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A CONVENIENT METHOD FOR THE PREPARATION OF γ-ARYLIDENE-α,β-UNSATURATED γ-LACTONES

APPLICATION TO THE SYNTHESIS OF THE THIOPHENE LACTONE OBTAINED FROM *CHAMAEMELUM NOBILE* L.[1]

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Abstract—A facile synthesis of γ-arylidine-α,β-unsaturated γ-lactones was achieved: a keto lactone (e.g., **4**) which is readily obtained from a keto acid (**1**) was dehydrated to conjugated lactones (**9** and **10**) with acetic anhydride in the presence of either *p*-toluenesulfonic acid or sodium acetate. By application of this unusual dehydration reaction, a natural product, the thiophene lactone (**13**) was synthesized. Some reactions of the conjugated lactone (**9**) were carried out, leading to the formation of unsaturated γ-lactams (**19** and **20**).

WE HAVE developed a simple and convenient method of constructing a γ-arylidene-α,β-unsaturated γ-lactone system from readily available materials.

Treatment of γ-anisoylbutyric acid **1**[2] with bromine afforded a keto lactone **4** in good yield. When the keto lactone **4** was heated in Ac_2O in the presence of *p*-toluenesulfonic acid, dehydration occurred to give a conjugated lactone [m.p. 116–118°, mass 202 (M^+)], which showed the following spectral properties: the UV spectrum showed absorptions at 361 nm and 241 nm; in the IR spectrum a strong C=O band appeared at 1765 cm^{-1} with a weak band at 1795 cm^{-1}; the NMR spectrum revealed a singlet (1H) at δ 5·99 and a quartet (2H) of an AB type at δ 6·14 (J = 5·5 Hz) and 7·45 (J = 5·5 Hz), in addition to signals due to the *p*-methoxyphenyl group. Based on these spectral data, the structure of the conjugated lactone was deduced to be **9** (Determination of the stereochemistry of the *exo* double bond is described below). By catalytic hydrogenation the compound **9** was led to a saturated γ-lactone **15**, which showed a C=O band at 1775 cm^{-1}. Further, in order to exclude the possibility unambiguously that the conjugated lactone is an α-pyrone derivative **17** which would be formed from **4** *via* acid-catalyzed cleavage of the γ-lactone ring followed by recyclization, the keto acid **1** was converted by treatment with Ac_2O to an enol lactone **16**, which was dehydrogenated with 10% Pd—C in *p*-cymene[3] to afford the α-pyrone **17**. The α-pyrone **17** was clearly different from the conjugated lactone described above.

The keto lactone **4**, on being refluxed in Ac_2O—AcONa produced a mixture of two compounds, which was separated by preparative layer chromatography, affording the conjugated lactone **9** (m.p. 116–118°) as a major product and the isomer **10** (m.p. ~124°). Assignment of the geometrical configuration to each of the two lactones could be made by the NMR spectral data:[4] while the benzylic vinyl proton (H_c) appeared as a singlet at δ5·99 in the major isomer **9**, the corresponding proton (H_c) in the minor isomer **10** was observed as a broad doublet (J = 1·5 Hz) at δ 6·72 which

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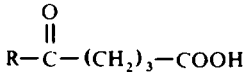
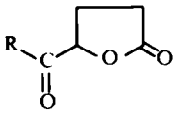


1: R = *p*-MeO—C_6H_4
2: R = C_6H_5
3: R = 5-methyl-2-thienyl



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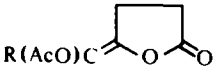
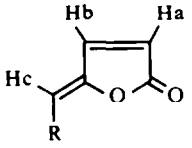
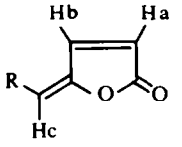
5: R = C_6H_5
6: R = 5-methyl-2-thienyl



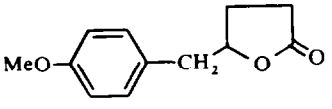
7: R = C_6H_5
8: R = 5-methyl-2-thienyl



9: R = p-MeO—C_6H_4
11: R = C_6H_5
13: R = 5-methyl-2-thienyl



10: R = *p*-MeO—C_6H_4
12: R = C_6H_5
14: R = 5-methyl-2-thienyl



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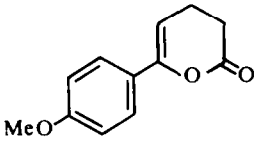

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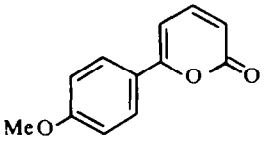

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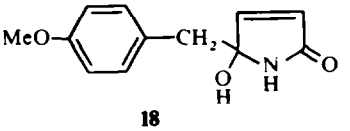

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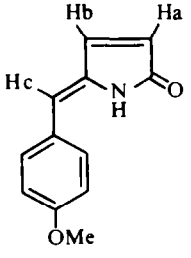

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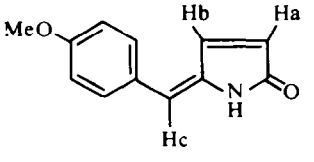

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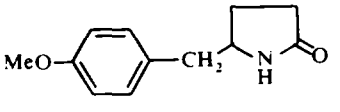

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coupled to a vinyl proton H_a (doublet of doublets. J = 5·5. 1·5 Hz) at δ 6·29. Since the larger couplings have been observed for protons with *trans* relationships over many bonds than those with *cis* relationships.[5] the asignments of the major isomer (m.p. 116–118°) to **9** and the minor one (m.p. ~ 124°) to **10** were made. The minor isomer **10** was unstable and liable to isomerize during TLC process and on heating in solutions. Even at room temperature isomerization of one isomer (**9** or **10**) to the other took place gradually (20 days) in chloroform. affording an equilibrium mixture (**9**:**10**. 5:2. estimated by the NMR spectrum). It was thus established that the stable isomer **9** which was formed almost exclusively by treatment with Ac_2O–*p*-toluenesulfonic acid has a *cis* configuration regarding the lactone-ether oxygen and the *p*-methoxyphenyl group.

Further. some reactions of the conjugated γ-lactone **9** were carried out. On standing in an ethanolic solution saturated with ammonia (or an aqueous ammonia–ethanol solution). **9** was almost quantitatively converted to a lactam alcohol **18** ($\nu_{C=O}$ 1710 cm^{-1}). Although the open-chain from (*viz* $ArCH_2COCH{=}CH{-}CONH_2$) is also conceivable for this compound, the lactam form seems most likely, since: (i) a sharp singlet (1H. δ 3·10. OH) and a broad signal (1H. δ *ca* 7·5. —CONH—) in the NMR spectrum disappeared on addition of D_2O; (ii) the M^+-H_2O peak (*m/e* 201) was a base peak in the mass spectrum. The lactam alcohol **18** was dehydrated in refluxing benzene to give a mixture of two compounds. The mixture was separated. giving a conjugated γ-lactam **19** (m.p. 151–152°) and the isomer **20** (m.p. 146–148°). The stereostructures of two conjugated lactams were determined in the same way using the NMR spectra* as described in the conjugated γ-lactones (**9**. **10**): one isomer (**19**. m.p. 151–152°) revealed a singlet due to the benzylic vinyl proton (H_d) at δ 6·07. and the other isomer (**20**) of m.p. 146–148° showed a broad doublet (J = 1·5 Hz) arising from H_c at δ6·60 which coupled to a vinyl proton. H_a (doublet of doublets. J = 5·5. 1·5 Hz) at δ6·33. Both conjugated γ-lactams (**19** and **20**) were led to a saturated γ-lactam **21** ($\nu_{C=O}$ 1690 cm^{-1}) by catalytic hydrogenation.

The same type of reaction as described above (**4**→**9**) was carried out employing the keto lactone **5** which was prepared from γ-benzoylbutyric acid **2**.[6] By the action of Ac_2O–*p*-toluenesulfonic acid the keto lactone **5** afforded mainly a conjugated γ-lactone **11** together with a small amount of the isomer **12** which was obtained in the impure state. On the other hand. treatment of **5** with Ac_2O–AcONa gave a mixture of three products: two conjugated γ-lactones (**11** and **12**) and a γ-lactone acetate **7**. Assignments of the geometrical configurations of two conjugated γ-lactones (**11**, **12**) were made as in the case of **9** and **10** by means of the NMR spectra: the stable isomer **11** obtained as a major product has a *cis* configuration regarding the lactone–ether oxygen and the phenyl group. The structure of the γ-lactone acetate was deduced to be **7** from the spectral data, although the streochemical problem of the *exo* double bond remained unsettled. The γ-lactone acetate **7** would be an intermediate in the reaction forming **11** and **12** from **5**. since the conjugated γ-lactone **11** was obtained by treatment of **7** with Ac_2O–AcONa (reflux. 36 hr).

The structure of a thiophene lactone **13** isolated from *Chamaemelum nobile* L.[7] belongs to the type of conjugated γ-lactones described above.

* In order to facilitate the analysis of the spectra. the NMR spectra of two γ-lactams described in the text were taken in $CDCl_3$–D_2O. in which the weak coupling of each of the vinyl protons (Ha. Hb. Hc) to the NH group was no more observed.

For the synthesis of this thiophene lactone **13**, γ-(5-methyl-2-thenoyl)butyric acid **3**[8] was converted to a keto γ-lactone **6** ($\nu_{C=O}$ 1790, 1660 cm^{-1}), which was refluxed in Ac_2O–AcONa, giving a thiophene lactone **13** (m.p. 113–115°) as a major product together with the isomer **14**. In cases where the reaction time was rather short (~20 hr), a γ-lactone acetate **8** was also obtained together with **13**. While the thiophene lactone **13** obtained as a major product showed a singlet due to the vinyl proton, H_c at δ 6·23 in the NMR spectrum, the isomer **14** revealed a broad doublet (J = 1·8 Hz) of the corresponding proton (H_c) at δ 6·73 which coupled to a vinyl proton, H_a (doublet of doublets, J = 5·5, 1·8 Hz) at δ 6·26. On the basis of these NMR spectral findings, the structure including the geometrical configuration of the thiophene lactone obtained as a major product was established as **13**, which is in accordance with the stereostructure assigned by Bohlmann and Zdero.[7] The synthetic thiophene lactone **13** was shown to be identical with the natural one by IR spectral comparison. UV and NMR spectral features of the synthetic compound **13** were in good agreement with those of the natural one reported.[7]

EXPERIMENTAL

M.ps were uncorrected. UV spectra were determined in EtOH unless otherwise specified, on a Perkin–Elmer Model 202 spectrophotometer. IR spectra were recorded in chloroform unless otherwise specified, on a JASCO Model IR-S spectrophotometer. NMR spectra were recorded on a JNMC-60H spectrometer; chemical shifts are expressed in ppm downfield from TMS as internal standard (δ); s, singlet; d, doublet; dd, doublet of doublets; q, quartet; dq, doublet of quartets; m, multiplet; br., broad; coupling constants are given in Hz; peaks due to benzene ring protons are not cited. Mass spectra were obtained on a Hitachi RMU-6D mass spectrometer equipped with an all glass inlet system and operating with an ionization energy of 70 eV. TLC and preparative layer chromatography were carried out on silica gel GF_{254} and PF_{254} (E. Merck, A. G., Germany) and column chromatography on silicic acid (100 mesh, Mallincrodt, USA). The organic solutions were dried over anhydrous Na_2SO_4 and evaporated by rotary evaporator.

γ-Anisoyl-γ-butyrolactone **4**

Bromine (6·8 g) was added dropwise to a soln of **1**[2] (7·2 g) in dioxan (100 ml)—ether (40 ml) with stirring at 20–25°. The soln was kept at room temp for 30 min and poured into ice-water. The mixture was extracted with AcOEt several times and the AcOEt extracts were washed with water, $NaHCO_3$ aq. and a saturated NaCl soln, and dried. Evaporation of AcOEt afforded 7·1 g of crude crystals, recrystallization of which from benzene–hexane gave 6·1 g (87%) of **4**, m.p. 122–124°; UV 283 (ε 17,800), 223 nm (ε 10,100); IR 1790, 1685 cm^{-1}; NMR ($CDCl_3$) ~ 2·5 (4H, complex pattern, $-CH_2CH_2CO-$), 3·88 (3H, s, MeO), 5·81 (1H, m, —OC—CH—O—CO—); mass 220 (M^+). (Found: C, 65·52; H, 5·31. $C_{12}H_{12}O_4$ requires: C, 65·44; H, 5·49%).

Action of acetic anhydride on the keto lactone **4**: *formation of* **9** *and* **10**

(a) *In the presence of p-toluenesulfonic acid.* A soln of **4** (440 mg) and *p*-toluenesulfonic acid (180 mg) in Ac_2O (20 ml) was refluxed for 40 hr, and concentrated *in vacuo* to give a residue, which was taken up in chloroform (20 ml)–water (20 ml). The organic layer was separated, washed with $NaHCO_3$ aq and water, dried, and evaporated. The resulting oily residue was chromatographed on silicic acid with chloroform, affording 236 mg (58%) of **9**, m.p. 116–118° (recrystallization from benzene-hexane); UV (MeOH) 361 (ε 28,900), 241 nm (ε 11,000); IR 1795 (weak), 1765 cm^{-1}; NMR ($CDCl_3$) 3·85 (3H, s, MeO), 5·99 (1H, s, vinyl H_c), 6.14 and 7·45 (2H, AB q, J = 5·5, vinyl H_a and H_b); mass 202 (M^+). (Found: C, 70·98; H, 4·88. $C_{12}H_{10}O_3$ requires: C, 71·28; H, 4·99%).

(b) *In the presence of* AcONa. A mixture of **4** (4·36 g) and AcONa (4·00 g) in Ac_2O (100 ml) was refluxed for 110 hr. The progress of the reaction was examined by TLC (chloroform as solvent) and, after 110 hr two yellow spots were observed: a major one (R_f, 0·48) and a minor one (R_f, 0·43). The mixture was diluted with toluene and filtered. The filtrate was evaporated and the residue was taken up in chloroform. The chloroform

soln was washed with $NaHCO_2$ aq. water, and a sat NaCl aq. dried, and evaporated, giving an oil. The oily residue was chromatographed on silicic acid (200 g) with chloroform. Early fractions afforded 2·02 g (51%) of yellow crystals of **9** and later fractions gave a mixture of **9** and **10**: a part of the mixture of **9** and **10** was separated repeatedly using preparative layer chromatography with benzene—chloroform (v/v, 1:1), affording **10**, m.p. ~ 124° (recrystallization from benzene—hexane); IR 1795 (weak), 1763 cm^{-1}; NMR ($CDCl_3$) 3·85 (3H, s, MeO), 6·72 (1H, br. d, J = 1·5, vinyl Hc), 6·29 (1H, dd, J = 5·5, 1·5, part of an AB system; vinyl Ha), 7·78 (1H, d, J = 5·5, part of an AB system; vinyl H_b); mass 202 (M^+). (Found: C, 71·20; H, 4·90. $C_{12}H_{10}O_3$ requires: C, 71·28; H, 4·99%).

Catalytic hydrogenation of the conjugated γ-lactone **9**

The lactone **9** (205 mg) in EtOH (20 ml) was hydrogenated at room temp in the presence of 10% Pd-C (20 mg) under atm press. The catalyst was removed and the solvent was evaporated giving an oil. Chromatography of the oily residue on silicic acid afforded crystals of the saturated γ-lactone **15**, m.p. 49–51° (recrystallization from benzene–hexane); UV 284 (ε 1400), 278 (ε 1700), 228 nm (ε 8500); IR 1775 cm^{-1}; NMR (CCl_4) ~ 2·2 (4H, complex pattern, $—CH_2CH_2—CO—$), 2·85 (2H, complex pattern, benzyl H), 3·72 (3H, s, MeO), 4·53 (1H, m, $-CH—O—CO-$); mass 206 (M^+). (Found: C, 70·21; H, 6·51. $C_{12}H_{14}O_3$ requires: C, 69·88, H, 6·84%).

The enol lactone **16**

A soln of **1** (1 g) in Ac_2O (5 ml) was refluxed for 1·5 hr and evaporated, giving an oily residue, which was taken up in ether. The ethereal soln was washed with water and $NaHCO_3$, aq, dried, and evaporated to afford a crystalline solid. Recrystallization from ether gave 640 mg (70 %) of **16**, m.p. 61–66°; IR 1760, 1670 (C=C) cm^{-1}.

The α-pyrone **17**

A mixture of the dried **16** (404 mg) and 10% Pd–C (180 mg) in *p*-cymene (25 ml) was refluxed in a flask equipped with a water-separator for 5 hr, and filtered. The filtrate was evaporated and the residue was recrystallized from benzene–hexane, giving 325 mg (80%) of needles, **17**, m.p. 99–101° ;UV 352 (ε 19.000), 257 (ε 9100), 240 nm (ε 7000, shoulder); IR 1730, 1705 (shoulder) cm^{-1}; NMR ($CDCl_3$) 3·83 (3H, s, MeO), 6·19 (1H, d, J = 9·5, α-pyrone H), 6·55 (1H, d, J = 6·5, α-pyrone H), 7·40 (1H, dd, J = 9·5, 6·5, α-pyrone H); mass 202 (M^+). (Found: C, 71·56; H, 4·86. $C_{12}H_{10}O_3$ requires: C, 71·28; H, 4·99%).

The lactam alcohol **18**

A soln of **9** (1·20 g) in EtOH (50 ml) was sat with NH_3 gas under ice-bath cooling, stirred for 8hr at 0°, and evaporated, affording crude crystals (*ca* 1·3 g). Recrystallization from benzene gave 1·25 g (96%) of **18**, m.p. 138–139°; UV 284 (ε 1400), 278 (ε 1700), 228 nm (ε 7700); IR 3600, 3460, 3350, 1710 cm^{-1}; NMR (acetone-d_6) 3·10 (2H, s, benzyl H), 3·10 (1H, s, OH, disappeared on addition of D_2O), 3·75 (3H, s, MeO), 5·72 and 6·92 (2H, AB q, J = 6·0, vinyl H), *ca* 7·5 (1H, br.m, —CONH—, disappeared on addition of D_2O); mass 219 (M^+), 201 (M^+ – 18, base peak). (Found: C, 65·38; H, 5·93; N, 6·35. $C_{12}H_{13}O_3N$ requires: C, 65·74; H, 5·98; N, 6·39%).

The conjugated lactams **19**, **20**

A mixture of the lactam alcohol **18** (102 mg) in benzene (10 ml) was refluxed for 10 hr, and diluted with ice-water. The benzene layer separated was dried and evaporated to give an oily residue, which showed two spots [R_f, 0·6 (major product) and 0·4] in TLC with chloroform—MeOH (v/v, 19:1). The mixture was separated by preparative layer chromatography, affording 51 mg (53%) of **19** and 36 mg (38%) of **20**.

19, m.p. 151–152° (needles; recrystallization from benzene–hexane); UV 356 (ε 34,000), 243 nm (ε 11·000); IR 3500, 1690 cm^{-1}, NMR ($CDCl_3$–D_2O) 3·83 (3H, s, MeO), 6·07 (1H, s, vinyl H_c), 6·18 and 7·06 (2H, AB q, J = 5·5, vinyl H_a and H_b); a signal at 9·0 (1H, br. s, —CONH—, disappeared on addition of D_2O) was observed before addition of D_2O; mass 201 (M^+). (Found: C, 71·35; H, 5·48; N, 6·86. $C_{12}H_{11}O_2N$ requires: C, 71·62; H, 5·51; N, 6·96%).

20, m.p. 146–148° (plates; recrystallization from benzene–hexane); UV 365 (ε 26.000), 249 nm (ε 12.000); IR 3500, 1690 cm^{-1}; NMR ($CDCl_3$–D_2O) 3·83 (3H, s, MeO), 6·33 (1H, dd, J = 5·5, 1·5, part of an AB system: vinyl H_a), 6·60 (1H, br. d, J = 1·5, vinyl H_c), 7·45 (1H, d, J = 5·5, part of an AB system; vinyl H_b); signal at 9·75 (1H, br.s, —CONH—, disappeared on addition of D_2O) was observed before addition of D_2O; mass 201 (M^+). (Found: C, 71·50; H, 5·40; N, 6·90. $C_{12}H_{11}O_2N$ requires: C, 71·62; H, 5·51; N, 6·96%).

Catalytic hydrogenation of the conjugated γ-lactams. **19** *and* **20**

The lactam **19** (40 mg) in EtOH (5 ml) was hydrogenated in the presence of 10% Pd–C (6 mg) as described in the catalytic reduction of **9**. After the usual work-up the saturated lactam **21** (30 mg) was obtained. m.p. 77–78° (recrystallization from benzene–hexane); IR 3440. 1690 cm^{-1}; NMR ($CDCl_3$) 1·8–2·5 (4H. complex pattern. $-CH_2CH_2-CO-$). 2·73 (2H. d. $J = 6·5$. benzyl H). 3·77 (3H. s. MeO). 3·85 (1H. m. $-CH-N-CO-$). 6·6 (1H. m. $-CONH-$. disappeared on addition of D_2O); mass 205 (M^+). 122. 121. 84 (base peak). (Found: C. 70·49; H. 7·54; N. 7·20. $C_{12}H_{15}O_2N$ requires: C. 70·22; H. 7·37; N. 6·82%). In the same procedure the saturated lactam **21** was obtained by catalytic hydrogenation of **20**.

γ-Benzoyl-γ-butyrolactone **5**

A solution of Br_2 (1·2 g) in 9 ml of dioxan-ether (v/v, 5:2) was added to a stirred soln of **2**[6] (1·15 g) in 40 ml of dioxan–ether (5:2) at 30–35°, and the mixture was stirred for 4·5 hr. The same work-up as described in the preparation of **4** gave 1·12 g of crude crystals. recrystallization of which from benzene–hexane afforded 840 mg (74%) of **5**. m.p. 79–79·5°; IR 1790. 1693 cm^{-1}; NMR ($CDCl_3$) 2·6 (4H. complex pattern. $-CH_2CH_2-COO-$). 5·85 (1H. m. $-CO-CH-O-CO-$); mass 190 (M^+). (Found: C. 69·46; H. 4·98. $C_{11}H_{10}O_3$ requires: C. 69·46; H. 5·30%).

Action of acetic anhydride on the keto lactone **5**

(a) *In the presence of* p-*toluenesulfonic acid.* A soln of **5** (285 mg) and *p*-toluenesulfonic acid (285 mg) in Ac_2O (15 ml) was refluxed for 58 hr. and evaporated *in vacuo*. giving a residue which was taken up in chloroform. The chloroform extract was washed with $NaHCO_3$ aq. water. and a sat NaCl aq. dried. and evaporated. The residue was chromatographed on silicic acid (12 g) with chloroform. affording 226 mg (88%) of **11**. m.p. 85–87° (recrystallization from hexane); UV (MeOH) 334 (ε 26,000). 241 (ε 8000). 235 nm (ε 9000); IR 1793 (weak). 1765 cm^{-1}; NMR (CCl_4) 5·90 (1H. s. vinyl Hc). 6·14 (1H. d. $J = 5·5$. vinyl H_a). 7·41 (1H. d. $J = 5·5$. vinyl H_b); mass 172 (M^+). (Found: C. 77·05; H. 4·71. $C_{11}H_8O_2$ requires: C. 76·73; H. 4·68%).

(b) *In the presence of* AcONa. A mixture of **5** (1·14 g) and AcONa (1·20 g) in Ac_2O (30 ml) was refluxed for 70 hr (When the reaction time was 10 hr. a major product was shown to be the γ-lactone acetate **7** by TLC). The mixture was diluted with toluene and filtered. The filtrate was treated as described in the preparation of **9** and **10**. The resulting oily residue was chromatographed on silicic acid (115 g) with chloroform: early fractions afforded 225 mg (22%) of pure **11** and later fractions gave successively 205 mg of a mixture of **11** and **12**. 61 mg (6%) of **12**. and 80 mg (6%) of the lactone acetate **7**. A total amount of **11** and **12** was 490 mg (48%).

12. m.p. *ca* 93° (recrystallization from hexane); IR 1796 (weak). 1763 cm^{-1}; NMR (CCl_4) 6·31 (1H. dd. $J = 5·5$. 1·5. part of an AB system; vinyl H_a). 6·69 (1H. br.d. $J = 1·5$. vinyl H_c). 7·72 (1H. d. $J = 5·5$. part of an AB system; vinyl H_b); mass 172 (M^+).

7. m.p. 107–109° (recrystallization from benzene–hexane); UV (MeOH) 260 nm (ε 16.000); IR 1820. 1760. 1695 cm^{-1}; NMR ($CDCl_3$) 2·30 (3H. s. AcO). 2·5–3·2 (4H. A_2B_2 type. $-CH_2CH_2-CO-$); mass 232 (M^+). (Found: C. 67·11; H. 4·97. $C_{13}H_{12}O_4$ requires: C. 67·23; H. 5·21%).

γ-(5-Methyl-2-thenoyl)-γ-butyrolactone **6**

A soln of Br_2 (4·7 g) in 40 ml of dioxan–ether (v/v, 5:2) was added dropwise to a soln of **3**[8] (4·24 g) in dioxan (100 ml)–ether (40 ml) with stirring for 3·5 hr. The soln was stirred further for 1 hr. The same work-up as described in the preparation of **4** afforded 4·03 g of crude crystals. recrystallization of which from AcOEt–hexane gave 3·40 g (81%) of pure **6**. m.p. 109–110°; IR 1790. 1662 cm^{-1}; NMR (acetone-d_6) 2·57 (3H· s. vinyl Me). 2·3–2·9 (4H. complex pattern. $-CH_2CH_2-CO-$). 5·77 (1H. m. $-CO-\underset{|}{CH}-O-CO-$).

6·94 (1H, br.d. $J = 4·0$, thiophene H). 7·78 (1H, d, $J = 4·0$, thiophene H); mass 210 (M^+). (Found: C, 57·15; H. 4·99. $C_{10}H_{10}O_3S$ requires: C. 57·14; H. 4·80%).

Action of acetic anhydride—sodium-acetate on the keto lactone **6**: *Synthesis of the thiophene lactone* **13**

(a) A mixture of **6** (1·29 g) and AcONa (1·00 g) in Ac_2O (25 ml) was refluxed for 110 hr. The same work-up as described in the preparation of **9** and **10** afforded an oily residue, which was chromatographed on silicic acid (130 g) with chloroform. giving 590 mg (50%) of a crystalline mixture of **13** and **14**. A mixture was separated by preparative layer chromatography with AcOEt–hexane (v/v. 1:1). affording 503 mg (43%) of pure **13** and 48 mg (4%) of the impure isomer **14**.

13. m.p. 113–115° (recrystallization from benzene–hexane; lit.[7] 117°); UV (ether) 372 (ε 28.000), 283 (ε 4600), 239 nm (ε 9000); IR (CCl_4) 1793, 1763, 1643 cm^{-1}; NMR ($CDCl_3$) 2·54 (3H, d, J = 1·0, Me), 6·13 (1H, d, J = 5·5, H_a), 6·23 (1H, s, Hc), 6·73 (1H, dq, J = 3·5, 1·0, thiophene H) 7·17 (1H, d, J = 3·5, thiophene H), 7·43 (1H, d, J = 5·5, H_b); mass 192 (M^+). (Found: C, 62·44; H, 4·24. $C_{10}H_8O_2S$ requires: C, 62·50; H, 4·20%).

14. m.p. ~105° (needles; isomerization seemed to occur by heating); IR 1795, 1760 cm^{-1}; NMR ($CDCl_3$) 2·53 (3H, d, J = *ca* 1, Me), 6·73 (1H, br.d, J = 1·8, vinyl Hc), 6·26 (1H, dd, J = 5·5, 1·8, vinyl Ha; part of an AB system), 7·96 (1H, d, J = 5·5, vinyl H_b; part of an AB system), 6·68 (1H, m, thiophene H), 6·95 (1H, br.d, J = 3·5, thiophene H); mass 192 (M^+).

(b) A mixture of **6** (1·00 g) and AcONa (4·00 g) in Ac_2O (50 ml) was refluxed for 20 hr. After the work-up the residue was chromatographed on silicic acid (90 g) with chloroform, giving 98 mg (11%) of a crystalline mixture of **13** and **14**, and 91 mg (8%, after recrystallization from benzene–hexane) of pure **8**.

8. m.p. 108·5–109°. UV (MeOH) 290 nm (ε 16.000); IR 1818, 1770, 1698 cm^{-1}; NMR ($CDCl_3$) 2·28 (3H, s, AcO), 2·48 (3H, d, J = 1·0, Me), 2·5–3·0 (4H, complex pattern, $—CH_2CH_2—CO—$), 6·66 (1H, dq, J = 3·5, 1·0 thiophene H), 6·90 (1H, d, J = 3·5, thiophene H); mass 252 (M^+). (Found: C, 57·24; H, 4·99. $C_{12}H_{12}O_4S$ requires: C, 57·14; H, 4·80%).

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* The assignments of geometrical isomers quite similar to our compounds by means of the NMR spectra have been reported.