positions of **4b**. Even larger values of J_{para} for coupled fluorines have been reported.[13] Both NMR spectra and analytical HPLC established that the samples of **2a**, **3b**, and **4b** were free of cross-contamination.

Since the electrolysis was run at a controlled potential near the $E_{1/2}^{ox}$ of **1**,[14] it is unlikely that dications were formed. The pathway for the formation of **4b** more likely consists of the formation of radical cations from **2b** and/or **3b** and subsequent trapping by $H_2F_3^-$ near the controlled potential used. The marked preference for the formation **3b** relative to **2b** may be partially due to steric hindrance to the attack of the fluoride complex at C-12, since simple Huckel calculations indicate only a slight preference for the radical cation at C-7 relative to C-12.

Notably, **4b** is unstable to room light in CH_2Cl_2 but not in cyclohexane. Benz[*a*]anthracene 7,12-dione, **1**, **2b**, and **3b** were not detected among the products. Tumor studies, currently in progress, have been designed to evaluate the activity of **1** when fluoride and/or methyl are substituted at positions 7 and/or 12. Both 7-fluoro-12-methyl- and 7-methyl-12-fluorobenz[*a*]anthracene[15] are included in these studies.

Experimental Section

Methods. Melting points were determined on a Thomas-Hoover apparatus in capillary tubes and are corrected. NMR spectra were measured with a JEOL FX-100 spectrometer in $CDCl_3$ solvent. Mass spectra were obtained with a Finnigan 1015 mass spectrometer operated in the CI mode ($NO-N_2$). Analytical and preparative HPLC were done on a Waters Associates Model M6000 pump, and compounds were detected in the column effluent by absorbance (254 nm) and refractive index change. Synthesis of **3a** was as described [mp 138.0–138.5 °C (lit.[16] mp 139.6–140.0 °C)].

Anodic Fluorination. The electrolyses were conducted in a 300-mL resin flask with platinum electrodes. The Ag/Ag^+ (0.01 M) reference electrode was made from polyethylene tubing with a porous Vycor plug and was placed as close to the anode as possible. Current was supplied by a modified Lingane-Jones potentiostat[17] constructed in the Boston College Electronics Shop. Acetonitrile was obtained from Burdick and Jackson and $(C_4H_9)_4NF\cdot 2HF$ from Ozark Mahoniny. The solvent was introduced through a column of alumina. Additions of the salt and benz[*a*]anthracene (Aldrich) were made in a drybox. Argon was passed through the cell during the electrolysis. The current at the start was approximately 500 mA, and the electrolysis was stopped when it had fallen to 10 mA. In a typical run, 1.10 g of **1** was dissolved in 200 mL of 0.5 M solution of the electrolyte and was electrolyzed at 1.1 Vs. Ag/Ag^+ (0.01 M) for 3.75 h. After evaporation of the solvent, the residue was washed with water to remove the salt.

Chromatographic Isolation. In a typical experiment, 1.2 g of crude fluorination product was applied to the top of a Florisil column (2 × 23 cm, 100–200 mesh, Fisher) packed in CH_2Cl_2. Elution with 120 mL of CH_2Cl_2 removed all of the unreacted **1** and the fluorinated derivatives of **1** from the column (730 mg). A gradient of acetone in hexane up to pure acetone eluted first an unidentified red band (34 mg) followed by a yellow band (315 mg). A combination of analytical techniques, including mixture melting point, identified this material as benz[*a*]anthracene-7,12-dione (Aldrich). The benz[*a*]anthracene fraction was further separated by HPLC on a Whatman Magnum-9 Partisil column eluted with 1% CH_2Cl_2 in cyclohexane (11 mL/min, 230 psi). Each injection consisted of 70 mg of the mixture in 10 mL of mobile phase to provide 140 mg of **1**, 42 mg of **4b**, and 472 mg of the mixture of **2b** and **3b**. The very small α value (~1.12) for the latter two compounds required subsequent chromatography for their separation. The same column was used, but the solvent was changed to hexane (10 mL/min). Samples of 85 mg of the mixture were injected onto the column in 5 mL of hexane. A combination of selective peak shavings during four recycles allowed a 90% recovery of the pure components: **2b** (39 mg) and **3b** (386 mg). Properties of the three fluoro compounds are given in Table I.

Acknowledgment. We are grateful to Dr. H. J. C. Yeh of the NIH for determining the NMR spectra and to Professor M. S. Newman of the Ohio State University for a sample of **2a** which was synthesized as previously described.[18] We also thank Dr. J. M. Sayer of the NIH for examining the photostability of **4b**.

Registry No. **1**, 56-55-3; **2b**, 77450-63-6; **3b**, 23683-26-3; **4b**, 77450-64-7.

(13) Emsley, J. W.; Phillips, L.; Wray, V. "Fluorine Coupling Constants"; Pergamon Press: New York, 1977; pp 511–567.
(14) Peover, M. E.; White, B. S. *J. Electroanal. Chem.* **1967**, *13*, 93.
(15) Newman, M. S.; Khanna, J. M. *J. Org. Chem.* **1979**, *44*, 866.
(16) Wood, J. L.; Fieser, L. F. *J. Am. Chem. Soc.* **1940**, *62*, 2674.
(17) Lingane, J. J.; Jones, S. L. *Anal. Chem.* **1950**, *22*, 1169.
(18) Newman, M. S.; Khanna, J. M.; Lilje, K. C. *Org. Prep. Proced. Int.* **1979**, *11*, 271.

A Reaction Mechanism Change in the Lewis Acid Catalyzed Perezone-Pipitzol Transformation

I. H. Sánchez, R. Yáñez, and R. Enríquez

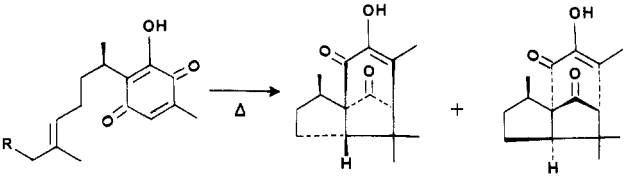
Departamento de Química Orgánica, Division de Estudios de Postgrado, Facultad de Química, Universidad Nacional Autónoma de México, Ciudad Universitaria 20, D.F., Mexico

P. Joseph-Nathan*

Departamento de Química del Centro de Investigación y de Estudios Avanzados, Instituto Politécnico Nacional, P.O. Box 14-740, México 14, D.F., Mexico

Received February 10, 1981

Although perezone (**1a**) has been known[1] since 1852, its transformation into pipitzols (**2** and **3**) was first performed almost a century ago[2] and recognized as an irreversible rearrangement[3] in 1913; it was not until 1965 that the structure of the starting sesquiterpenic benzoquinone[4] (**1a**) and those of the thermal rearrangement cedranolides[5] (**2** and **3**) were established. The chirality of perezone (**1a**) has been known[6] since 1954, while that of the pipitzols (**2** and **3**) was rigorously proven very recently.[7] The remarkable thermolysis **1** → **2** + **3** was postulated[4a,8] and

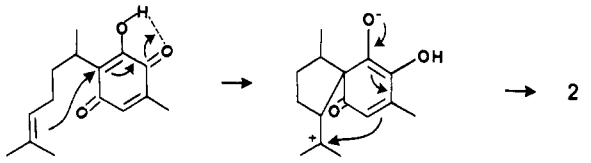


1 a: R = H; b: R = D **2** **3**

(1) L. Río de la Loza, "Disertación presentada a la Academia de Medicina", Mexico 1852.
(2) R. Anchütz and W. Leather, *Chem. Ber.*, **18**, 715 (1885).
(3) F. G. P. Remfry, *J. Chem. Soc.*, **103**, 1076 (1913).
(4) (a) F. Walls, J. Padilla, P. Joseph-Nathan, M. Salmón, and J. Romo, *Bol. Inst. Quim. Univ. Nac. Auton. Mex.*, **17**, 3 (1965); (b) D. A. Archer and R. H. Thomson, *Chem. Commun.*, 354 (1965); (c) R. B. Bates, S. K. Paknikar, and V. P. Talacher, *Chem. Ind.*, 1793 (1965); (d) E. R. Wagner, R. D. Moss, R. M. Brooker, J. P. Heeschen, W. J. Potts, and M. L. Dilling, *Tetrahedron Lett.*, 4233 (1965).
(5) F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, and J. Romo, *Tetrahedron Lett.*, 1577 (1965); F. Walls, J. Padilla, P. Joseph-Nathan, F. Giral, M. Escobar, and J. Romo, *Tetrahedron*, **22**, 2387 (1966).
(6) D. Arigoni and O. Jeger, *Helv. Chim. Acta*, **37**, 881 (1954).
(7) P. Joseph-Nathan, L. U. Román, J. D. Hernández, Z. Taira, and W. H. Watson, *Tetrahedron*, **36**, 731 (1980).

0022-3263/81/1946-2818$01.25/0

Scheme I

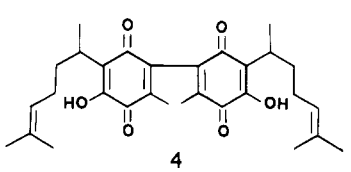


then shown[9] to be a concerted $[_\pi 4_s + _\pi 2_s]$ cycloaddition.[10] It was also noted that there is a lack of stereochemical induction by the already present chiral center of perezone (**1a**), since both α- (**2**) and β-pipitzol (**3**) are obtained in equal molar amounts, the best yield for the transformation being 70% after reflux in cumene for 20 h.

During the mechanistic study[7] of the thermolysis, an alternate[4d] stepwise path (Scheme I) was eliminated. However, if one could induce the transformation of perezone (**1a**) under mild reaction conditions by the latter mechanism, a highly stereoselective reaction should occur, since the attack of the π electrons of the double bond from the side chain is α to a chiral center. To favor such a Michael-type addition, it is necessary to polarize the quinonoid carbonyl group that is vicinal to the enol of perezone (**1**) with a suitable Lewis acid that does not contain metal atoms in order to avoid the formation of stable chelates.

When perezone (**1a**) is treated at 0 °C with 8 equiv of boron trifluoride during 30 min, it is transformed, through a highly stereoselective process, into a mixture containing 90% α-pipitzol (**2**) and 10% β-pipitzol (**3**), in 98% overall yield of isolated material. The isomerization follows the stepwise reaction mechanism since when perezone (**1b**) is used, regioselectively[11] deuterated at one of the isopropylidene methyl groups, one obtains α-pipitzol (**2**) in which the deuterium is scrambled over the two methyl groups of the *gem*-dimethyl, as was clearly seen in the 90-MHz ^{1}H NMR spectrum. The spectrum was identical with that of unlabeled pipitzols, except for the two singlets at 1.03 and 1.08 ppm, which showed the expected deuterium incorporation.

When the reaction is performed in the presence of only 0.1 equiv of BF_3, 29% of the pipitzols and 30% diperezone (**4**) were obtained. As the amount of BF_3 is increased, the



4

yield of the pipitzols increases, the pertinent data being in the experimental section. The dimer was identical, by TLC and comparison of ^{1}H and ^{13}C NMR spectra, with a sample of **4** that we have isolated very recently from the roots of *Perezia alamani* var *oolepis*.

The change in stereoselectivity for the cyclization maybe attributed to asymmetric induction at a lower reaction temperature in a process leading to a relatively stable intermediate. Since the predominant reaction product, α-pipitzol (**2**), has the same chirality as many naturally occurring cedranolides,[12] this transformation may open new avenues for biomimetic syntheses of natural products, some of them already being inspired[13] by the perezone–pipitzol transformation.

Table I

BF_3:1[a]	% pipitzols	% diperezone
0.1	29	30
0.4	32	27
0.8	37	20
1.2	65	13
4.0	76	9
8.0	98	-

[a] Molar ratio.

Experimental Section

^{1}H NMR spectra were measured with a Varian Associates EM-390 spectrometer at 90 MHz in $CDCl_3$ solutions containing tetramethylsilane as internal standard. Similar solutions were used to determine ^{13}C NMR spectra with a Varian Associates XL-100A-FT-16K system. Optical rotations, measured by using a Perkin-Elmer 141 M polarimeter, were performed at room temperature at 589 nm. Thin-layer chromatography was carried out with SiO_2 GF-254 (Merck).

Reactions of Perezone (1) with BF_3. Solutions containing 149 mg (0.6 mmol) of perezone (**1**) in anhydrous dichloromethane (10 mL) were cooled to 0 °C and treated with variable amounts (see Table I) of freshly distilled boron trifluoride etherate in dichloromethane (1 mL). After 30 min, the reaction mixtures were poured into ice–water and extracted with AcOEt. The organic layers were washed with diluted $NaHCO_3$ solutions and water, dried ($MgSO_4$), and evaporated under vacuum. The residues were separated by preparative thin-layer chromatography (SiO_2), using a mixture of hexane–benzene–chloroform–methanol (20:20:1:1). The yields of isolated products are given in Table I.

The isolated pipitzol mixture [R_f 0.53; $[\alpha]_D$ +174° (dioxane) (lit.[5] **2**, $[\alpha]_D$ +192°; **3**, $[\alpha]_D$ −172°)] was identical in all respects with an authentic mixture containing 90% **2** and 10% **3**.

Diperezone (**4**) showed R_f 0.41 and its identity was established by ^{1}H and ^{13}C NMR spectral comparison with an authentic sample.

Acknowledgment. We thank CoNaCyT (Mexico) for partial financial support.

Registry No. **1a**, 3600-95-1; **2**, 2211-20-3; **3**, 2211-21-4; **4**, 77416-47-8; BF_3, 7637-07-2.

(8) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry", Academic Press, New York, 1970, p 87.
(9) P. Joseph-Nathan, V. Mendoza, and E. García, *Tetrahedron*, **33**, 1573 (1977).
(10) I. Fleming, "Frontier Orbitals and Organic Chemical Reactions", Wiley, New York, 1976, p 92.
(11) P. Joseph-Nathan, G. Mejía, and D. Abramo-Bruno, *J. Am. Chem. Soc.*, **101**, 1289 (1979).
(12) G. Stork and R. Breslow, *J. Am. Chem. Soc.*, **75**, 3291 (1953); Pl. A. Plattner, A. Fürst, A. Eschenmoser, W. Keller, H. Klau, St. Meyer, and M. Rosner, *Helv. Chim. Acta*, **36**, 1845 (1953); Pl. Plattner, A. Fürst, St. Meyer and W. Keller, *ibid.*, **37**, 266 (1954); P. Yates and G. F. Field, *J. Am. Chem. Soc.*, **82**, 5764 (1960); B. Tomita, Y. Hirose and T. Nakatsuka, *Tetrahedron Lett.*, 843 (1968); K. H. Baggaley, H. Erdtman, and T. Norin, *Tetrahedron*, **24**, 3399 (1968); R. Kaiser and P. Naegeli, *Tetrahedron Lett.*, 2009 (1972); A. N. Singh, A. D. Upadhye, V. V. Mhasker, S. Dev, A. V. Pol, and V. G. Naik, *Tetrahedron*, **30**, 3689 (1974).
(13) G. Büchi and C.-P. Mak, *J. Am. Chem. Soc.*, **99**, 8073 (1977).

New Procedure for the Chlorination of Pyrimidine and Purine Nucleosides[1]

Eung K. Ryu and Malcolm MacCoss*

Division of Biological and Medical Research, Argonne National Laboratory, Argonne, Illinois 60439

Received January 13, 1981

The 5-halo-substituted pyrimidine nucleosides and 8-halo-substituted purine nucleosides have been shown to exhibit interesting chemotherapeutic, biochemical, and

(1) A preliminary account of this work has been presented: E. K. Ryu and M. MacCoss, Abstracts, 179th National Meeting of the American Chemical Society, Houston, TX, Mar 23–28, 1980, ORGN 011.

0022-3263/81/1946-2819$01.25/0