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# THE REACTION OF GIBBERELLINS $A_1$ AND $A_7$ WITH NEUTRAL MANGANESE DIOXIDE

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**Abstract**—Neutral manganese dioxide brings about oxidative lactonization and oxidative decarboxylation of gibberellins $A_1$ and $A_7$. The presence of a $\Delta^{16}$-double bond is necessary for the occurrence of oxidative lactonization at C-15.

In our previous communication[1] it was shown that the treatment of gibberellin $A_3$(**1**) with neutral $MnO_2$ prepared according to Mancera *et al.*[2] gives rise to the products of oxidative decarboxylation and oxidative lactonization. The general nature of these transformations in the series of gibberellins has been demonstrated using $GA_1$(**2**) and $GA_7$(**3**) as examples.

The reaction of $GA_1$(**2**) with neutral $MnO_2$ in acetone (200 hr at 20–22°C) affords a diene $C_{18}H_{22}O$(**4**) and a dilactone $C_{19}H_{22}O_6$(**5**) in yields 3–5 and 11–15%, respectively. This result is analogous to that observed in the case of $GA_3$. In both cases the recovery of the starting acid (**2** or **1**) is more than 50%.

The structure of the main product was formulated as **5** for the following reasons. The IR spectra of both crystalline modifications of **5** display two intense bands characteristic for $\gamma$-lactones (1765 and 1755–1752 $cm^{-1}$) and also the bands corresponding to the alcoholic OH groups (between 3625 and 3420 $cm^{-1}$) and to the grouping $\diagdown C{=}CH_2$ (3085–3060, 1675 and 900–910 $cm^{-1}$). The presence of two lactonic groups can be also deduced from the comparison of the CD of **5** ($[\theta]_{227} - 4500°$, in dioxane) with that of gibberellin $A_1$ methyl ester (**2a**) ($[\theta]_{232} - 1680°$, in dioxane, *cf* Meguro *et al.*[3]). The difference between CD maxima for **2a** and **5** ($-2820°$) almost coincides with $\Delta[\theta] = -2900°$ observed earlier[1] for gibberellin $A_3$ methyl ester (**1a**) and the dilactone (**6**) derived from **1**. The NMR spectrum of **5** (in $d_5$-pyridine) displays a one-proton doublet at $\delta$ 5.78 due to the coupling with one of two methylene protons at C-17 (J = 1.2 Hz). Therefore, the C–O bond of the second lactonic bridge is allylic in respect to the $\Delta^{16}$-double bond and hence attached to C-15. The fragmentation of **5** upon electron impact is very similar to that observed earlier[1] for dilactone **6**. Finally, when dilactone **6** was hydrogenated over 5% $Pd/CaCO_3$ in the presence of pyridine **5** was isolated in 8% yield from the neutral fraction of hydrogenation products.

The second product, the diene **4**, was characterised by its IR, NMR and mass spectra which are very similar to those of **7** obtained earlier[1] upon oxidative decarboxylation of **1**. Partial hydrogenation of **7** over 5% $Pd/CaCO_3$ (poisoned with pyridine) afforded **4** in ~5% yield.

In addition to compounds **4** and **5** the oxidation of $GA_1$ gives yet another neutral product more polar than these two. This compound, obtained in ~1.5–2% yield, is tentatively formulated as epoxy dilactone $C_{19}H_{22}O_7$ (**8**) on the basis of its IR, NMR and mass spectra. In spite of the noticeable IR absorbtion at 1702 $cm^{-1}$ it does not react with diazomethane or with Girard reagent. The presence of two OH groups was proved mass spectrometrically after isotopic exchange with MeOD. Finally, strong absorbtion at 1240-1200 $cm^{-1}$ which is more prominent than in the IR spectra of dilactones **5** and **6** coupled with the presence of a three-line AB-system at $\delta$ 3.20 ($J_{AB}$ = 6 Hz) and the disappearance of signals of olefinic protons at C-17 speak in favour of an epoxide grouping. The signal assigned to the proton at C-15 ($\delta$ 5.20) is shifted upfield in respect to the corresponding signals in the NMR spectra of **5** and **6** ($\delta$ 5.78 and 5.61, respectively); this is consistent with the diamagnetic shielding exercised by an adjacent epoxide ring.[4,5] When dilactone **5** was exposed to peracetic acid it afforded a product chromatographically indistinguishable from **8** in several solvent systems (TLC-data).

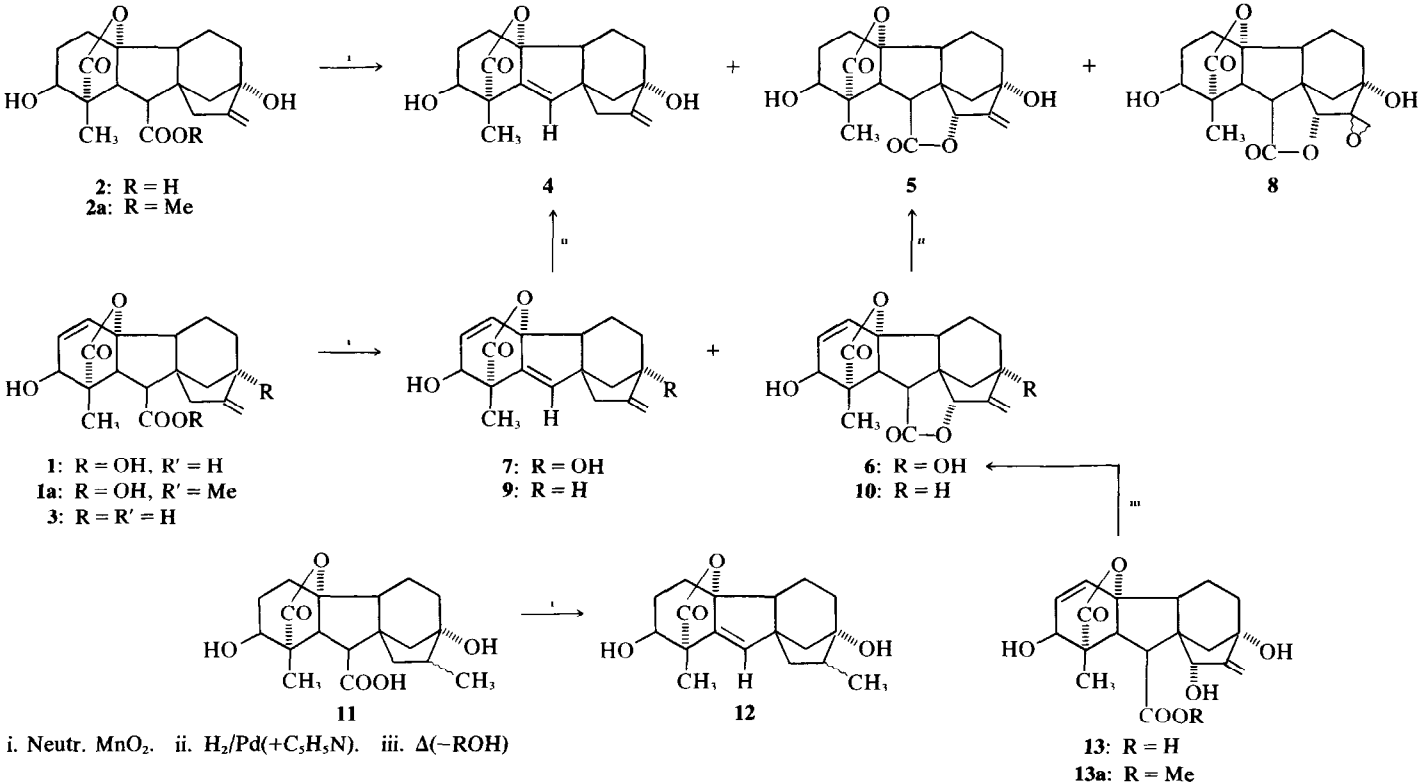
The reaction of $GA_7$(**3**) with neutral $MnO_2$ in acetone (200 hr at 20–22°C) proceeds in a similar way. In this case two neutral products, one corresponding to oxidative decarboxylation and the other to oxidative lactonization, were obtained in about 3 and 11% yields, respectively. The former, $C_{18}H_{22}O_3$(**9**) was characterized by its IR and mass spectra ($M^+$ 284 → $M^+$ 286 m.u. upon isotopic exchange with MeOD). The latter, $C_{19}H_{22}O_5$(**10**), displays IR, NMR and mass spectra very similar to those of dilactones **5** and **6**.

It appears that oxidative decarboxylation and lactonization induced by neutral $MnO_2$ may be fairly general for all gibberellins. The presence of $\Delta^{16}$-double bond is necessary for oxidative decarboxylation to occur since the reaction of neutral $MnO_2$ with tetrahydrogibberellic acid (**11**, a mixture of C-16 epimers) gives an olefin $C_{18}H_{24}O_4$(**12**) in ~5% yield as the only reaction product. This compound was characterized by its IR and mass spectra (olefinic absorbtion at 3060, 1675 and 930 $cm^{-1}$, $M^+$ 304).

Earlier we suggested[1] that oxidative lactonization of **1** at C-15 takes place without prior hydroxylation at this allylic centre, for in all cases when the reaction was TLC-monitored the spot of the corresponding trihydroxy acid (**13**) could not be detected. However, when oxidation of **1** was once performed with a less active (under-dried) batch of $MnO_2$ and the yields of **4** and **5** were lower than usual, that acid, $C_{19}H_{24}O_7$, was isolated in about 9% yield as an amorphous powder and characterized by the corresponding methyl ester (**13a**). Both **13** and **13a** are very unstable and easily form dilactone **5** on heating and even on prolonged storage at room temperature.

## EXPERIMENTAL

M.ps are corrected. IR spectra: in KBr-pellets, with UR-10 instrument (Zeiss, Jena). NMR spectra ($\delta$ in ppm): Varian HA-100


2: R = H
2a: R = Me
4
5
8
1: R = OH, R′ = H
1a: R = OH, R′ = Me
3: R = R′ = H
7: R = OH
9: R = H
6: R = OH
10: R = H
11
12
13: R = H
13a: R = Me
i. Neutr. MnO2. ii. H2/Pd(+C5H5N). iii. Δ(−ROH)

instrument. Mass spectra: Varian-MAT CH-6 instrument with all-glass inlet system, at 190–230°. Chromatography: silica gel L (40–100 μ). Circular dichroism: Cary-60 instrument (*c* 0.16 in dioxane). Preparation of neutral $MnO_2$: see.[1] Gibberellin $A_1$(**2**): m.p. 251–254°, $[\alpha]_D + 39°$; Gibberellin $A_7$(**3**): m.p. 172–175°, $[\alpha]_D + 22°$; tetrahydrogibberellic acid; m.p. 293-298° (lit.[5] m.p. 300–301°). Compounds **6** and **7** were obtained according to Ref. 1.

*$GA_1$(**2**) and neutral manganese dioxide.* To a soln of **2** (800 mg) in 160 ml abs acetone, neutral $MnO_2$ (10 g) was added and the suspension was shaken for 200 hr at 20–22°. The supernatant was carefully decanted, and the ppt was thoroughly washed first with acetone (5 × 200 ml) and then with acetone–AcOH 4:1 (200 ml)by decantation. Clear solns combined after filtration through a bed of silica gel (~ 10 g) were evaporated and the solid residue (749 mg) was chromatographed on 50 g of silica gel pretreated with 10 ml of phosphate buffer (pH 6.7). Elution with $CHCl_3$–EtOAc (95:5) afforded 7,20 - bisnor - 3β, 10α, 13α, trihydroxy - ent - gibberell - 5,16 - dien - 19 - oic acid 19→10 lactone (**4**), yield 31 mg, m.p. 209–214° (prisms from EtOAc–$Et_2O$); IR spectrum: 3390–3350, 3090, 3050, 1745, 1660, 1200, 1110, 1055, 925, 890, 880 $cm^{-1}$; NMR spectrum (in $d_6$-acetone): 1.26 (3 H, s), 3.82(1H), 4.90(1H), 5.07(1H), 5.58(1H). Mass spectrum: $M^+$302 (0.48); *m/e* 284 (0.28), 266 (0.52), 257 (0.14), 256 (0.24), 240 (0.47), 239 (0.43), 238 (0.24), 211 (0.38), 185 (1.00), 183 (0.39), 143 (0.43) and 133 (0.34). Elution with $CHCl_3$–EtOAc (85:15) gave 20-nor-3β, 10α, 13α, 15α - tetrahydroxy - ent - gibberell - 16 - en - 7,19 - dioic acid 7→15/19→10 dilactone (**5**), yield 108 mg, m.p. 267–269° (needles, from acetone–hexane) or 264–267° (prisms, from EtOAc–hexane); IR spectrum: 3570, 3430, 3085, 3060, 1765 < 1752, 1675, 1270, 1220, 1195, 1155, 1050, 910 $cm^{-1}$ (needles) or 3625, 3460, 3420, 3075, 1765 > 1755, 1280, 1220, 1150, 1045, 900 $cm^{-1}$ (prisms); NMR spectrum (in $d_5$-pyridine, both forms): 1.72 (3H, s), 3.16 and 3.62 (2H, AB-system, $J_{AB}$ = 9 Hz), 4.10 (1 H, half-width 6 Hz) 5.10 (1H), 5.40 (1 H, d, J = 1.2 Hz) and 5.78(1 H, d, J = 1.2 Hz). Mass spectrum (both forms): $M^+$346 (1.00); *m/e* 328 (0.03), 318 (0.04), 300 (0.10), 284 (0.06), 272 (0.07), 271 (0.07), 255 (0.11), 239 (0.07), 211 (0.06), 195 (0.18), 185 (0.07), 135 (0.07). CD-spectrum: $[\theta]_{227} - 4500°$. Further elution with $CHCl_3$–EtOAc (75:25) gave 20-nor-16,17ξ-epoxy-3β, 10α, 13α, 15α - tetrahydroxy - ent - gibberellan - 7,19 - dioic acid 7→15/19→10 dilactone (**8**), yield 14 mg, m.p. 223–227° (needles; washed with cold EtOAc); IR spectrum: 3570, 3525, 3490, 1765, 1740, 1702, 1240, 1232, 1218, 1205, 1150, 1060, 1030, 875 $cm^{-1}$; NMR spectrum (in $d_6$-pyridine): 1.62 (3H, s), 3.20 (2H, AB-system, $J_{AB}$ = 6 Hz), 3.40 and 3.78 (another AB-system, $J_{AB}$ = 7 Hz), 4.10 (1H) and 5.20(1H). Mass spectrum: $M^+$362 (0.51); *m/e* 344 (0.30), 334 (0.31), 326 (0.26), 316 (0.76), 299 (0.26), 298 (1.00), 288 (0.24), 269 (0.36), 262 (0.96), 251 (0.24), 245–241 (0.06–0.12), 227–225 (0.12–0.16), 200 (0.26), 180 (0.32), m* 309 (362→334). Finally, elution with $CHCl_3$–EtOAc (40:60 and 30:70) afforded 437 mg of starting $GA_1$(**2**).

*$GA_7$(**3**) and neutral manganese dioxide.* To a soln of **3** (140 mg) in 60 ml of abs acetone neutral $MnO_2$ (2.0 g) was added and the mixture was shaken for 200 hr at 20–22°. The supernatant was carefully decanted, the ppt washed with acetone (5 × 50 ml) and the combined actone solns were filtered through 3 g of silica gel. A solid residue obtained on evaporation (109 mg) was chromatographed on 10 g of silica gel pretreated with phosphate buffer (pH 6.7). Elution with benzene–$CHCl_3$ (20:80) gave 7,20-bisnor-3β, 10α - dihydroxy - ent - gibberell - 1,5,16 - trien - 19 - oic acid 19→10 lactone (**9**), yield 4 mg, m.p. 151–160° (washed with ether); IR spectrum: 3420, 3390–3250, 3090, 3065, 1748, 1665, 1210, 1060, 895 $cm^{-1}$; Mass spectrum: $M^+$284 (0.43), *m/e* 266 (0.35), 239 (0.43), 238 (1.00), 221 (0.19), 193 (0.56). Elution with $CHCl_3$–EtOAc (90:10) afforded 20-nor-3β, 10α, 15α - trihydroxy - ent - gibberell - 1,16 - dien - 7,19 - dioic acid 7→15/10→19 dilactone (**10**), yield 16 mg, m.p. 237-242° (needles, from EtOAc–hexane); IR spectrum: 3580, 3425, 3080, 3060, 1770, 1748 (sh), 1665, 1235, 1210, 1065, 895 $cm^{-1}$. NMR spectrum (in $d_5$-pyridine): 1.59 (3 H, s), 3.05 and 3.55 (2H, AB-system, $J_{AB}$ = 8 Hz), 4.26 (1H, d, J = 4 Hz), 4.85 (1H), 4.95 (1H), 5.45 (1H), 6.00 and 6.27 (2H, another AB-system with $J_{AB}$ = 9 Hz and additional splitting at 6.00 with J = 4 Hz). Mass spectrum: $M^+$328 (1.00), *m/e* 310 (0.11), 284 (0.14), 283 (0.09), 266 (0.05), 239 (0.09), 221 (0.06), 193 (0.04). Further elution with $CHCl_3$–EtOAc (80:20 and 75:25) gave 76 mg of starting **3**.

*Tetrahydrogibberellic acid* (**11**) *and neutral* $MnO_2$. To a soln of **11** (200 mg) in 100 ml abs acetone neutral $MnO_2$ (3.0 g) was added, the mixture was shaken for 200 hr at 20–22° and then worked up as described above. Chromatography on 10 g of silica gel (elution with 5% EtOAc in $CHCl_3$) afforded 7,20-bisnor-3β, 10α, 13α, 15α - tetrahydroxy - ent - gibberell - 5 - en - 19 - oic acid 19→10 lactone (**12**), yield 9 mg, m.p. 115–125° (amorphous powder pptd with hexane from EtOAc); IR spectrum: 3520, 3380–3270, 3060, 1755, 1675, 1215, 1150, 1060, 930 $cm^{-1}$. Mass spectrum: $M^+$304 (0.22), *m/e* 286 (0.03), 268 (0.04), 261 (1.00), 259 (0.07), 258 (0.11), 215 (0.07), 197 (0.31). Further elution with more polar $CHCl_3$–EtOAc mixtures gave only the starting acid (169 mg).

*Partial hydrogenation of triene* **2**. Triene **2** (100 mg) was dissolved in a mixture of pyridine (2 ml) and THF (20 ml) and hydrogenated over 5% Pd/$CaCO_3$ until the uptake of $H_2$ amounted to 10 ml (~ 1.3 moles $H_2$). After evaporation the crude product was dissolved in EtOAc and the organic layer was washed with dil HCl, then with conc $NaHCO_3$ and finally with water. The neutral fraction was chromatographed on 5 g of silica gel in a gradient system benzene–EtOAc to give diene **4** (5.5 mg), m.p. 205–211°, identical by its IR and mass spectra with the specimen obtained from **2**.

*Selective hydrogenation of dilactone* **6**. Dilactone **6** (200 mg) was dissolved in a mixture of pyridine (5 ml) and THF (200 ml) and hydrogenated over 5% Pd/$CaCO_3$ until the uptake of $H_2$ ceased (~ 2.1 moles $H_2$). The products of hydrogenation were worked up as described above and the neutral fraction was chromatographed on 10 g of silica gel. Elution with $CHCl_3$–EtOAc (80:20) gave dilactone **5**, yield 18 mg, m.p. 262–265°, identical by its IR and mass spectra with a specimen obtained from **2**.

*Trihydroxy acid* (**13**) *and its methyl ester* (**13a**). To a soln of $GA_3$(**1**) in 900 ml of abs acetone neutral $MnO_2$ (90 g, dried at 120° only) was added and the mixture was shaken for 200 hr at 20–22°. After filtration the ppt was carefully washed with acetone (5 l) and MeOH (1 l). Methanolic filtrate on evaporation afforded a solid foam (2.43 g) which was chromatographed on 120 g of silica gel pre-washed with water and methanol and dried at 120°. Gradient elution with $CHCl_3$–EtOAc afforded successively **7**, **6** and **1**. Further elution with EtOAc–MeOH (9:1 and 8:2) gave 20-nor-3β, 10α, 13α, 15α - tetrahydroxy - ent - gibberell - 1,16 - dien - 7,19 - dioic acid 19→10 dilactone (**13**), yield 760 mg, m.p. 145–160° (dec, amorphous powder pptd with ether from EtOAc); IR spectrum: 3600–3200, 3080, 3045, 1765, 1705, 1665, 1165, 1050, 900 $cm^{-1}$. Mass spectrum: $M^+$362 (0.02), *m/e* 344 (1.00), 316 (0.06), 300 (0.15), 299 (0.09), 298 (0.12), 282 (0.10), 271 (0.07), 255 (0.08), 155 (0.04) and 135 (0.09). On treatment with etheral diazomethane **13** gave **13a**-white amorphous powder, m.p. 118–130° (pptd with hexane from EtOAc); IR spectrum: 3600–3450, 3080, 3045, 1765, 1738, 1165, 1050, 905 $cm^{-1}$. NMR spectrum (in $d_6$-acetone): 1.20 (3 H, s), 2.80 and 3.15 (2H, AB-system, $J_{AB}$ = 9 Hz), 3.63 (3H, s), 4.22 (1H, d, J = 4 Hz), 4.38 (1H), 4.88 (1H), 5.25 (1H), 6.00 and 6.36 (2H, AB-system, $J_{AB}$ = 9 Hz: additional splitting at 6.00 with J = 4 Hz). Mass spectrum: $M^+$376 (0.005), *m/e* 358 (0.09), 344 (1.00), 326 (0.13), 300 (0.03), 298 (0.04), 282, 271, 255, 209, 155 and 135 (all below 0.1). Like dilactone **6** compounds **13** and **13a** give purple colouring with conc $H_2SO_4$.

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