Tetrahedron. Vol. 24, pp. 2049 to 2054. Pergamon Press 1968. Printed in Great Britain

# TOTAL SYNTHESIS OF RACEMIC DEHYDROFUROPELARGONES

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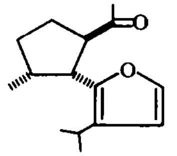
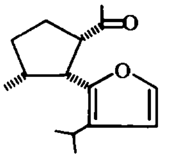
(*Received in UK 22 June 1967; accepted for publication 21 July 1967*)

Abstract—The two racemic dehydrofuropelargones **12** and **13** were prepared by total synthesis and found to be identical with the natural furopelargones C and D respectively.

RECENT investigations on constituents of *Geranium Bourbon Oil* have led to the isolation and structural characterization of a few sesquiterpenes of novel types. The hydrocarbon fraction of the oil yielded α- and β- bourbonenes[1,2] while the furopelargones A (**1**) and B (**2**)[3,4] were found to be present among the carbonyl containing products. Both the bourbonenes[5] and the furopelargones[6] have been prepared by total synthesis.



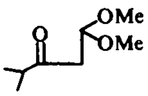
**1**



**2**

Continuing their analysis of the ketonic constituents the group in Gif sur Yvette very recently isolated two new constituents which were named furopelargones C and D.[7] Both have the composition $C_{15}H_{20}O_2$ and their catalytic reduction to furopelargone B (**2**) demonstrated that both are dehydrofuropelargones. NMR and IR data communicated to us by Professor E. Lederer were not in disagreement with structures **12** and **13** and we now report on a synthesis of these two dehydrofuropelargones which supports this structural assignment in detail. A synthetic scheme proceeding through furopelargones A (**1**) and B (**2**) was considered by the French group but efforts to convert these to dehydrofuropelargones have not yet led to useful results.[8]

In our approach it was envisaged that cyclization of the diketone **11** might afford a convenient synthesis and efforts were made to prepare this intermediate. The β-ketoacetal **3**[9] was condensed with methyl chloroacetate in the presence of sodium methoxide and the resulting crude glycidic ester **4** on heating to 150° was transformed to methyl 3-isopropyl-2-furoate (**5**).[10] Base hydrolysis furnished the crystalline 3-isopropyl-2-furoic acid (**6**) which was converted to the corresponding acid chloride **7** by the agency of thionyl chloride.



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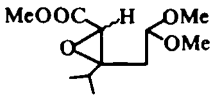

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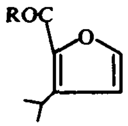
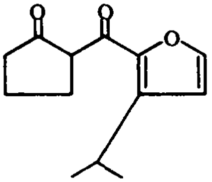
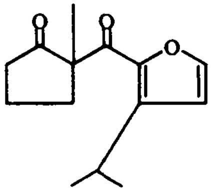


5 R = OMe
6 R = OH
7 R = Cl

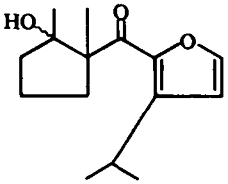
Treatment of the chloride with the morpholine enamine of cyclopentanone[11] followed by hydrolysis afforded the β-diketone **8**. The presence of a high percentage of an enolic form was evident from both UV and IR spectra (Experimental) but an effort to quantitatively measure the enol content failed when it was found that the enol proton gave rise to a very broad signal in the NMR spectrum which could not be integrated properly. A crystalline homologous diketone **9** was obtained upon treatment of a dimethylformamide solution of the original diketone **8** consecutively with sodium hydride and with methyl iodide. Condensation of **9** with one equivalent of methyl magnesium iodide was expected to and did give a mixture of diastereomeric tertiary alcohols **10** and no effort was made to isolate pure isomers. It is clear that these aldols containing four substituents other than hydrogen on two neighboring cyclopentane carbon atoms represent highly crowded molecules and we could assume with confidence that both would be unstable in relation to the isomeric diketone **11**.[12] Indeed, when heated in 5% ethanolic sodium hydroxide for 2 hr the mixture of hydroxyketones **10** was smoothly transformed to the diketone **11** contaminated with approximately 10% of dehydrofuropelargones **12** and **13**. Prolonged treatment of either the aldols **10** or the diketone **11** under the same conditions led directly to the β, γ-unsaturated ketone **13** and minor amounts of the α, β-unsaturated isomer **12**.



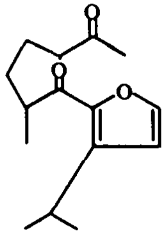
8



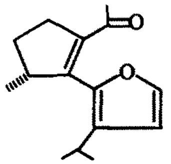
9



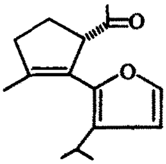
10



11



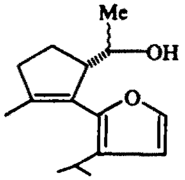
**12**



**13**

This demands that the conversion of the diketone **11** to the α,β-unsaturated ketone **12** be slower than isomerization of the latter to the more stable isomer **13**. Equilibration of the two bicyclic ketones in the presence of sodium hydroxide led indeed to mixtures containing approximately 92% of **13** and 8% of **12**. The greater stability of the non-conjugated ketone appears surprising but may be rationalized as follows. Steric crowding in the fully conjugated isomer **12** prevents the furan ring from being coplanar with the double bond and the carbonyl group. Comparison of the UV spectrum of **12**, $\lambda_{max}^{EtOH}$ 224 and 308 mμ (ε 10,000 and 5620) with that of 4-(2-furyl)-3-buten-2-one $\lambda_{max}^{EtOH}$ 236, 316 mμ (ε 1,900 and 23,000)[13] does indeed suggest the presence of two separate chromophores in **12**. IR absorption at 1650 $cm^{-1}$ demands an essentially planar α,β-unsaturated ketone grouping and depending on whether it has the s-*cis* or the s-*trans* conformation the molecule is destabilized by steric interference of the furan ring with either the carbonyl oxygen atom or the Me group. The β,γ-unsaturated isomer **13** on the other hand can assume a relatively uncrowded conformation in which the double bond and the furan ring are nearly coplanar. Comparison of the UV spectra of **13**, $\lambda_{max}^{EtOH}$ 256 mμ (ε 7100) and 2-vinyl furan $\lambda_{max}^{EtOH}$ 260 mμ (ε 15,800)[13] does not contradict this.

Comparison of IR, UV, NMR and mass spectra as well as VPC behavior (both in Gif and in these laboratories) established identity of the two racemic dehydrofuropelargones **12** and **13** with the natural furopelargones C and D respectively. Following a known reaction in the natural series[7] reduction of the β,γ-unsaturated ketone **13** with sodium borohydride in methanol furnished a mixture of epimeric alcohols **14a** and **b** separable by absorption chromatography. The individual epimers were found to be identical with those prepared from natural furopelargone D.



**14a, b**

## EXPERIMENTAL

M.ps were determined on a hot stage microscope and are uncorrected. IR spectra were recorded on a Perkin–Elmer Model 237 instrument and UV spectra were obtained on a Cary Model 14 recording spectrophotometer. TLC was used routinely for monitoring reactions and chromatographic separations. NMR spectra were measured on a Varian A-60 instrument using TMS as internal standard. Chemical shifts are presented in δ values (ppm downfield from standard). Elemental analyses were performed in the laboratory of Dr. E. Palluy, Firmenich et Cie, Geneva.

### *Glycidic ester* 4

A 500 ml 3-necked flask was equipped with a stirrer, a thermometer inserted through an adapter with a side arm connected to a source of $N_2$, and a 50-ml Erlenmeyer addition flask. The apparatus was dried with a free flame in a slow stream of $N_2$ and subsequent operations were conducted in an $N_2$ atm. A mixture of 3[9] (21·3 g, 133 mmoles), methyl chloroacetate (23·2 g, 213 mmoles), and dry ether (100 ml) was placed in the reaction vessel and the addition flask was charged with NaOMe (11·5 g, 213 mmoles). The soln was cooled in a dry ice-acetone bath to −10° and the NaOMe was added gradually at such a rate that a temp below −5° could be maintained (approx 30 min). The mixture was stirred for an additional 2 hr and then allowed to come to room temp overnight. It was then cooled again to 0° and made slightly acidic by addition of glacial AcOH (1·5 ml) in water (20 ml). The ether was decanted, and the residual slurry was extracted 3 times with ether. The combined ether solns were washed in a separatory funnel with 20 ml sat NaClaq to which was added 0·4 g portions of $NaHCO_3$ until the washings were no longer acidic. After each bicarbonate addition, the mixture was shaken for at least 1 min before a test for acidity was made. Finally, the ether phase was washed with sat NaClaq and dried over $Na_2SO_4$. Distillation of the solvents left 28 g of crude glycidic ester.

### *Methyl 3-isopropyl-2-furoate* (5)

The crude ester 4 was placed in a distillation flask and heated in an oil bath. When the bath temp reached 150°, MeOH began to distill. Heating was continued until the production of MeOH had ceased. After the heating bath had been allowed to cool, the product was distilled to give 14·6 g (65 %) of 5, b.p. 97° (12 mm).

An analytical sample was obtained by esterification of 6 with diazomethane. It had IR bands ($CHCl_3$) at 1715 and 1600 $cm^{-1}$ and UV absorption (EtOH) at 253 mμ (ε 3,830). NMR ($CCl_4$) 7·4 (1H, d, $J$ = 2 c/s); 6·4 (1H, d, $J$ = 2 c/s); 3·85 (3H, s); 3·6 (1H, septet $J$ = 8 c/s); 1·2 (6H, d, $J$ = 8 c/s). (Found: C, 64·15; H, 7·03. Calc. for $C_9H_{12}O_3$: C, 64·27; H, 7·19 %.)

### 3-*Isopropyl-2-furoic acid* (6)

A mixture of 5 (10·5 g, 62 mmoles) and 20 % NaOHaq (25 ml) was heated under reflux for 2 hr. The soln was cooled and acidified with conc HCl, while stirring vigorously. The product was collected by suction filtration, washed with water and dried in a dessicator. The acid obtained (8·02 g, 84 %) had m.p. 94–97°. A sample was purified for analysis by recrystallization from hexane. It had m.p. 96–98°; IR absorptions (KBr) 1680, 1580 $cm^{-1}$; NMR ($CCl_4$) 12·4 (1H, s); 7·5 (1H, d, $J$ = 2 c/s); 6·45 (1H, d, $J$ = 2 c/s); 3·7 (1H, septet, $J$ = 7 c/s); 1·25 (6H, d, $J$ = 7 c/s). (Found: C, 62·53; H, 6·60. Calc. for $C_8H_{10}O_3$: C, 62·32; H, 6·54 %.)

### 3-*Isopropyl-2-furoic acid chloride* (7)

A mixture of 6 (15·1 g, 98 mmoles), $SOCl_2$ (13·1 g, 110 mmoles) and dry benzene (50 ml) was allowed to reflux for 4 hr. After removal of the solvent *in vacuo*, the residue was distilled to yield 15·1 g (87·5 %) of the acid chloride, b.p. 108° (17 mm).

### β-*Diketone* 8

To a soln of cyclopentanone–morpholine enamine (13·8 g, 90 mmoles) and $Et_3N$ (9·1 g, 90 mmoles) in EtOH-free $CHCl_3$ (100 ml) was added dropwise, at 0°, the acid chloride (15·1 g, 87 mmoles) diluted with $CHCl_3$ (30 ml). The reaction mixture was kept under $N_2$ and left overnight at room temp. It was then added to 10 % HCl (30 ml) and after stirring at reflux temp for 2 hr it was cooled and the $CHCl_3$ layer was separated and washed consecutively with 5 % HCl, water, 5 % $NaHCO_3$aq, water, dried over $Na_2SO_4$, and evaporated. Distillation of the remaining oil gave 16·5 g (86 %) of 8, b.p. 97–100° (0·01 mm); $n_D^{25}$ 1·5576; IR absorptions ($CHCl_3$) at 1740, 1655, (broad) 1610 (broad) $cm^{-1}$; UV absorptions (EtOH) 235 (ε 2,950), 279 (ε 8,700), 350 mμ (ε 10,500); (dil NaOH) 232 (ε 5,600); 277 (ε 6,100), 346 mμ (ε 12,000). (Found: C, 70·84; H, 7·26. Calc. for $C_{13}H_{16}O_3$: C, 70·89; H, 7·32 %.)

### *Methylation of diketone* 8

Diketone 8 (16·1 g, 73 mmoles) in dry DMF (25 ml) was added over a period of 45 min to a stirred suspension of NaH (1·92 g, 80 mmoles) in DMF (50 ml). The reaction was performed under $N_2$ at room temp. After $H_2$ evolution had ceased (1 hr) MeI (11·4 g, 80 mmoles) in DMF (20 ml) was added in the course of 15 min and stirring was continued at room temp for 1 hr. The resulting mixture was poured onto ice and extracted with ether twice. The organic layers were washed with water, dried over $Na_2SO_4$, and evaporated.

The solid residue was crystallized from $CHCl_3$–hexane to give 13·2 g (77 %) of **9**, m.p. 103–108°. A sample recrystallized from EtOAc had m.p. 106–108°; IR absorptions ($CHCl_3$) at 1735, 1660, 1575 $cm^{-1}$; NMR ($CCl_4$), 7·2 (1H, d, $J$ = 2 c/s); 6·3 (1H, d, $J$ = 2 c/s); 3·6 (1H, septet, $J$ = 7 c/s); 1·5–2·7 (6H, m); 1·25 (3H, s); 1·15 (6H, d, $J$ = 7 c/s); UV absorption (EtOH) 276 mμ. (Found: C, 72·19; H, 7·86. Calc. for $C_{14}H_{18}O_3$: C, 71·77; H, 7·74 %.)

### *Hydroxyketone* **10**

The Grignard reagent prepared from MeI (9·2 g, 65 mmoles) and Mg (1·46 g, 60 mg-atoms) in anhyd ether (50 ml) was added over a period of 1 hr at 20° to a soln of **9** (12·7 g, 54 mmoles) in ether (300 ml). A yellow oil precipitated rapidly but stirring was continued at reflux for 1 hr. The mixture was then cooled and added to sat $NH_4Cl$ aq (50 ml). The organic layer was separated, washed with water, dried over $Na_2SO_4$ and evaporated. From a soln of the remaining oil in hexane, starting material (2·3 g) crystallized on cooling to −20°. The mother liquors were concentrated to give 11·0 g of crude hydroxy-ketone; IR absorptions ($CHCl_3$) at 3580, 1640, 1510 $cm^{-1}$.

### *Diketone* **11**

A soln of crude **10** (11·0 g) in EtOH (150 ml) and 5 % NaOH aq (60 ml) was refluxed under $N_2$ for 2 hr. The alcohol was partly removed *in vacuo* and the resulting mixture extracted with pentane twice. Organic layers were washed with water, dried over $Na_2SO_4$, and evaporated. The residue was distilled to give 8·35 g (75 %, based on 10·4 g of **9**) of **11**, b.p. 118–125° (0·2 mm), containing about 10 % dehydrofuropelargone (VPC). A pure sample was obtained by chromatography on silicic acid using a mixture of hexane and EtOAc as eluent. It had b.p. 122° (0·1 mm); $n_D^{25}$ 1·4898; IR absorptions ($CHCl_3$) at 1715, 1665, 1575 $cm^{-1}$; NMR ($CCl_4$); 7·2 (1H, d, $J$ = 2 c/s); 6·3 (1H, d, $J$ = 2 c/s); 3·6 (1H, septet, $J$ = 7 c/s); 3·3–1·3 (7H, m); 2·0 (3H, s); 1·15 (6H, d, $J$ = 7 c/s); 1·1 (3H, d, $J$ = 6 c/s). (Found: C, 72·19; H, 8·75. Calc. for $C_{15}H_{22}O_3$: C, 71·97; H, 8·86 %.)

### *Furopelargones C* (**12**) *and D* (**13**)

A soln of **11** (3·17 g) in 25 ml of 5 % NaOH aq (water: EtOH 1:1) was allowed to reflux under $N_2$ for 7 hr. The mixture was diluted with water and extracted twice with pentane. The organic layers were washed to neutrality, dried over $Na_2SO_4$ and evaporated. Gas chromatography of the residue indicated the presence of some starting material **11**, and the furopelargones C and D (12 % and 88 % respectively). For separation on a preparative scale the residue (2·9 g) was chromatographed on silicic acid (180 g). Elution with hexane containing 2·5 % EtOAc gave 55 mg of **12**. Later fractions eluted with the same mixture of solvents yielded 1·58 g of **13**. Finally, elution with hexane containing 20 % EtOAc produced 950 mg of recovered **11**.

Pure α,β-unsaturated ketone **12** (furopelargone C) obtained by distillation, b.p. ~90° (0·1 mm) had IR absorptions ($CHCl_3$) at 1650, 1575, 1490 $cm^{-1}$; UV absorptions at 224 (ε 10,000) and 308 mμ (ε 5,650). NMR ($CCl_4$) 7·25 (1H, d, $J$ = 2 c/s); 6·25 (1H, d, $J$ = 2 c/s); 3·4–1·0 (6H, m); 1·8 (3H, s); 1·18 (3H, d, $J$ = 7 c/s) 1·1 (3H, d, $J$ = 7 c/s); 0·95 (3H, d, $J$ = 7 c/s). Mass spectrum *m/e* 232 (parent peak), *m/e* 189 (base peak). Identity with the optically active, natural furopelargone C was established by comparison of retention times in a gas chromatograph, mobility on TLC, IR, UV, NMR and mass spectra.

The β,γ-unsaturated ketone **13** (furopelargone D) was also purified by distillation, b.p. ~90° (0·1 mm). IR absorptions ($CHCl_3$) 1700, 1510 $cm^{-1}$; UV absorption (EtOH) 252 mμ (ε 9,650); NMR ($CDCl_3$) 7·3 (1H, d, $J$ = 2 c/s); 6·3 (3H, d, $J$ = 2 c/s); 3·9 (1H, m); 2·6 (1H, septet, $J$ = 7 c/s); 2·3–1·0 (4H, m); 1·92 (3H, s); 1·8 (3H, s broad); 1·2 (3H, d, $J$ = 7 c/s); 1·1 (3H, d, $J$ = 7 c/s). Mass spectrum *m/e* 232 (parent peak); 189 (base peak). (Found: C, 77·25; H, 8·73. Calc. for $C_{15}H_{20}O_2$: C, 77·55; H, 8·68 %.)

Identity with optically active, natural furopelargone D was again established by comparison of retention times in gas chromatography, mobility on TLC, IR, UV, NMR and mass spectra.

### *Equilibration of furopelargones C* (**12**) *and D* (**13**)

To a soln of 5 % NaOH aq in water–EtOH 1:1 (1 ml) was added furopelargone (20 mg, 60 % C and 40 % D-isomer). The mixture was allowed to reflux under $N_2$ for 4 hr. It was then diluted with water, extracted with pentane, washed with water, dried over $Na_2SO_4$, and evaporated. The remaining oil showed two peaks in the ratio of 7:93 on VPC, corresponding to furopelargones C and D respectively. Pure furopelargone D was treated in the same manner. A gas chromatogram of the resulting mixture revealed two components in the ratio of 6:94. The retention times were identical with those of furopelargones C and D respectively.

### *Alcohols* **14a** *and* **b**

To a soln of furopelargone D (469 mg) in 80% MeOH (12 ml) was added $NaBH_4$ (200 mg). The mixture was stirred for 1 hr at room temp, then it was diluted with water and extracted twice with pentane. The organic layers were washed with water and dried over $Na_2SO_4$. Evaporation of the solvent left an oil (464 mg) which showed two peaks in the ratio of 43:57 on VPC using a Carbowax 2 ft-column at 170°. The retention times were 21 and 29 min respectively. The two alcohols were quantitatively separated by silicic acid chromatography using a mixture of hexane (95%) and EtOAc (5%) as eluant.

*Alcohol* **14a** (less polar): b.p. ~90° (0·05 mm); $n_D^{25}$ 1·5096; IR absorptions ($CHCl_3$) 3560, 3420 $cm^{-1}$; UV absorption (EtOH) 247 mμ (ε 10,000). NMR ($CDCl_3$) 7·3 (1H, d, $J = 2$ c/s); 6·3 (1H, d. $J = 2$ c/s); 3·8 (1H, d of q, $J = 7$ c/s and 3 c/s); 3·3–1·0 (6H, m); 1·75 (3H, s, broad); 1·55 (1H, s) (disappears on exchange with $D_2O$); 1·3–1·0 (9H, 6 sharp lines). Mass spectrum: *m/e* 234 (present peak); *m/e* 189 (base peak). (Found: C, 76·93; H, 9·43. Calc. for $C_{15}H_{22}O_2$: C, 76·88; H, 9·46%.)

*Alcohol* **14b** (more polar): b.p. ~90° (0·05 mm); $n_D^{27}$ 1·5137; IR absorptions ($CHCl_3$) 3590, 3560, 3430 $cm^{-1}$; UV absorption (EtOH) 247 mμ (ε 8,900). NMR ($CDCl_3$); 7·3 (1H, d, $J = 2$ c/s); 6·3 (1H, d, $J = 2$ c/s); 3·7 (1H, quintet $J = 7$ c/s); 3·3–1·0 (6H, m); 1·7 (3H, s, broad); 1·65 (1H, s) (disappears on exchange with $D_2O$); 1·2 (3H, d, $J = 7$ c/s); 1·05 (3H, t, $J = 7$ c/s). Mass spectrum: *m/e* 234 (parent peak); *m/e* 189 (base peak). (Found: C, 76·76; H, 9·50. Calc. for $C_{15}H_{22}O_2$: C, 76·88; H, 9·46%.)

*Acknowledgements*—We are indebted to Firmenich et Cie., Geneva for financial support and to Prof. E. Lederer for a pleasant collaboration. Mass spectra were kindly measured by Dr. B. Willhalm, Firmenich et Cie.

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