation of V.

All lactones of type II and V−VIII from III and IV have been tested and found to be more or less cytotoxic. The tests were performed in KB cell culture systems by National Cancer Institute, Bethesda, Md., USA.

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Derivatives of Hydrazine

III. Dithio- and Diselenocarbazic Acid

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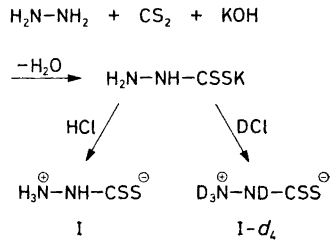
In 1895 Curtius and Heidenreich [1] reported that dithiocarbazic acid (I) could not be prepared either by adding acids or benzaldehyde to hydrazinium dithiocarbazate, or by treating silver(I) dithiocarbazate with hydrogen sulfide. Instead, decomposition products were obtained, which were later characterised by Losanitch.[2,3] These results contrast to those recently obtained [4] by an investigation of *N,N*-dimethyldithiocarbazic acid, which proved to be moderately stable in the crystalline state at room temperature. The stability was believed to arise from the compound existing principally in the dipolar hydraziniodithiocarbazate form, a form which might also be readily attained by unsubstituted dithiocarbazic acid. Even the possibility of (I) having a nonpolar structure does not necessarily prevent it from possessing the stability necessary for preparation. Thus, dithiocarbamic acid [5] has recently been described and found to be more stable than expected.

The preparation of (I) has been accomplished by the sequence of reactions shown in the following reaction scheme:



The preparation of potassium dithiocarbazate from hydrazine, potassium hydroxide, and carbon disulfide in aqueous ethanol has been described by Busch and Starke.[6] However, the yield of pure product was very small owing to the formation of an oily contaminant, probably arising from the formation of potassium xanthate as by-product. It was proposed by Professor K. A. Jensen, and confirmed by experiment, that the shortcoming of this method could be avoided by using dioxane as solvent.

When hydrochloric acid was added to the potassium salt at 0°C (I) could be prepared without difficulty. The experiment reported by Curtius and Heidenreich [1] was therefore repeated, and it was found that (I) could equally well be prepared from hydrazinium dithiocarbazate by addition of hydrochloric acid provided that the reaction mixture was kept in an ice-bath. Elemental analysis showed (I) to loose sulfur rapidly at room temperature and a correct sulfur analysis was not obtained.