Tetrahedron. Vol. 29, pp. 621 to 624. Pergamon Press 1973. Printed in Great Britain

CYCLIC CARBONATES FORMED DURING PERFORMIC ACID OXIDATION OF ATRACTYLIGENIN

F. PIOZZI, G. SAVONA and M. L. MARINO
Institute of Organic Chemistry, University of Palermo, Italy

(*Received in the UK* 19 *September* 1972; *Accepted for publication* 3 *October* 1972)

Abstract—The performic oxidation of the kaurenic double bond of atractyligenin and derivatives affords cyclic carbonates between the 15α-OH and 16α-OH or the 16α-OH and 17-OH. Their formation is quite unusual and novel for natural substrates.

We have reported the oxidation of atractyligenin (**1a**)[1] and diacetyl-atractyligenin (**1b**)[2] with performic acid, followed by alkaline hydrolysis at room temperature, as a method for the preparation of the tetrol **2**. We observed that the raw material before alkaline hydrolysis showed a strong, unidentified carbonyl band at 1800 cm^{-1}, therefore we decided to reinvestigate this reaction on the methylesters **1c** and **1d**.

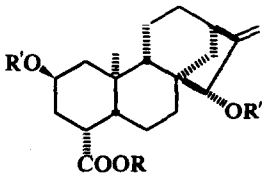
Three crystalline products were isolated from the oxidation of atractyligenin methylester (**1c**) with performic acid. From spectroscopic evidence (experimental), the products were assigned structures **3a**, **3b** and **3c**, all having a 5-ring cyclic carbonate ester between the 15α-OH and 16α-OH hydroxy groups; alkaline hydrolysis of these products gave the tetrol **2**. Prpduct **3c** was also prepared by treatment of **3a** or **3b** with formic acid.

Oxidation of diacetyl-atractyligenin methylester (**1d**) with performic acid gave two products which were assigned structures **4** and **5**. 5-Ring cyclic carbonate esters are therefore present between 16α-OH and 17-OH in **4** and between 16α-OH and 15α-OH in **5**. Both products were hydrolized to the tetrol **2**.

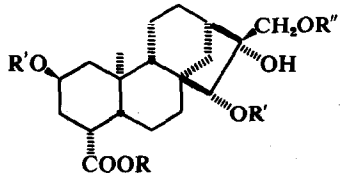
The structure of **4** was confirmed by OsO_4 oxidation of **1d** to the diacetyl-tetrol methylester **6** and phosgene carbonation of the latter: the product obtained was identical with **4** from the performic oxidation. This also proved the configuration of **4** at C-16, as it is known that OsO_4 hydroxylates the kaurene skeleton from the less hindered α side.

As expected, treatment of the epoxyderivative of atractyligenin methylester (**7a**) with performic acid yielded the above described carbonates **3a**, **3b** and **3c**.

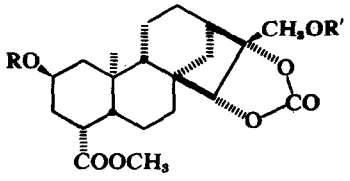
Product **7a** was easily prepared by treatment of



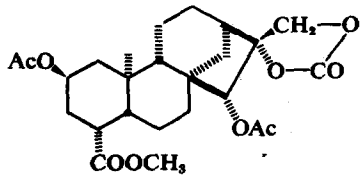
1a: R = H R′ = H
1b: R = H R′ = Ac
1c: R = CH_3 R′ = H
1d: R = CH_3 R′ = Ac



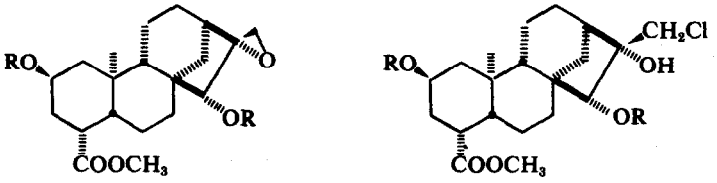
2: R = H R′ = H R″ = H
6: R = CH_3 R′ = Ac R″ = H
12: R = CH_3 R′ = H R″ = H
13: R = CH_3 R′ = Ac R″ = CHO



3a: R = H R′ = H
3b: R = CHO R′ = H
3c: R = CHO R′ = CHO
5: R = Ac R′ = H



4



7a: R = H
7b: R = Ac

8a: R = H
8b: R = Ac

SCHEME 1

1c with *p*-nitroperbenzoic acid in ether. Treatment of 1c with perbenzoic acid in $CHCl_3$ always gave minor quantities of **7a** and the chloroderivative **8a** as main product; clearly, some hydrogen chloride from the hydrolysis of $CHCl_3$ cleaved the epoxy ring of **7a** in an S_N2 manner to give **8a**.

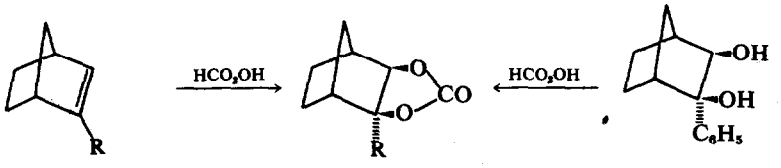
Analogously, treatment of epoxyderivative **7b** with performic acid gave carbonates **4** and **5**. Product **7b** was prepared by epoxidation of **1d** with *p*-nitroperbenzoic acid.

The formation of cyclic carbonates during oxidation with performic acid is rather unusual and must involve the oxidation of a formate ester to a carbonate. As far as we know, there is only one precedent to such behaviour: Kleinfelter and Schleyer[3] reported the transformation of 2-phenylnorbornene (**9a**) and 2-*p*-chlorophenyl-norbornene (**9b**) into the related cyclic carbonates **10a** and **10b** by reaction with performic acid.

Kleinfelter and Schleyer also observed that performic acid transformed diol **11** into carbonate **10a**. Indeed, when submitted to treatment with performic acid, tetrol methylester **12** gave the above described cyclic carbonates **3a**, **3b** and **3c**; no carbonate ester was observed between the 17-OH and the 16α-OH. Here the carbonate ester is believed to originate from the formylation of the 15α-OH and subsequent cyclisation and oxidation.

Treatment of epoxyderivative **7b** with formic acid yielded primary formyl ester **13**; we believe that the ring opening originally formed a 16α-OCHO derivative, whose formyl group migrated from the tertiary to the primary hydroxyl group through an orthoformate intermediate. Product **13** was also prepared by esterification of **6** by formic acid.

No carbonate was obtained during the oxidation of diketoatractyligenin methylester (**14**) with performic acid: the only product isolated with the 17-formylderivative **15**. The latter product was also prepared by treatment of diketodiol **16** with formic acid.



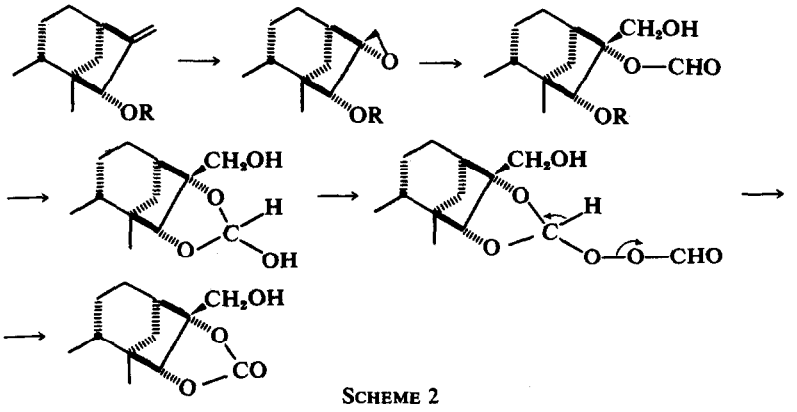
9a: R = C_6H_5
9b: R = C_6H_4—Cl p.

10a: R = C_6H_5
10b: R = C_6H_4—Cl p.

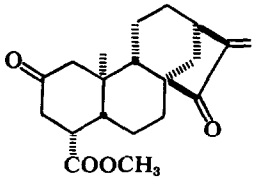
11

Kleinfelter and Schleyer suggested a reaction pathway, application of which, as shown in the following scheme, accounts for our obtaining **3a**, **3b**, **3c** and **5**; the reaction giving **4** follows the same pathway but the 16α-OCHO group attacks the 17-OH instead of the 15α-OH.

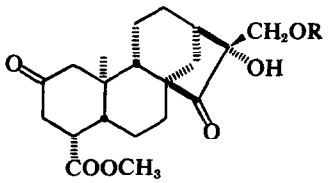
The results reported here indicate that the hydroxylation of the kaur-16-en-15α-ol double



SCHEME 2



14



15: R = CHO
16: R = H

bond gives a system of coplanar 16α and 15α oxygenated functions suitable for closure to a cyclic carbonate. The formation of a 16α,17-carbonate seems less likely because the related hydroxyl groups are not rigidly coplanar.

EXPERIMENTAL

M.p.: capillary tubes, uncorrected. IR: Nujol mull, Perkin Elmer Infracord 137. NMR: (δ) 60 MHz, Jeol C60-H, TMS internal standard. MS: Hitachi Perkin Elmer RMU-6D or Perkin Elmer 270 (courtesy of Dr. A. Selva, Institute of Chemistry, Polytechnic School, Milano). Chromatography: 0·05–0·20 mm Merck silica gel.

Atractyligenin methylester (**1c**) *and performic acid: carbonates* **3a**, **3b** *and* **3c**. **1c** (1 g) in 99% formic acid (20 ml) was heated with stirring to 50° and 36% H_2O_2 (4 ml) added. The solution was stirred at 50° for 1 h, left overnight at room temp, added to water (75 ml) and ether extracted. The residue from distillation of the ether was chromatographed on silica gel (40 g), eluting with benzene–AcOEt 9:1, 8:2 and 7:3 mixtures.

The benzene–AcOEt 9:1 fraction gave a trace of a product, m.p. 218° (from AcOEt); MS: 450 (M^+), 404, 372, 344; IR: 1800 cm^{-1} (5-ring cyclic carbonate),[4] 1725 cm^{-1} ($COOCH_3$ and O—CHO). The substance proved identical (m.m.p., IR, MS) with the product obtained by heating **3a** or **3b** with formic acid, and was attributed structure **3c**.

The benzene–AcOEt 8:2 fraction yielded 200 mg of a product, m.p. 205–206° (from AcOEt); (Found: C, 62·72; H, 7·29. $C_{22}H_{30}O_8$ requires: C, 62·54; H, 7·16%); MS: 422 (M^+), 404, 394, 390, 376, 344; IR: 3545 cm^{-1} (OH), 1795 cm^{-1} (5-ring cyclic carbonate), 1725 cm^{-1} ($COOCH_3$ and O—CHO); NMR (acetone-d_6): 1·00 (s, 10α-CH_3), 3·68 (s, $COOCH_3$), 3·93 (d, J 5·8 Hz, C$\underline{H}_2$OH), 4·45 (t, J 5·8 Hz, CH_2OH), 4·44 (d, J 1·5 Hz, H-15), 5·48 (tt, $J_{ax,ax}$ 11·5 Hz, $J_{ax,eq}$ 4·8 Hz, axial H-2), 8·10 δ (d, J 1 Hz, CHO); on addition of D_2O, the signal at 4·45 disappeared and the doublet at 3·93 collapsed to a singlet. Therefore the product was assigned structure **3b**.

The benzene–AcOEt 7:3 fraction gave 400 mg of a product, m.p. 248° (from AcOEt); (Found: C, 63·64; H, 7·90. $C_{21}H_{30}O_7$ requires: C, 63·94; H, 7·66%); MS: 394 (M^+), 376, 362, 344; IR: 3450 cm^{-1} (OH), 1795 cm^{-1} (5-ring cyclic carbonate), 1700 cm^{-1} ($COOCH_3$); NMR (acetone-d_6): 0·93 (s, 10α-CH_3), 3·63 (s, $COOCH_3$), 3·93 (d, J 5·5 Hz, CH_2OH), 3·49 (d, J 5 Hz, 2β-O$\underline{H}$), 4·20 (m, 2α-H), 4·44 (t, J 5·5 Hz, CH_2O$\underline{H}$), 4·38 (d, J 2 Hz, H-15); on addition of D_2O the signals at 3·49 and 4·44 disappeared and the doublet at 3·93 collapsed to a singlet. The product was assigned structure **3a**.

Carbonates **3a** or **3b** (20 mg) were refluxed with 99% formic acid (2 ml) for 3 h; the solution was evaporated to dryness under reduced pressure giving **3c**, m.p. 218° (from AcOEt).

The carbonates **3a** or **3b** (20 mg) were refluxed with 10% ethanolic KOH (5 ml) for 6 h; the solution neutralized with 50% sulphuric acid and evaporated, the residue was crystallized from water yielding tetrol **2**, m.p. 246–248°, identified by m.m.p. and IR.[1,2]

Diacetyl-atractyligenin methylester (**1d**) *and performic acid: carbonates* **4** *and* **5**. Methylester **1d** (1 g) was treated as described above for **1c**. Chromatography on silica gel (40 g), eluent benzene–AcOEt 85:15, yielded two main products: minor quantities of other substances could not be isolated and were neglected.

The first product (200 mg) was isolated as an oil: it was homogeneous on TLC, but it could not be crystallized. MS: 478 (M^+), 435, 418, 403, 386, 358. $C_{25}H_{34}O_9$ requires 478·52; IR: 1800 cm^{-1} (5-ring cyclic carbonate), 1725 cm^{-1} (COOR), 1240 cm^{-1} (CH_3COOR); NMR ($CDCl_3$): 0·95 (s, 10α-CH_3), 2·01 and 2·10 (s, CH_3COO), 3·66 (s, $COOCH_3$), 4·24 (broad s, H-15), 4·40 (two-lines signal, separation 5 Hz, —CH_2—O—), 5·25 (m, H-2). The substance was therefore assigned structure **4**.

The second product (200 mg) was isolated as an amorphous, exceedingly soluble solid: it was homogeneous on TLC but it could not be crystallized. MS: 436 (M^+), 393, 376, 344, 316. $C_{23}H_{32}O_8$ requires 436·49; IR: 3350 cm^{-1} (OH), 1810 cm^{-1} (5-ring cyclic carbonate), 1725 cm^{-1} (COOR), 1250 cm^{-1} (CH_3COOR); NMR ($CDCl_3$): 0·94 (s, 10α-CH_3), 2·02 (s, CH_3COO), 3·66 (s, $COOCH_3$), 3·92 (s, C$\underline{H}_2$OH), 4·34 (s, H-15), 5·30 (m, H-2). The substance was attributed structure **5**.

By refluxing with ethanolic KOH as described above, carbonates **4** and **5** yielded tetrol **2**, m.p. 246–248°.

Osmium tetroxide oxidation of (**1d**): *diacetyltetrol methylester* (**6**). A solution of diacetyl-atractyligenin methylester[2] (**1d**) (420 mg) and OsO_4 (250 mg) in CH_2Cl_2 (15 ml) was left at room temp for 12 days. H_2S was bubbled through: after filtering the precipitate, the solution was evaporated. The residue underwent repeated chromatography on silica gel (eluent benzene–AcOEt 95:5) yielding diacetyltetrol methylester (**6**) (60 mg), m.p. 145° (from AcOEt); (Found: C, 63·85; H, 8·13. $C_{24}H_{36}O_8$ requires: C, 63·70; H, 8·02%); MS: 434 (M-18), 421 (M-31), 392 (M-60), 374, 361, 314, 304, 301; IR: 3380 cm^{-1} (OH), 1725 cm^{-1} (COOR), 1250 cm^{-1} (CH_3COOR).

Diacetyltetrol methylester (**6**) *and phosgene: carbonate* **4**. Excess of a solution of phosgene in toluene was added dropwise to a solution of diacetyltetrol methylester (**6**) (50 mg) in anhydrous pyridine (5 ml) at −15°. After 24 h the solution was diluted with water and ether extracted: the extract was washed with dilute HCl, dried and evaporated giving an oily residue (one component on TLC) which did not crystallize even after silica gel chromatography. The product proved to be identical (TLC, IR, NMR, MS) with carbonate **4** obtained by performic acid

oxidation of diacetyl-atractyligenin methylester (**1d**) (above).

p-Nitroperbenzoic acid oxidation of atractyligenin methylester (**1c**): *epoxyderivative* **7a**. *p*-Nitroperbenzoic acid (0·55 g) was added to a solution of **1c** (1 g) in ether (100 ml). After 24 h at room temp, the solution was washed with $NaHCO_3$ aq, dried and evaporated; the residue was chromatographed on silica gel (20 g), eluent benzene–AcOEt 4:1, to purify product **7a** from minor amounts of unreacted **1c**: m.p. 150° (from cyclohexane), yield 750 mg; (Found: C, 68·45; H, 8·75. $C_{20}H_{30}O_5$ requires: C, 68·54; H, 8·63%); MS: 350 (M^+), 335, 332, 317, 314, 299; IR: 3585 and 3470 cm^{-1} (OH), 1720 cm^{-1} ($COOCH_3$); NMR ($CDCl_3$): 0·93 (s, 10α-CH_3), 3·05 (s, CH_2 in epoxy ring), 3·45 (s, H-15), 3·66 (s, $COOCH_3$), 4·75 (m, H-2).

Perbenzoic acid oxidation of atractyligenin methylester (**1c**): *epoxyderivative* **7a** *and chloroderivative* **8a**. A solution of **1c** (1 g) in $CHCl_3$ (50 ml) was treated with a $CHCl_3$ solution (20 ml) of perbenzoic acid (about 0·6 g). After 48 h at room temp, solvent was evaporated and the residue taken up in ether: the solution was washed with $NaHCO_3$ aq. and evaporated. The soft residue gave two crystalline substances after chromatography on silica gel (20 g), eluent benzene–AcOEt.

The more polar product (50 mg), m.p. 150° (from cyclohexane), was identical (m.m.p., IR, NMR) with epoxyderivative **7a** obtained by *p*-nitroperbenzoic acid oxidation of **1c** (above).

The less polar product (200 mg), m.p. 241° (from AcOEt), was attributed structure **8a**. (Found: C, 62·31; H, 8·24; Cl, 9·35. $C_{20}H_{31}O_5Cl$ requires: C, 62·09; H, 8·08; Cl, 9·16%); MS: 388 and 386 (M^+), 373 and 371, 370 and 368, 350; IR: 3300 and 3200 cm^{-1} (OH), 1725 cm^{-1} ($COOCH_3$); NMR (pyridine-d_5): 0·98 (s, 10α-CH_3), 3·66 (s, $COOCH_3$), 3·72 (broad, H-15), 4·00 (s, C—CH_2Cl), 4·80 (broad m, H-2). The substance gave diacetate **8b** by treatment with Ac_2O and pyridine, m.p. 147–149° (from cyclohexane); NMR ($CDCl_3$): 0·94 (s, 10α-CH_3), 2·03 and 2·15 (s, CH_3COO), 3·67 (s, $COOCH_3$), 3·74 (s, CH_2Cl), 4·82 (s, H-15), 5·30 (m, H-2).

Cleavage of epoxyderivative **7a** *by HCl: chloroderivative* **8a**. Dry HCl was bubbled into a cold solution of epoxyderivative **7a** (50 mg) in $CHCl_3$ (20 ml). The solution was left for 24 h at room temp and evaporated; the residue gave 40 mg of chloroderivative **8a**, m.p. 241° (from AcOEt), identical (m.m.p., IR, NMR) with the product described above.

p-Nitroperbenzoic acid oxidation of diacetyl-atractyligenin methylester (**1d**): *epoxyderivative* **7b**. *p*-Nitroperbenzoic acid (0·15 g) was added to **1d** (0·25 g) in ether (100 ml). After 24 h at room temp, the solution was washed with $NaHCO_3$ aq., dried and evaporated; the residue was chromatographed on silica gel (5 g) eluting with benzene–AcOEt 85:15. Product **7b** was obtained as an amorphous, exceedingly soluble solid; it was homogeneous on TLC but it would not crystallize. MS: 434 (M^+), 419, 374, 359, 314, 299. $C_{24}H_{34}O_7$ requires 434·51.

Formate ester **13**. (a) Diacetyltetrol methylester (**6**) (10 mg) was refluxed with 99% formic acid for 3 h; the solution was evaporated to dryness under reduced pressure and the residue crystallized, giving **13**, m.p. 145° (from ethyl ether); (Found: C, 62·02; H, 7·42. $C_{25}H_{36}O_9$ requires: C, 62·48; H, 7·55%); MS: 420 (M-60), 374, 361, 314; IR: 3400 cm^{-1} (OH), 1720 cm^{-1} (COOR), 1245 cm^{-1} (CH_3COO).

(b) Epoxyderivative **7b** (50 mg) was dissolved in 99% formic acid (2 ml). The solution was left overnight at room temp, diluted with water (10 ml) and ether extracted. The product, m.p. 145° (from ether), was identical to the above described. NMR ($CDCl_3$): 0·94 (s, 10α-CH_3), 2·04 and 2·12 (s, CH_3COO), 3·65 (s, H-15), 3·70 (s, $COOCH_3$), 4·20 and 4·40 (q_{AB}, J 12 Hz, CH_2—O—CHO), 5·40 (m, H-2), 8·13 (broad s, CHO).

Epoxyderivative **7a** *and performic acid: carbonates* **3a**, **3b** *and* **3c**. The epoxyderivative **7a** (0·3 g) dissolved in 99% formic acid (8 ml) was heated at 50° with stirring and treated with 36% H_2O_2 (1·3 ml) as described above for the oxidation of **1c** with performic acid. Chromatography on silica gel yielded traces of **3c**, 40 mg of **3b** and 90 mg of **3a**, which were found to be identical (m.m.p., IR) with the products obtained from **1c**.

Epoxyderivative **7b** *and performic acid: carbonates* **4** *and* **5**. The epoxyderivative **7b** (50 mg) dissolved in 99% formic acid (2 ml) was treated at 50° with three drops of 36% H_2O_2 as described above. By chromatography small amounts of **4** and **5** were isolated, identical (IR, TLC) with the products obtained from **1d**.

Tetrol methylester **12** *and performic acid: carbonates* **3a**, **3b** *and* **3c**. A solution of tetrol methylester[2] **12** (0·4 g) in 99% formic acid (20 ml) heated to 50° was added with stirring to 36% H_2O_2 (4 ml), as described above for the oxidation of **1c** with performic acid. By chromatography on silica gel traces of **3c**, 60 mg of **3b** and 130 mg of **3a** were isolated, identical (m.m.p., IR) with the products obtained from **1c**.

Formate ester **15**. (a) A cold solution of diketoatractyligenin methylester[2] (**14**) (300 mg) in 99% formic acid (5 ml) was treated with 36% H_2O_2 (0·1 ml) and left overnight at room temp. Pouring on ice gave a precipitate of starting product **14** (150 mg); ether extraction of the solution yielded an oil which solidified when moistened with AcOEt, m.p. 246–248° (from AcOEt), yield 50 mg. (Found: C, 64·47; H, 7·26. $C_{21}H_{28}O_7$ requires: C, 64·27; H, 7·19%); MS: 392 (M^+), 361, 346; IR: 3350 cm^{-1} (OH), 1730, 1718, 1695 cm^{-1} (CO); NMR ($CDCl_3$): 0·92 (s, 10α-CH_3), 3·62 (s, $COOCH_3$), 4·11 and 4·57 (q_{AB}, J 11 Hz, CH_2OCHO), 8·07 (s, CHO). Hence the product was assigned structure **15**.

The above oxidation gave an unresolvable mixture of products when performed at 50°: neither unaltered **14** nor **15** were detected by TLC.

(b) The diketodiol methylester **16** was prepared as previously described;[1] NMR ($CDCl_3$): 0·93 (s, 10α-CH_3), 3·66 (s, $COOCH_3$), 3·63 and 4·00 (q_{AB}, J 11·5 Hz, CH_2-OH). The product (20 mg) was refluxed with 99% formic acid (2 ml) for 3 h; the solvent removed under vacuum and the residue crystallized from AcOEt, m.p. 246–247°, identical (m.m.p., IR, TLC) with product **15** obtained as described above.

REFERENCES

[1]F. Piozzi, A. Quilico, R. Mondelli, T. Aiello, V. Sprio and A. Melera, *Tetrahedron* **8**, 515 (1966)
[2]T. Aiello, F. Piozzi, A. Quilico and V. Sprio, *Gazz. Chim. Ital.* **93**, 867 (1963)
[3]D. C. Kleinfelter and P. von R. Schleyer, *J. Am. Chem. Soc.* **83**, 2329 (1961)
[4]J. L. Hales, J. Idris Jones and W. Kinaston, *J. Chem. Soc.* 618 (1957); W. A. Mosher, F. W. Steffgen and P. T. Lansbury, *J. Org. Chem.* **26**, 670 (1961)