to charge removal from the pentadienyl unit, it ought to be reflected in a downfield shift of the protons of the double bond (H_6, H_7) relative to an appropriate model. Two possible models are cyclohexene[10] (vinyl protons at τ 4.41) and 1,4,7-cyclononatriene[11] (vinyl protons at τ 4.66). It is clear that H_6 and H_7 of II are both deshielded significantly relative to either model; we attribute this to charge delocalization onto C_6 and C_7. Thus, there can be little doubt that charge is dispersed onto the double bond from the pentadienyl unit to yield the 1,3-bishomotropylium ion, II, although the amount of charge transfer appears to be less than in the 1,4-bishomotropylium ions[1] (where charge is dispersed from an allyl moiety to a butadiene segment).

In light of the ring current which would be expected for II, it is interesting to examine the inner and outer methylene protons. These were differentiated on the basis of the larger $J_{1,8i}$ (J_{trans}) relative to $J_{1,8o}$ (J_{cis}).[12] Also, $J_{7,8i}$ is quite small. Examination of models indicates that the repulsion between H_{8i} and H_{9i} forces the methylene carbons apart, whereby a proper dihedral angle for the observed small coupling constant is achieved.[12,13] The methylene protons of 1,4,7-cyclononatriene appear to be an appropriate model for comparison with those of II.[14] As reported,[10] the chemical-shift difference between the methylene protons of the former is 1.50 ppm. Close scrutiny of the nmr pattern[14] reveals that the inner protons of 1,4,7-cyclononatriene are at lower field than the outer ones. As seen in Table I, this situation is reversed for II.[12] Therefore, the relatively small chemical-shift difference of 1.9 ppm between the inner and outer protons of II is not a true reflection of the size of the ring current in II; a $\Delta\delta$ of 3.4 ppm might give a more accurate picture.[12]

Of considerable interest, with regard to the protonation of I, is the stereochemistry of the process. Unlike cyclooctatetraene, which was found to stereoselectively (80%) deuterate on the endo side to give the monohomotropylium ion with the deuteron mostly inside,[15] I showed stereoselective (70%) deuterium incorporation on the exo side to yield II-d_1, with the deuterium atom mainly on the outside.[14] Obviously, the small change in energy (less than 1 kcal/mol) required to produce this switch in stereochemistry could come from subtle conformational factors.

Acknowledgment. We are grateful to Dr. D. L. Harris for help in obtaining the 100-MHz spectra, and for valuable discussions regarding their interpretation.

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[10] K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **83**, 1226 (1961).

[11] P. Radlick and S. Winstein, *ibid.*, **85**, 344 (1963).

[12] A referee has questioned the basis of our assignments of H_{8i} and H_{8o}, as well as our analysis of the chemical-shift difference between inner and outer methylene protons (particularly the use of 1,4,7-cyclononatriene as a model). While we feel that a full discussion should be reserved for a full paper, we give the following analysis. The C_8–C_9 distance in II (relative to the comparable distance in 1,4,7-cyclononatriene) is shortened by the flattening of the pentadienyl unit of II (as seen in models). When this distance is restored, the approximate dihedral angles obtained from either Dreiding or Framework molecular orbital models are $\angle 1{,}8i = 160°$, $\angle 1{,}8o = 20°$, $\angle 7{,}8i = 120°$, $\angle 7{,}8o = 0°$. While these angles cannot be precisely related to coupling constants, it is clear that the $\angle 7{,}8i$ is consistent with the small $J_{7,8i}$. Therefore, we cannot reconcile the data with a reversed assignment of the methylene hydrogens. Further, the models show that, in both 1,4,7-cyclononatriene and II, the inner methylene hydrogens are not in the shielding area above the double bonds. The geometry change incurred on going from 1,4,7-cyclononatriene to II does not seem to appreciably affect the position of the inner methylene hydrogens with respect to the double bonds. Lastly, the van der Waals deshielding effect on the inner methylene protons of II should be more severe than in 1,4,7-cyclononatriene. Therefore, our estimate of $\Delta\delta = 3.4$ ppm is, we feel, a lower limit.

[13] E. Garbisch, Jr., *J. Amer. Chem. Soc.*, **86**, 5561 (1964).

[14] From the analysis of a 60-MHz nmr spectrum, $|J_{\text{gem}}| = 12.5 \pm 0.5$ Hz, $J_{\text{trans}} = 9.0 \pm 0.5$ Hz, and $J_{\text{cis}} = 6.3 \pm 0.5$ Hz. The inner protons resonate at τ 6.32, while the outer ones appear at 7.82.

[15] S. Winstein, H. D. Kaesz, C. G. Kreiter, and E. C. Friedrich, *J. Amer. Chem. Soc.*, **87**, 3267 (1965).

[16] Address correspondence to this author at the Department of Chemistry, Yale University, New Haven, Conn. 06520.

[17] National Science Foundation Predoctoral Fellow, 1966–1970.

[18] Deceased Nov 23, 1969.

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Received August 28, 1970

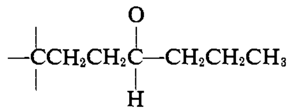
Oudenone, a Novel Tyrosine Hydroxylase Inhibitor from Microbial Origin

Sir:

In the course of the studies on enzyme inhibitors produced by microorganisms in our laboratories, oudenone was discovered in a culture filtrate of *Oudemansiella radicata* very recently,[1] and it showed inhibition of tyrosine hydroxylase and exhibited significant hypotensive effect.[1]

We report herein the structural elucidation and total synthesis of oudenone (**1**), which undergoes a dynamic skeletal change to afford the β-trione **2b** through **2a** by simple addition of water.

Oudenone (**1**), soluble not only in usual organic solvents but also in water, has the formula $C_{12}H_{16}O_3$ (M^+ 208.112), and shows: mp 77–78°; $[\alpha]^{21}D$ −10.8° (c 0.69, EtOH); pK_a = 4.1; $FeCl_3$ test positive; CHI_3 test positive; uv max [MeOH] 285 (ϵ 19,000), 220 (ϵ 12,000) [0.1-1 N NaOH], 247 (ϵ 23,000), 270 mμ (sh); ir (KBr) 3440 (w), 1715 (w), 1662 (s), 1563 (s), 1198 (m), 1018 (m); (CCl_4) 3420 (w), 1735 (w), 1673 (s), 1578 (s), 1185 (m), 1007 cm^{-1} (m). The nmr spectrum is shown in Figure 1. The unique signals of ABXY system at δ 3.19 and 3.57 are assigned to the geminal methylene (H_A, H_B) adjacent to the double bond. The large geminal coupling constant and relatively low chemical shift suggest that the methylene is adjacent to exo or endo unsaturation of a five- or six-membered ring[2] and under the influence of a carbonyl group,[3] respectively. The unsymmetrical triplet signal at δ 0.98 suggests the presence of a side chain longer than ethyl.[4] The lowest signal at δ 4.91 (quintet, J = 6.0 Hz) is reasonably assigned to a hydrogen on the carbon attached to the ether linkage. A partial structure



$$-\overset{|}{\underset{|}{C}}CH_2CH_2\overset{\overset{\textstyle O}{|}}{\underset{\underset{\textstyle H}{|}}{C}}-CH_2CH_2CH_3$$

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[1] H. Umezawa, T. Takeuchi, H. Iinuma, K. Suzuki, M. Ito, M. Matsuzaki, T. Nagatsu, and O. Tanabe, *J. Antibiot.*, **23**, 514 (1970).

[2] R. Cahill, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **25**, 4711 (1969), and references contained therein.

[3] L. M. Jackman and S. Sternhell, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, London, 1969, p 207.

[4] For such virtual coupling, see, for instance, ref 3, pp 143–150.

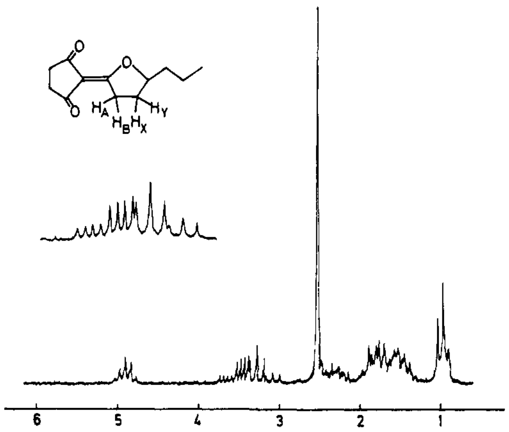
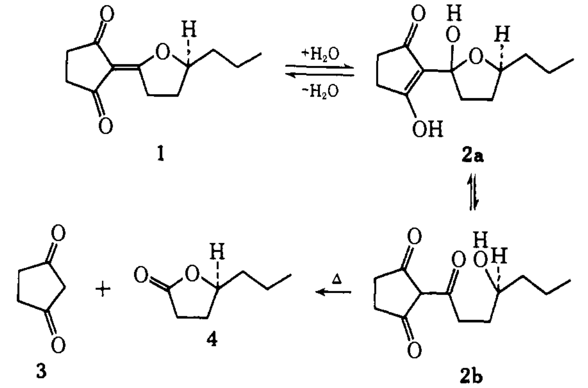


Figure 1. Nmr spectrum of oudenone (1) in CDCl$_3$ at 100 MHz.

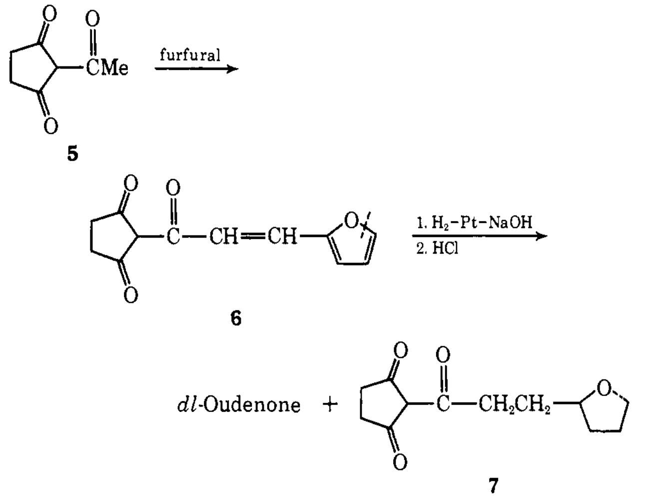
is compatible with the above spectral evidence and has been confirmed by the application of double and triple resonance technique.

Chart I



Ozonolysis or oxidation with KMnO$_4$ afforded succinic acid and γ-propylbutyrolactone[5] (4), showing that the singlet at δ 2.53 corresponds to four hydrogens of succinic acid. Finally, hydrolysis of **1** at 150° in a sealed tube split it into two known fragments without loss of any carbon affording 1,3-cyclopentanedione[6] (**3**) and the γ-lactone[7] (**4**).

By combining the above chemical and spectral results and mechanistic considerations, structure **1** has been proposed for oudenone, and the acidic property and positive iodoform test characteristic of oudenone can be reasonably explained by the β-trione structure **2b** which is well demonstrated by spectral data (ir, uv, and nmr) and by conversion into the metal salts.[8] The Hudson–Klyne lactone rule[9] permits assignment of the *S* configuration to γ-propylbutyrolactone, since the γ-lactone has negative rotation[7] and negative Cotton effect. Therefore, the absolute structure of oudenone is (*S*)-2-[4,5-dihydro-5-propyl-2(3*H*)-furylidene]-1,3-cyclopentanedione.



The synthetic approach to oudenone was designed to prove the most interesting feature of oudenone or the dynamic skeletal change between structures **1** and **2**.

2-Acetyl-1,3-cyclopentanedione[6] (**5**) was condensed with furfural in the presence of morpholine to afford a condensation product **6** in excellent yield. Hydrogenation over Pt in the presence of 1 mol equiv of sodium hydroxide followed by neutralization with hydrochloric acid afforded *dl*-oudenone[10] in good yield along with 2-[3-(2-tetrahydrofuryl)propionyl]-1,3-cyclopentanedione (**7**). The racemic oudenone was resolved with brucine hydrate. It should be mentioned here that *dl*-oudenone and *d*-oudenone have equally strong activity inhibiting tyrosine hydroxylase and reducing blood pressure as *l*-oudenone.

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(5) E. Schwenk, D. Papa, H. Hankin, and H. Ginsberg, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 742.

(6) F. Merényi and M. Nilsson, *Acta Chem. Scand.*, **17**, 1801 (1963).

(7) The ir and nmr spectra were confirmed to be identical with those of authentic samples described in ref 5 and 6. The γ-lactone from ozonolysis and hydrolysis has $[\alpha]^{21}\mathrm{D}$ −47.2° (*c* 1.08, CHCl$_3$) and −45.0° (*c* 0.78, CHCl$_3$), respectively, providing evidence to support that the mechanism of ring opening of **1** is Michael addition of water followed by the opening of the ether linkage to keep retention of the asymmetric center, as shown in Chart I.

(8) For instance, the treatment of **1** with sodium hydroxide afforded the sodium salt, mp 145–148°, a crystalline powder with satisfactory elemental analysis.

(9) W. Klyne, P. M. Scopes, and A. Williams, *J. Chem. Soc.*, 7237 (1965).

(10) The identity of the racemic form with the natural one was confirmed by spectroscopic data such as ir, uv, and nmr.

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Received December 28, 1970

Theories of the Isotropic Shift in Complexes with T Ground States. An Experimental Test

Sir:

The use of nuclear magnetic resonance in studying structural, electronic, and chemical problems in paramagnetic transition metal complexes has developed[1] remarkably in recent years. With the widening scope and utility of this technique, the early equations[2] which relate the observed nmr shift to the contact and dipolar interactions have been modified and ex-

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(1) D. R. Eaton and W. D. Phillips, *Advan. Magn. Resonance*, **1**, 103 (1965); E. DeBoer and H. van Willigen, *Progr. Nucl. Magn. Resonance Spectrosc.*, **2**, 111 (1967); R. H. Holm, *Accounts Chem. Res.*, **2**, 307 (1969).

(2) H. M. McConnell and R. E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958).