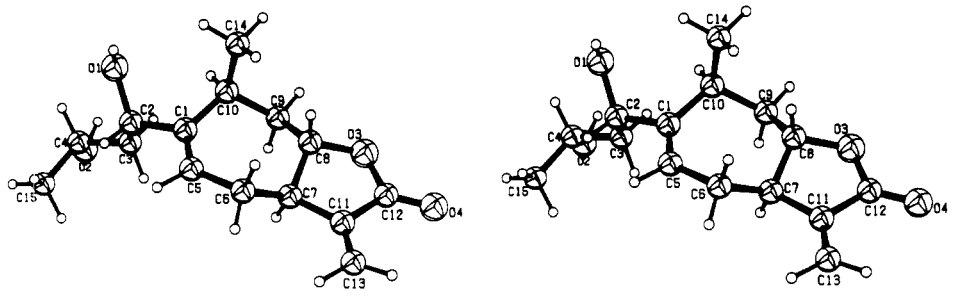
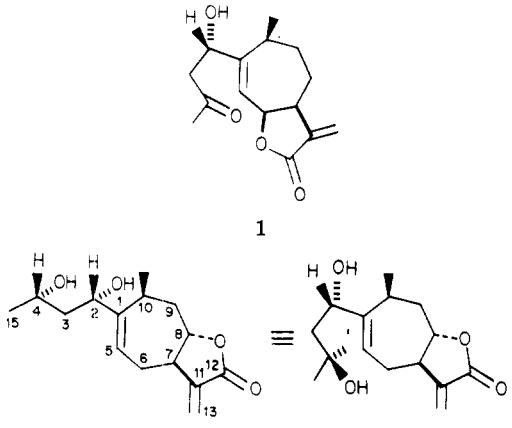


Figure 1. Stereoscopic view of ivalbin.

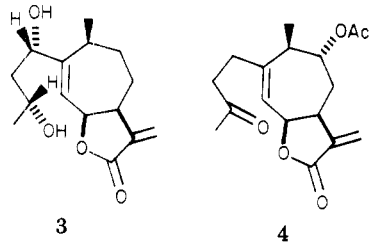
thus corresponds with the observed[7] (positive) Cotton effect (Beecham's generalization) as appears to be generally true for trans-fused lactones on six- or seven-membered rings. McPhail and Sim[10] have pointed out that because of the relative regidity of trans-fused lactone systems it would be expected that the chirality of the C=C—C=O chromophore would be determined by the position of the ring junction, whereas in the case of cis-fused lactones, such as parthemollin, the flexibility of the lactone ring allows no such generalization. They also noted that in both cis and trans lactones the signs of the C=C—C=O and C-(α)-C(β)-C(γ)-O torsion angles were paired. This is true for ivalbin where C(O(3))-C(8)-C(7)-C(11) is 30°; however, parthemollin[2b] and more recently alatolide,[11] a *trans,trans*-1(10),4,5-germacradienolide, constitute exceptions.

Since ^{13}C NMR spectra of xanthanolides have not been reported previously, we list in Table VII ^{13}C NMR spectra of ivalbin (2) parthemollin (1), ivambrin (3)[12] and ivalbatin acetate (4)[7] which will facilitate further work in this area.



1

2



3 4

Multiplets were assigned by single-frequency off-resonance decoupling. The observed chemical shift differences are self-explanatory except for the C-2 signal in **2** and **3** for which $\Delta\delta$, due primarily to the difference in stereochemistry at C-4, seems unusually large. The 10-ppm upfield shift of C-2 in ivambrin probably reflects a large rotamer population with steric interactions between substituents on C-2 and C-4 whereas, at least in the crystalline state of ivalbin (Figure 1), such interactions seem to be minimized.

Experimental Section

Single crystals of ivalbin were prepared by slow crystallization from methanol and were monoclinic, space group $P2_1$, with a = 7.271 (1) Å, b = 6.829 (1) Å, c = 14.739 (2) Å, β = 97.22 (1)° and d_{calcd} = 1.215 g cm^{-3} for z = 2 ($C_{15}H_{22}O_4$, M_r = 266.34). The intensity data were measured on a Hilger-Watts diffractometer (Ni filtered Cu Kα radiation, θ-2θ scans, pulse-height discrimination). The size of the crystal used for data collection was approximately 0.20 × 0.25 × 0.5 mm. A total of 1073 reflections were measured for θ < 57°, of which 1049 were considered to be observed [$I > 2.5\sigma(I)$]. The structure was solved by a multiple-solution procedure[13] and was refined by full-matrix least-squares methods. Seven reflections which were strongly affected by extinction were excluded from the final refinement and difference map. In the final refinement anisotropic thermal parameters were used for the heavier atoms, and isotropic temperature factors were used for the hydrogen atoms. The hydrogen atoms were included in the structure factor calculations, but their parameters were not refined. The final discrepancy indices are R = 0.033 and R_w = 0.045 for the remaining 1042 observed reflections. The final difference map had no peaks greater than ±0.2 e Å^{-3}.

Registry No. 1, 23264-32-6; 2, 7544-65-2; 3, 33204-43-2; 4, 37163-91-0.

Supplementary Material Available: Tables I–IV listing final atomic parameters, final thermal parameters, bond lengths, and bond angles of ivalbin (3 pages). Ordering information is given on any current masthead page.

(10) McPhail, A. T.; Sim, G. A. *Tetrahedron* **1973**, *29*, 1751.
(11) Cox, P. J.; Sim, G. *J. Chem. Soc., Perkin Trans. 2* **1977**, 255.
(12) Yoshioka, H.; Higo, A.; Mabry, T. J.; Herz, W.; Anderson, G. D. *Phytochemistry* **1971**, *10*, 401.
(13) Germain, G.; Main, P.; Woolfson, M. M. *Acta Crystallogr., Sect. A* **1971**, *27*, 368.

Chlorination and Deoxygenation in the Vilsmeier Reaction of 1-Hydroxypyrazoles and 1-Hydroxypyrazole 2-Oxides

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Pyrazole does not undergo formylation under the conditions of the Vilsmeier reaction, but various 1-substituted pyrazoles do react to give pyrazole-4-carboxaldehydes.[2,3] We wish to report the results of an investigation of the

(1) Visiting Research Professor, on leave from Hong-Ik University, Seoul, Korea.
(2) Mal'tseva, S. P.; Borodulina, Z. A.; Stepanov, B. I. *J. Org. Chem. USSR (Engl. Transl.)* **1973** *9*, 840.
(3) Schofield, K.; Grimmett, M. R.; Keene, B. R. T. "Heteroaromatic Nitrogen Compounds—The Azoles"; Cambridge University Press: Cambridge, England, 1976; p 31.

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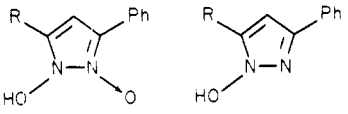
Vilsmeier reaction of some 1-hydroxypyrazole 2-oxides **1** and 1-hydroxypyrazoles **2**. These compounds react readily

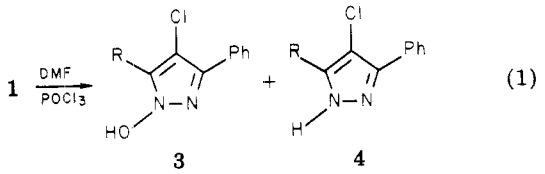


1 **2**

a, R = Ph; b, R = Me

with the Vilsmeier reagent, but instead of formylation, they undergo deoxygenation and chlorination to give 4-chloropyrazole derivatives.

Reaction of **1a** with the Vilsmeier reagent ($POCl_3$ and *N,N*-dimethylformamide (DMF)) proceeded readily around 0 °C to give two products identified as **3a** and **4a** (eq 1). The assignment of **3a** was based upon satisfactory

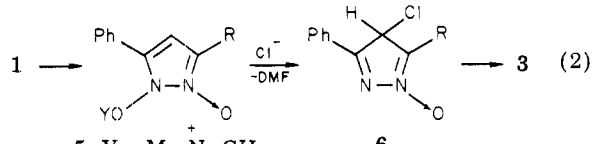


(1)

3 **4**

elemental analysis and spectral data, and the compound was also prepared by an alternate route from **2a** by reaction with *N*-chlorosuccinimide.[4] The identity of **4a** was established by comparison with an authentic sample prepared by chlorination of 3,5-diphenylpyrazole.[5] The corresponding products **3b** and **4b** were obtained from the reaction of **1b** and were characterized by similar alternate syntheses.

A likely mechanism for the conversion of **1** to **3** is suggested in eq 2. The formation of the *O*-formyl equivalent



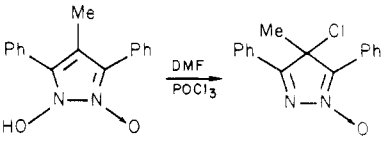
(2)

5, Y = $Me_2N{=}CH$
7, Y = MeCO

6

5 by attack of the Vilsmeier reagent at the hydroxyl group is proposed as the initial step in the mechanism. The N-O bonds in *O*-acyl[6] and *O*-alkyl[7] derivatives of 1-hydroxypyrazole 2-oxides are known to be quite labile, and the displacement of DMF from **5** to give **6** might involve a vinylogous substitution in a single step, or possibly a two-step process in which loss of DMF from **5** could give a cationic intermediate which is subsequently attacked by the chloride ion at C-4. The overall process would appear to be directly analogous to the rearrangement of 1-acetoxypyrazole 2-oxides to 4-acetoxy-4*H*-pyrazoles reported by Freeman.[6a] In support of this proposal, it was found that **1** was converted to **3** by reaction with acetyl chloride, a process which almost certainly involves the acetate **7**.

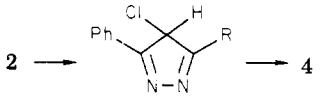
Careful workup of the reaction of **1b** led to isolation of a compound which, in fact, appears to be the intermediate **6b**. This compound was relatively stable when stored in the cold, but it rearranged over a few days in the solid state at room temperature, or more rapidly in solution, to give **3b**. The spectral characteristics of **6b** were consistent with the assigned structure. Furthermore, the analogous compound **9** could be obtained from the Vilsmeier reaction of **8** (eq 3), and **9** was readily identified by comparison with an authentic sample.[8]



(3)

8 **9**

The 1-hydroxypyrazoles **2** also reacted with the Vilsmeier reagent, although somewhat more vigorous conditions were required. The products in these reactions were the 4-chloropyrazoles **4**, presumably formed by an analogous mechanism through the intermediacy of **10** (eq 4).



(4)

10

Reaction of **3a** with an additional equivalent of the Vilsmeier reagent produced **4a**, a process which appears similar to the deoxygenation reported in the Vilsmeier reaction of 1-hydroxy-2-phenylindole,[9] thus explaining the origin of **4** as a byproduct in the reaction of **1**.

The Vilsmeier reaction of 1-hydroxypyrazole derivatives does not provide a route to the pyrazole-4-carboxaldehydes. The reaction which does occur provides an interesting example of nucleophilic substitution with rearrangement which seems to be rather common for N-oxygenated pyrazoles.

Experimental Section

Compounds **1** and **2** were prepared as previously described.[10] The *N,N*-dimethylformamide (DMF) was distilled under reduced pressure from NaH, and $POCl_3$ was distilled before use. Infrared spectra were recorded as Nujol mulls with a Perkin-Elmer 700 spectrophotometer, ^1H NMR spectra were run in $CDCl_3$ on a Perkin-Elmer R32, 90-MHz spectrometer with values reported as δ values relative to Me_4Si as an internal standard, and ultraviolet spectra were run in $CHCl_3$ with a Beckman ACTA MVI spectrophotometer. Melting points were determined with the Thomas-Hoover Uni-melt apparatus and are corrected. Elemental analyses were performed by Microanalysis, Inc., Wilmington, DE.

Vilsmeier Reaction of 1b. A solution of 3.21 g (21 mmol) of $POCl_3$ in 15 mL of DMF was cooled in ice–salt below 0 °C and stirred while 3.80 g (20 mmol) of **1b** was added in portions over 45 min. The solution was stirred below 0 °C for 60 min and was poured into 100 mL of iced 10% KOH. The mixture was extracted with two 50-mL portions of ether, and the ether solution was washed with saturated NaCl and evaporated without heating under vacuum. The residue was triturated with a few milliliters of cold 95% ethanol, and 0.72 g (16%) of yellow solid assigned as **6b** was collected by filtration. The product was recrystallized as yellow needles, mp 68–69 °C, from CH_2Cl_2–pentane without heating: IR 1515 cm^{-1}; UV 347 nm (log ϵ 3.17), 256 (4.34); ^1H NMR 7.87 (m, 2 H) and 7.48 (m, 3 H) (C_6H_5), 6.50 (s, 1 H, C-4 H), 2.04 (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.57; H, 4.35; N, 13.42; Cl, 16.99. Found: C, 58.02; H, 4.45; N, 12.94; Cl, 16.05.[11]

Evaporation of the ethanol filtrate from above and chromatography of the residue on alumina gave 0.38 g (10%) of **4b**, mp 110–12 °C, which was identical with an authentic sample.[5]

The basic aqueous solution was cooled in ice and acidified with acetic acid to give 1.71 g (41%) of **3b**, which gave white crystals

(4) A full report of these halogenation reactions is in preparation.
(5) Auwers, K. v.; Stuhlman, H. *Ber. Dtsch. Chem. Ges. B* **1926**, *59*, 1043.
(6) (a) Freeman, J. P.; Janiga, E. *J. Org. Chem.* **1974**, *39*, 2663. (b) Freeman, J. P.; Gannon, J. J. *Ibid.* **1969**, *34*, 194.
(7) Boyle, F. T.; Jones, R. A. Y. *J. Chem. Soc., Perkin Trans. 1* **1973**, 167.
(8) Freeman, J. P.; Janiga, E. R.; Lorenc, J. F. *J. Org. Chem.* **1977**, *42*, 3721.
(9) Nagoyoshi, T.; Saeki, S.; Hamana, M. *Heterocycles* **1977**, *6*, 1666.
(10) Hansen, J. F.; Vietti, D. E. *J. Org. Chem.* **1976**, *41*, 2871.
(11) More satisfactory analytical data were not obtained due to the instability of the compound. The significance of analytical data is questionable due to at least partial isomerism to **3b** before analysis could be performed.

from acetic acid: mp 161–62 °C; IR 2630 cm^{-1} (brd, OH); ^1H NMR 11.22 (brd s, 1 H, OH), 7.72 (m, 2 H) and 7.47 (m, 3 H) (C_6H_5), 2.10 (s, 3 H, CH_3).

Anal. Calcd for $C_{10}H_9N_2OCl$: C, 57.57; H, 4.35; N, 13.42; Cl, 16.99. Found: C, 57.84; H, 4.43; N, 13.26; Cl, 17.02.

Vilsmeier Reaction of 1a. Reaction of **1a** under the conditions above gave, from the ether extract, 27% of **4a**, mp 210–11 °C,[12] which was identical with a sample prepared by chlorination of 3,5-diphenylpyrazole with SO_2Cl_2.[5]

Neutralization of the basic aqueous solution gave 48% of **3a**: mp 191–93 °C (from acetic acid); IR 2650 cm^{-1} (brd, OH), ^1H NMR 8.50 (brd, 1 H, OH), 7.15–7.60 (m, 10 H, C_6H_5).

Anal. Calcd for $C_{15}H_{11}N_2OCl$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.67; H, 3.84; N, 10.28.

Vilsmeier Reaction of 2b. A solution of 1.7 g (11 mmol) of $POCl_3$ in 10 mL of DMF was cooled below 10 °C and treated with 1.74 g (10 mmol) of **2b**. The solution was stirred at room temperature for 150 min, poured into 100 mL of ice–water, and neutralized with $NaHCO_3$. The solid was collected, washed with water, and dried to give 1.49 g (77%) of **4b**.

Vilsmeier Reaction of 2a. Reaction using the same method as for **2b** gave 96% of **4a**.

4-Chloro-3,5-diphenyl-4-methyl-4*H*-pyrazole 1-Oxide (9). A solution of 0.85 g (5.5 mmol) of $POCl_3$ in 10 mL of DMF was cooled below 10 °C and treated in portions with 1.31 g (5 mmol) of **8**. After 60 min at 0–10 °C the solution was poured into 50 mL of ice–water and extracted with three 50-mL portions of ether. The ether solution was washed with saturated NaCl, dried (Na_2SO_4), and evaporated under reduced pressure without heating. The residue was crystallized from CH_2Cl_2 without heating to yield 0.41 g (29%) of **9**.[8]

Reaction of 1b with Acetyl Chloride. A mixture of 0.95 g (5 mmol) of **1b** in 25 mL of dry benzene was treated over 30 min with 0.4 g (5 mmol) of acetyl chloride in 5 mL of benzene. After 2 h at room temperature, the solution was washed with water, dried (Na_2SO_4), and evaporated. Recrystallization from ethanol gave 0.57 g (55%) of **3b**.

Acknowledgment. Y.I.K. wishes to acknowledge the support of Hong-Ik University and the Ministry of Education of the Republic of Korea during the course of this work.

Registry No. 1a, 59434-82-1; **1b**, 55026-66-9; **2a**, 59434-85-4; **2b**, 59434-84-3; **3a**, 71582-22-4; **3b**, 71549-27-4; **4a**, 71549-28-5; **4b**, 71549-29-6; **6b**, 71549-30-9; **8**, 17953-33-2; **9**, 61355-02-0; 3,5-diphenylpyrazole, 1145-01-3.

(12) A melting point of 179–80 °C for this compound has been reported: Grandberg, I. I.; Kost, A. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1961**, *31*, 3454.

1,2:6,7-Dibenzo-1,7-homotropylium Cation. Examination of Steric Effects Operating in Homoaromatic Overlap

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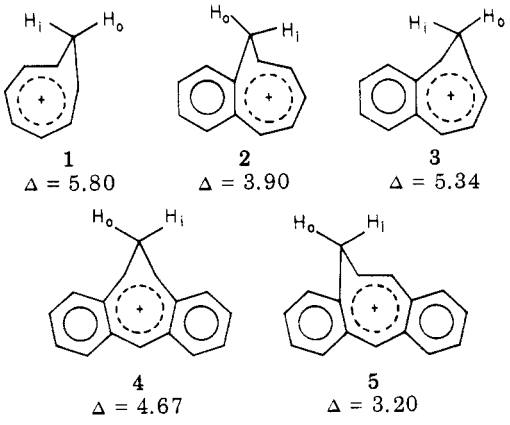
Monohomoaromatic systems include an sp^3-hybridized carbon inserted into a cyclic framework of $p\pi$ orbitals containing $4n + 2$ π electrons, with the result that the topology of the system is no longer planar.[1,2] The influence of benzene annelation on homoaromatic systems seems to be of interest. In order to achieve maximum overlap of the $p\pi$ orbitals in these systems, the benzene rings must tilt to enable homoaromatic delocalization and at the same time the aromatic delocalization in the benzene rings must also be maintained. This distortion and the requirement to share common π bonds between benzenoid and homoaromatic components may introduce difficulties in achieving homoaromatic overlap followed by a depression of the homoaromatic character.

Chart I



1 Δ = 5.80 2 Δ = 3.90 3 Δ = 5.34 4 Δ = 4.67 5 Δ = 3.20

The homotropylium cation (**1**) represents the most widely investigated system in this series.[3] The different environment of the protons attached to the sp^3-hybridized carbon bridge (H_i, H_o) in **1** results in a difference (Δ) of the chemical shifts of these two protons ($\Delta = \delta_{H_o} - \delta_{H_i}$).[1,2] Several mono- and dibenzannelated homotropylium cations (**2–5**) have been investigated in recent years.[4-7] In these cations, the comparison of the Δ values (ppm) of the bridgehead protons showed decreased values attributed to benzene annelation (Chart I). However, inspection of the magnetic characteristics of the benzannelated homoaromatic species **2–5** reveals two significant phenomena: (a) When benzene annelation is adjacent to the bridge, as in **2** and **5**, Δ is significantly decreased relative to Δ for **1**.[4,7] On the other hand, a remote benzene annelation with respect to the bridge, as in **3**[5] and **4**,[6] decreases the magnitude of Δ to a lesser extent relative to Δ for **1**. (b) In homotropylium cations where benzene annelation is remote with respect to the sp^3 bridge, the protons attached at the α position to the bridge show an upfield shift relative to the shift of the other peripheral protons (δ_{H_α} is 5.5 and 4.2 ppm in **3** and **4**, respectively). It therefore seems that the location of the benzannelation relative to the bridge rather than the extent of benzannelation influences the homoaromatic overlap.

Results and Discussion

To gain insight into the parameters operative in achieving homoaromatic overlap in benzannelated homotropylium species we studied the 1,2:6,7-dibenzo-1,7-homotropylium cation (**6**). This system includes a double ben-

(1) For general reviews see: (a) Winstein, S. *Chem. Soc., Spec. Publ.* **1967**, *No. 21*, 5. (b) Haywood-Farmer, J. *Chem. Rev.* **1974**, *74*, 315. (c) Story, P. R.; Clark, Jr., B. C. *Carbonium Ions* **1972**, *3*, 1007. (d) Paquette, L. A. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 106.

(2) (a) Haddon, R. C. *J. Am. Chem. Soc.* **1975**, *97*, 3608. *Tetrahedron Lett.* **1974**, 2797. (b) Goldstein, M. J. *J. Am. Chem. Soc.* **1967**, *89*, 6357. (c) Bischof, P.; Gleiter, R.; Heilbronner, E. *Helv. Chim. Acta* **1970**, *53*, 1425. (d) Hehre, W. J. *J. Am. Chem. Soc.* **1972**, *94*, 8908; **1973**, *95*, 5807; **1974**, *96*, 5207.

(3) v. Rosenberg, J. L.; Mahler, J. E.; Pettit, R. *J. Am. Chem. Soc.* **1962**, *84*, 2842.

(4) Merk, W.; Pettit, R. *J. Am. Chem. Soc.* **1968**, *90*, 814.

(5) Corver, H. A.; Childs, R. F. *J. Am. Chem. Soc.* **1972**, *94*, 6201.

(6) Childs, R. F.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 6348.

(7) Mattescu, G. D.; Nenitzescu, C. D.; Olah, G. A. *J. Am. Chem. Soc.* **1968**, *90*, 6235.

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