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THE REACTION MECHANISM OF THE PEREZONE–PIPITZOL TRANSFORMATION†

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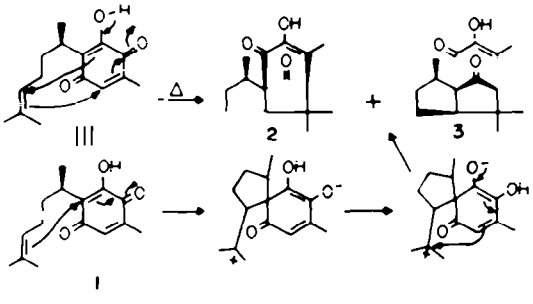
Abstract—Regioselective deuterium labeling of perezone (**1a**) allows to establish that its transformation into the mixture of pipitzols (**2a** and **3a**) takes place in a concerted process, as deduced from PMR measurements.

As a consequence of the structural elucidation[1] of α-(**2a**) and β-pipitzol[2] (**3a**), the structure of perezone was revised by us[1] and others[4-6] and two reaction mechanisms were postulated to account for the thermal transformation of the quinonoid natural product **1a** into a mixture of the also naturally occurring[7] cedranolides **2a** and **3a**. Both sequences are summarized on Scheme 1, where it can be seen that either a concerted reaction[1] or a stepwise process[6] can be invoked for the overall transformation.

The distinction of these two reaction paths should be possible if one is able to label unambiguously one of the two methyl groups of the isopropenyl moiety on the side chain of perezone (**1a**) and recognize the labeled positions in the reaction products **2a** and **3a**, since the stepwise process will lead to partial labelling on each methyl group of the *gem*-dimethyl due to racemization at the intermediate carbocation, while the concerted reaction will lead to stereospecific labeling in α-(**2a**) and β-pipitzol (**3a**). This paper provides experimental evidence that demonstrates that the stepwise mechanism does not operate.

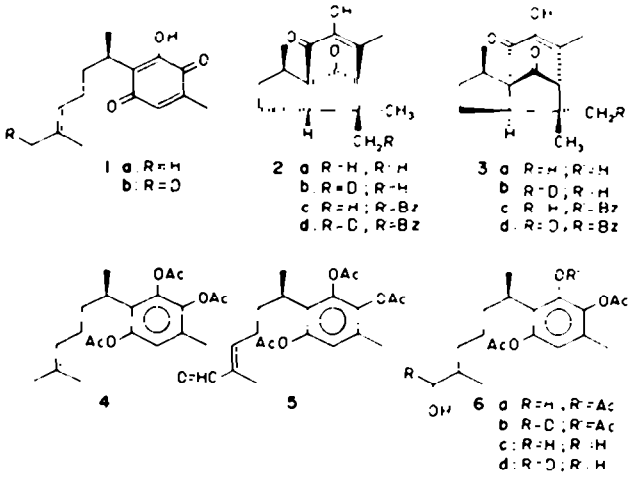


Scheme 1.

In order to test the reaction, a transformation of naturally occurring perezone (**1a**) into the regioselectively monodeuterated specie **1b** was undertaken according to the following series of reactions.

Treatment of perezone (**1a**) with acetic anhydride-sodium acetate in the presence[8] of zinc shot afforded the oily leucotriacetyl derivative **4**, which showed IR ester absorption at 1770 cm^{-1}. Its PMR spectrum shows the aromatic proton singlet at 6.76 ppm, the side chain vinillic proton as a triplet with additional long range couplings centered at 5.01 ppm, the three acetyl methyls at 2.23 ppm the aromatic methyl at 2.10 ppm, the vinillic methyls as broad singlets at 1.65 and 1.53 ppm and a doublet (J 7 Hz) centered at 1.18 ppm due to the secondary methyl group.

The protection of the quinonoid ring allows now an oxidation on the side chain in order to functionalize one of the vinillic methyl groups. This was indeed achieved by selenium dioxide treatment[9] of **4**, affording a mixture of the aldehyde **5** and the alcohol **6a**, which were separated by careful column chromatography on silica gel.



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Compound **5** showed in addition to the ester absorption at 1772 cm $^{-1}$, bands corresponding to an α,β-unsaturated aldehyde with the carbonyl at 1682 cm $^{-1}$ and combined double bond absorptions at 1640 cm $^{-1}$. The PMR spectrum differs from that of leucotriacetylperezone (**6**) in the presence of the aldehyde singlet at 9.28 ppm, a shift of the vinillic proton to 6.35 ppm and the presence of only one vinillic methyl signal at 1.66 ppm. For compound **6a** the IR spectrum shows hydroxyl absorption at 3500 cm $^{-1}$ in addition to the ester carbonyls at 1770 cm $^{-1}$ and in the PMR spectrum the vinillic proton appears at 5.26 ppm, one vinillic methyl is present at 1.55 ppm and a singlet (2H) at 3.88 ppm is attributed to the primary alcohol methylene group.

The NMR spectra of **5** and **6a** allow also establishment of the stereochemistry around the double bond since in compounds with similar geometry[10-12] the *trans*-aldehydes, as in the present case, appear near 9.3 ppm while *cis*-aldehydes are found in the 10.1 ppm region. This is additionally supported by the chemical shift of the primary alcohol methylene group, since *trans* signals have been described[10] around 3.9 ppm while *cis* signals appear near 4.1 ppm. Obviously reduction of the aldehyde **5** afforded the alcohol **6a** as described later (*vide infra*).

Elimination of the alcohol group in compound **6a** allowed the regeneration of perezone. After testing several classic procedures, it was found that this transformation could be done using[13] freshly prepared pyridine-sulfur trioxide complex, followed by lithium aluminium hydride reduction and air reoxidation of the intermediate triphenol. The sample isolated from this reaction was identical in all respects with the starting natural product **1a**.

Treatment of the aldehyde **5** with sodium borohydride in methanol afforded a mixture of two compounds which were separated by column chromatography on silica gel. The less polar compound is the alcohol **6a** as demonstrated by direct comparison with a sample obtained from the selenium dioxide treatment of leucotriacetylperezone (**4**). The more polar compound showed IR absorptions due to hydroxyl at 3585 and 3300 cm $^{-1}$, ester carbonyl band at 1770 cm $^{-1}$ and double bond absorptions at 1628 and 1585 cm $^{-1}$. Structure **6c** was assigned to the compound since in the PMR spectrum broad signals at 7.00 and 2.53 ppm corresponding to one proton each disappeared with deuterium oxide, only two acetate methyl signals are present at 2.23 and 2.20 ppm and the aromatic proton is found at 6.33 ppm instead at 6.78 ppm as in compound **6a**. The chemical shift difference of the aromatic proton on going from **6a** to **6c** is in good agreement for the substitution of an acetate group for a free hydroxyl at the *para* position, as deduced from published data,[14] indicating that this change causes shifts of 0.27, 0.13 and 0.42 ppm respectively for an aromatic proton localized at the *ortho*, *meta* or *para* position.

Compound **6c**, when treated with pyridine-sulfur trioxide followed by lithium aluminium hydride reduction and air reoxidation, also afforded a sample identical to natural perezone (**1a**).

Once it has been demonstrated, that perezone (**1a**) can be functionalized at one of the vinillic methyl groups of the side chain and reconverted back into the natural product, the introduction of a deuterium atom in a regioselective way is possible. This was achieved by sodium borodeuteride reduction of the aldehyde **5** to a mixture of the triacetate **6b** and the diacetate **6d**. These compounds were separated by chromatography and the labeled position tested by PMR, since their spectra are identical to the nondeuterated species **6a** and **6c** except for the primary methylene signals which are broader in the deuterated molecules due to a two bond proton-deuterium coupling and integrate for only one hydrogen. Both **6b** and **6d** were treated with pyridine–sulfurtrioxide complex, the intermediate salts reduced with lithium aluminium hydride and the triphenols air reoxidized to afford samples of monodeuteroperezone (**1b**).

The specificity of the labeling is seen by comparison of the 60 MHz PMR spectra of compounds **1a** and **1b** depicted in Fig. 1. The lower field vinillic methyl signal at

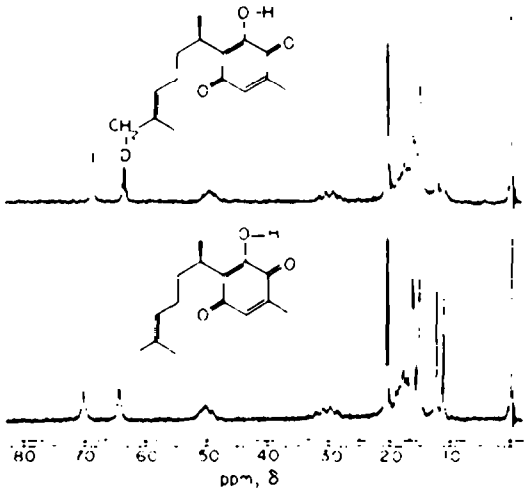

Fig. 1. The 60 MHz PMR spectra of perezone (**1a**) and monodeuteroperezone (**1b**).

1.63 ppm in **1b** contains all the deuterium while the other methyl at 1.52 ppm is unchanged, allowing also the assignment of this signals to the individual methyl groups.

The thermal transformation of perezone (**1a**) into the mixture of pipitzols (**2a** and **3a**) has been performed classically[7] by refluxing the quinone in either ethyleneglycol or tetralin for 3 h. We have found that the reaction occurs with better yields and in a cleaner way, using cumene as the solvent and refluxing for 20 h. Under these conditions monodeuteroperezone (**1b**) was converted with a 70% yield of isolated material into a mixture of the monodeuteropipitzols (**2b** and **3b**). The position for the dueterium atoms in **2b** and **3b** was inferred from a comparison of its PMR spectrum with that of a mixture of α-(**2a**) and β-pipitzol (**3a**) since the quaternary methyl signals have different shapes in these two spectra. Unambiguous assignment of each methyl singlet in each of the pipitzols is deduced from the shifts induced by benzoylation. In α-pipitzol (**2a**) the quaternary methyl signals are found[7] at 1.04 and 1.07 ppm, while in the benzoate (**2c**) they appear at 1.08 and 1.23 ppm, obviously that at lower fields corresponding to the methyl group nearer the benzoate introduced on the three carbon bridge. Similar situations arise when the signals of β-pipitzol (**3a**) found as one six proton singlet at 1.07 are compared with those of β-pipitzol benzoate (**3c**), which appear at 1.12 and 1.19 ppm. Therefore, in order to obtain a more objective test, the mixture of the deuterated pipitzols (**2b** and **3b**) was benzoylated and the

resulting mixture of the benzoates (**2d** and **3d**) were compared with a mixture of **2c** and **3c** and with individual compounds in the PMR spectrometer.

The comparison of the benzoates is shown in Fig. 2 in which the upper two spectra correspond to pure samples of pipitzol benzoates that show for α-pipitzol benzoate (**2c**) the two quaternary methyl singlets at chemical shifts between the *gem*-dimethyl signals of β-pipitzol benzoate (**3c**) as can additionally be judged in the lowest trace of Fig. 2, which corresponds to a mixture slightly enriched in β-pipitzol benzoate (**3c**). These comparisons show which high field singlets correspond to each isomer and the spectrum of the deuterated molecules (**2d** and **3d**) also included in Fig. 2, thus demonstrates that one methyl from each compound contains the deuterium label. Although the normal 60 MHz plots of Fig. 2 provide an idea of the stereochemical purity of the products **2d** and **3d**, this is much easier seen in Fig. 3, corresponding to the high field portions of 100 MHz spectra.

Therefore the transformation of perezone (**1a**) into the mixture of α-(**2a**) and β-pipitzol (**3a**) should be rationalized in terms of the concerted path. Due to the conservation of orbital symmetry, it appears logical to consider that this unique transformation is the coexistence of a sigmatropic change of order [1,9] and a class B cycloaddition.[15] A further point to comment upon, is that in this reaction, there is a lack of stereochemical induction by the already present chiral center of perezone (**1**), since as far as PMR measurements can tell, both pipitzols (**2** and **3**) are obtained in equimolecular amounts.

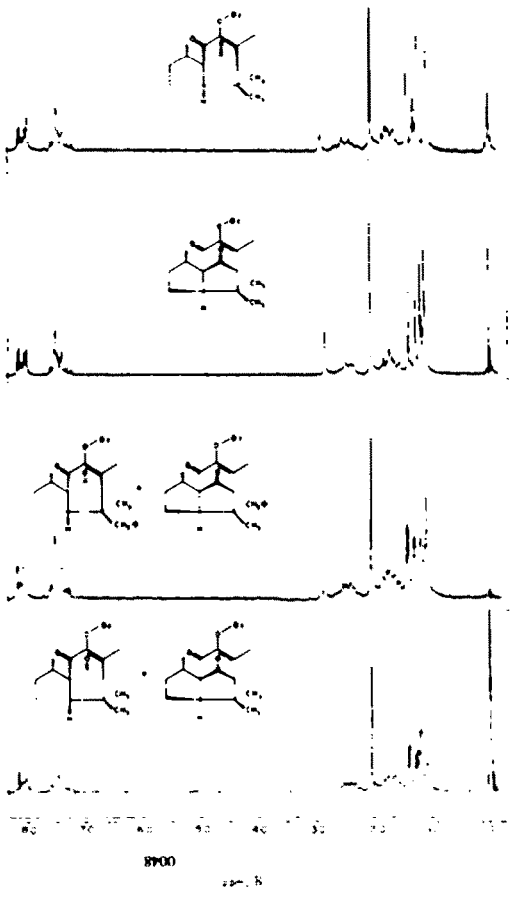

Fig. 2. The 60 MHz PMR spectra of α-pipitzol benzoate (**2c**), β-pipitzol benzoate (**3c**), a mixture of α-(**2d**) and β-monodeuteropipitzol benzoate (**3d**) and a mixture of **2c** and **3c** (top to bottom).

EXPERIMENTAL

M.ps and b.ps are uncorrected. IR spectra in $CHCl_3$ on Perkin Elmer 421 and UV spectra in 95% EtOH on Unicam SP-800. PMR spectra in $CDCl_3$ or CCl_4 with internal TMS on Varian Associates A-60 and XL-100A-12 in the CW mode using 5 mm tubes and deuterium pulse lock.

Leucotriacetyl perezone (**4**). A solution of 50 g of perezone (**1a**) in acetic anhydride was treated by known procedures[16] to yield 50 g of leucotriacetyl perezone (**4**) as a colorless oil b.p. 145–150°/~0.15 Torr. It showed IR bands at 1770 (enol ester) and

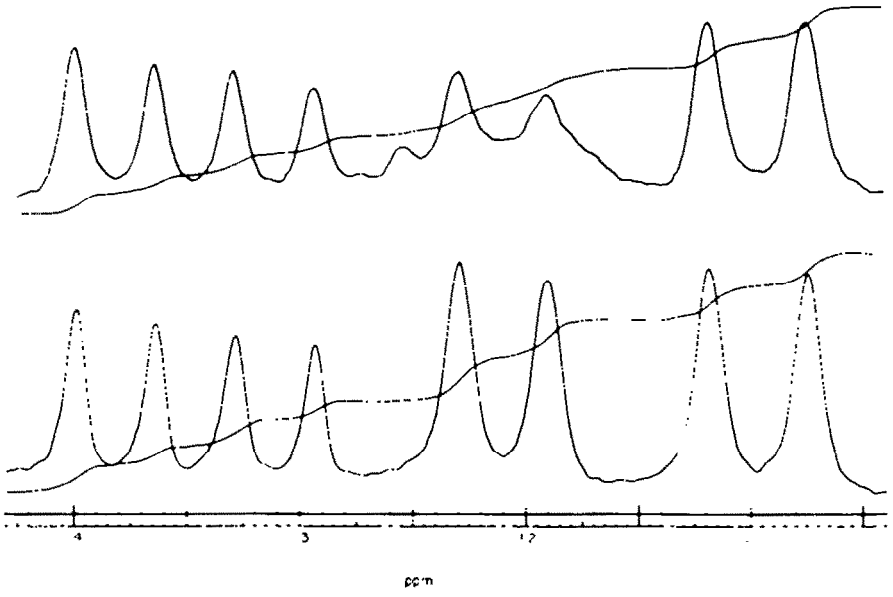

Fig. 3. High field regions of the 100.1 MHz PMR spectra of pipitzol benzoates. Top trace corresponds to **2d** and **3d** while bottom spectrum is from **2c** and **3c**.

1630 cm^{-1} (C=C) and λ_{max} 222, 266 and 270 nm; ϵ, 600, 7400 and 7100.

Selenium dioxide oxydation of **4**. A vigorously stirred solution of 10 g of **4** in 20 ml of ethanol was treated at 60° slowly with a solution of 5.5 g of selenium dioxide in 45 ml of methanol until the addition was completed (15 min). The mixture was refluxed during 50 min and filtered hot over a celite bed. The filtrate was placed directly in a solution of 11 g of thiourea[17] in 100 ml of 10% hydrochloric acid. The red precipitate that formed was removed over the same celite filter which was then washed with ethyl acetate. The organic solution was diluted with additional ethyl acetate and washed with dil hydrochloric acid, water, aq. sodium bicarbonate and water again, dried over anhydrous sodium sulfate and evaporated to dryness. The residue was chromatographed over 700 g of silica gel eluting with benzene first and then with chloroform–ethanol 9:1 yielding 3.9 g of the aldehyde **5** and 3.1 g of the alcohol **6a** both as oily materials.

The aldehyde **5** showed λ_{max} 230, 265 and 270 nm; ϵ, 12,500, 1200 and 1000; IR bands at 1772 (esters), 1682 (α,β-unsaturated aldehyde) and 1640 cm^{-1} (C=C); PMR: 9.28 (aldehyde), 6.78 (aromatic proton), 6.35 (t, vinillic proton), 2.83 (methine proton), 2.25 (three acetyl methyls), 2.11 (aromatic methyl), 1.83 (broad, two methylene groups), 1.66 (vinillic methyl) and 1.23 ppm (d, secondary methyl).

The alcohol **6a** showed IR bands at 3500 (hydroxyl), 1770 (esters) and 1665 and 1625 cm^{-1} (C=C); PMR: 6.78 (aromatic proton), 5.26 (t, vinillic proton), 3.88 (primary alcohol methylene), 2.86 (methine proton), 2.28 (three acetyl methyls), 2.11 (aromatic methyl), 1.75 (broad, two methylene groups), 1.55 (vinillic methyl) and 1.19 ppm (d, secondary methyl).

Reduction of **5**. A solution of 5 g of **5** in 40 ml of methanol in an ice bath was treated slowly with 0.3 g of sodium borhydride and stirred in the cold for 3 h. The reaction mixture was dropped over cold 10% hydrochloric acid and extracted with ethyl acetate. The organic layer was washed several times with saturated sodium chloride solution, dried over anhydrous sodium sulfate, filtered and evaporated to dryness, yielding 4.6 g of a pale yellow oil. This was chromatographed over 300 g of silica gel yielding in the fractions eluted with chloroform and with chloroform–ethanol 9:1 a colorless oil that showed two spots on TLC after development with iodine. This material was chromatographed again over 300 g of silica gel eluting with a mixture of chloroform–ethanol 98:2. The first usable fractions yield 3.73 g of the triacetate **6a** which was identified by standard procedures with a sample obtained in the selenium dioxide treatment of **4**. The last fractions from the chromatography yielded 0.23 g of the diacetate **6c** which showed IR bands at 3585 and 3300 (hydroxyls), 1770 (esters) and 1628 and 1585 cm^{-1} (C=C); PMR: 7.00 (phenol hydroxyl), 6.33 (aromatic proton), 5.28 (t, vinillic proton), 3.86 (primary methylene alcohol), 2.96 (methine proton), 2.53 (primary hydroxyl), 2.23 and 2.20 (two acetyl methyls), 2.0 (aromatic methyl), 1.85 (broad, two methylene groups), 1.51 (vinillic methyl) and 1.21 ppm (d, secondary methyl).

Sodium borodeuteride reduction of **5**. The reaction was carried out exactly under the above conditions, yielding samples of **6b** and **6d** whose identity were established by comparison of their PMR spectra with those of **6a** and **6c**.

Deuteroperezone (**1b**). A solution of 6 g of **6b** in 100 ml of anhydrous ether was treated with 10 g of pyridine–sulfur trioxide complex according to published instructions and then reduced with lithium aluminium hydride.[11] The reaction mixture was treated with aq. acetic acid and extracted with ethyl acetate. The organic layer was washed several times with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. The residue was chromatographed over 100 g of silica gel and the crystalline fractions eluted with benzene were combined and recrystallized from ether–hexane to yield 1.1 g of monodeuteroperezone (**1b**) which were characterized by mixed m.p. (100–102°) with an authentic sample of perezone (**1a**) and by the PMR spectra shown in Fig. 1.

α-(2b) and β-deuteropipitzol (**3b**). A solution of 0.5 g of deuteroperezone (**1b**) in 20 ml of cumene was refluxed during 20 h. The solvent was removed under vacuum and the residue recrystallized several times from acetone–hexane to yield 0.35 g of white crystals m.p. 138–140° which showed no depression with a mixture[7] of **2a** and **3a**.

α-(2d) and β-deuteropipitzolbenzoate (**3d**). The reaction of 0.2 g of the mixture of **2b** and **3b** was carried out as usual,[7] yielding 0.2 g of a mixture of **2d** and **3d** which were compared with a mixture and with individual constituents (**2c** and **3c**) as shown in Fig. 2.

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