The Stereochemistry of the Camphoketene Dimers[1]

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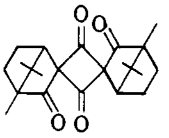
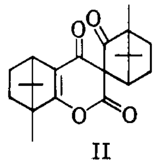
The stereochemistry of the camphoketene dimers has been deduced from optical rotatory dispersion and nuclear magnetic resonance data. The more dextrorotatory isomer has configuration S at C-3 of the pyronone ring as in formula III. This finding accords with theoretical assignments based on molecular rotation data for the dimers at 589 mμ.

Dehydrochlorination of *d*-camphor-3-carbonyl chloride with quinoline or triethylamine in ether gives two products of molecular formula $C_{22}H_{28}O_4$.[2] Staudinger and Schotz[2] assigned structure I to these isomers, but more recently Yates and Chandross[3] have shown that the two dimers should be represented by structure II.



I



II

The dimers were reported[2,3] to differ markedly in optical rotation; since they can differ in stereochemistry only at C-3 of the pyronone ring, it appeared likely that theoretical correspondences between optical rotation and stereochemistry could lead to an unambiguous prediction of configuration for the molecule. To check this prediction by degradation would be difficult, for the epimeric center is not very durable: both dimers give identical products upon acidic hydrolysis, basic hydrolysis, or thermal rearrangement.[3] Physical methods that would be sensitive to the stereochemical aspects of structure looked more promising.

Yates and Chandross[3] noted that the rates of alkaline hydrolysis of the dimers differed slightly, and that a tentative assignment of stereochemistry could be made on this basis.

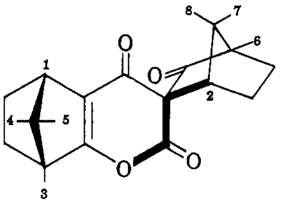
Results and Discussion

Preparation of the camphoketene dimers[2] gave materials having optical rotations in satisfactory agreement with the literature. Isomer A, the dimer which is less soluble in ether and forms compact crystals, had $[\alpha]_D$ +127° (lit.[2] +126.8°, lit.[3] +132°), while the second substance, which crystallizes in fine needles, had $[\alpha]_D$ +65° (lit.[2] +62.9°, lit.[3] +66.3°).

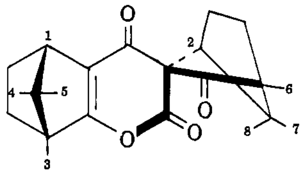
The nuclear magnetic resonance spectrum of the supposed second dimer, $[\alpha]_D$ +65°, was not comprehensible in terms of a single camphoketene dimer. For instance, the methyl region of the spectrum had peaks at 70, 63, and 54 c.p.s. (1.17, 1.05, and 0.90 p.p.m.) below tetramethylsilane with relative strengths in the ratios 1.1:3.3:1.5. Recrystallization of the material of $[\alpha]_D$ +65° from absolute methanol gave crystals having less positive rotations. The final recrystallization gave stout needles of m.p. 156–158°, $[\alpha]_D$ +23.7°. The n.m.r. spectrum of this resolved dimer, isomer B, was compatible with expectations for fully resolved material.

The crystals of $[\alpha]_D$ +62.9 to +66.3° are then a 1:1 mixture of the two diastereoisomeric camphoketene dimers. The slight discrepancy between the observed rotations and that calculated for an equimolar mixture of isomers A and B may be due either to incomplete resolution of isomer B, or to a small contamination of the 1:1 eutectic with isomer B.

The optical rotatory dispersion characteristics of dimers A and B are shown in Fig. 1. Both isomers have positive Cotton effects at the wave lengths corresponding to the K-bands for the α,β-unsaturated carbonyl moieties. Both of the α,β-unsaturated carbonyl systems, therefore, have the same chirality,[4] and are left-handed.[4] The dimers in question, then, are III and IV.



III



IV

The n.m.r. spectra of isomers A and B are strikingly different. In isomer A, $[\alpha]_D$ +127°, the two methine protons are centered at 172 and 166 c.p.s. (2.87 and 2.77 p.p.m.) and the methyl signals at 70, 63, and 54 c.p.s. (1.17, 1.05, and 0.90 p.p.m.) are of relative strength 1:4:1. For isomer B, $[\alpha]_D$ +23.7°, the two methine protons are found at 175 and 156 c.p.s. (2.82 and 2.60 p.p.m.), and the methyl absorptions at 70, 63, and 55 c.p.s. (1.17, 1.05, and 0.92 p.p.m.) are of relative strength 1:3:2. The two spectra are distinguishable by the chemical shift differences of one methine proton and of one methyl group. The stereochemistry of A results in substantial long-range deshielding of the methyl and methine protons in question, or that of B causes long-range shielding, or both influences may be operative.

The following assignments for the n.m.r. absorptions may be made at once. The tertiary methyl groups 3, 4, and 7 in each dimer appear at 63 c.p.s., and the methyl 6 is 7 c.p.s. lower, at 70 c.p.s. This chemical shift difference is close to that observed, 6.5 c.p.s., between the methyl group at C-1 and the two methyls at C-7 of camphor.[5] The methine proton at 172 or

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(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) H. Staudinger and S. Schotz, *Ber.*, **53**, 1105 (1920).

(3) P. Yates and E. A. Chandross, *Tetrahedron Letters*, **No. 20**, 1 (1959).

(4) C. Djerassi, R. Records, E. Bunnenberg, K. Mislow, and A. Moscowitz, *J. Am. Chem. Soc.*, **84**, 870 (1962).

(5) G. V. D. Tiers, "Table of Characteristic N.M.R. Shielding Values," Central Research Department, Minnesota Mining and Manufacturing Co., Minneapolis, Minn., Organic Section Project 737602, March 28, 1958.

175 c.p.s. in the dimers is 1; it is shifted downfield by the adjacent carbonyl group.[6] The methyl group 5 at 54 or 55 c.p.s. is shifted upfield in both dimers by the carbon–carbon double bond below it. These assignments leave only the methine proton 2 and the methyl group 8 unaccounted for.

From examination of Dreiding[7] stereomodels of the dimers III and IV, it is apparent that methyl group 8 in isomer III is in close proximity to and to the side of the C-4 carbonyl group and, hence, is deshielded.[6] The methine proton 2 in dimer III is to the side of carbonyl groups at C-2 and C-4 and, accordingly, is deshielded.[6] The methyl group 8 in isomer IV is located below the C-2 carbonyl function, and is therefore shifted to higher field.[6] The n.m.r. chemical shift data indicate that dimer A, which has the methine proton 2 and methyl group 8 at lower field, is isomer III, and B is IV. The more dextrorotatory isomer has the S configuration[8] at C-3 of the pyronone ring.

The assignments for n.m.r. absorptions are summarized in Table I.

Table I

N.m.r. Spectral Assignments for the Camphoketene Dimers

Dimer	Proton type	Number	Chemical shift, c.p.s.
III, A	Methine	1	172
	Methine	2	166
	Methyl	6	70
	Methyl	3, 4, 7, 8	63
	Methyl	5	54
IV, B	Methine	1	175
	Methine	2	156
	Methyl	6	70
	Methyl	3, 4, 7	63
	Methyl	5, 8	55

This stereochemical assignment is consistent with predictions based on Brewster's[9] correlations of configuration and optical activity. The total difference in molecular rotation between structures III and IV is expected to be $+k(2C_{11} - O)(Ca - C)$, where Ca represents a carbonyl group, C_{11} an olefinic carbon, and the other symbols have their usual[9] meanings. Then $\Delta M(\text{III} - \text{IV}) = +215°$. The calculation predicts that III is the more dextrorotatory isomer. In fact, $\Delta M(\text{A} - \text{B}) = +367°$, and the correspondence between theory and the observed molecular rotation difference is satisfactory when structure III represents isomer A, and IV, B.

New applications of Brewster's postulates are of particular interest when, as in the present instance, the skeletal system of the molecules is quite dissimilar to those of the compounds used in the development of the postulates. An earlier new application to norbornane derivatives[10] led to only partial success.

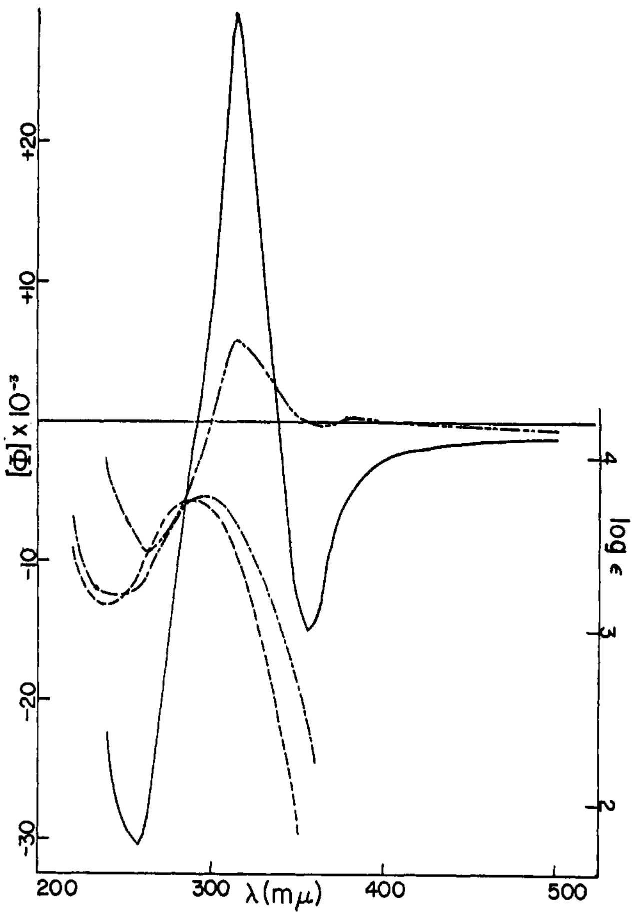

Fig. 1.—Optical rotatory dispersion and ultraviolet absorption curves for the camphoketene dimers A and B: o.r.d., A (—--—), B (———); ultraviolet, A (- - - -), B (— - —).

Experimental[11]

Camphoketene Dimers.—Treatment of crude *d*-camphor-3-carbonyl chloride[2,12] with triethylamine in ether, followed by the usual work-up,[2] gave a mixture of the camphoketene dimers as yellow crystals (87% from *d*-camphor-3-carboxylic acid). Recrystallization from ether[2] gave dimer A as compact crystals, m.p. 151–152°, $[\alpha]_D$ +127° (*c*, 2.6); lit.[2] m.p. 152–153°, $[\alpha]_D$ +126.8°; lit.[3] m.p. 150–151.5°, $[\alpha]_D$ +132°.

The second solid was obtained after crystallization from methanol and had $[\alpha]_D$ + 65° (*c*, 2.3); lit.[2] $[\alpha]_D$ +62.9°, lit.[3] $[\alpha]_D$ +66.3°. The n.m.r. spectrum of this solid of $[\alpha]_D$ +65° showed methyl signals at 70, 63, and 54 c.p.s. below the internal standard, tetramethylsilane, with relative intensities 1.1:3.3:1.5. Repeated recrystallization from methanol led from the solid of $[\alpha]_D$ +65° to stout needles, m.p. 156–158°, $[\alpha]_D$ +23.7° (*c*, 1.2). The identity of this material as a camphoketene dimer (dimer B) was confirmed by infrared, n.m.r., and ultraviolet spectroscopic comparisons between the solid of $[\alpha]_D$ +65° and that of $[\alpha]_D$ +23.7°.

The n.m.r. data for methine and methyl protons of dimers A and B are shown in Table I. The o.r.d. data are given in Fig. 1.

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(6) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p. 119f.

(7) A. Dreiding, *Helv. Chim. Acta*, **42**, 1339 (1959).

(8) *Cf.*, R. S. Cahn, C. K. Ingold, and V. Prelog, *Experientia*, **12**, 81 (1956); this designation requires comparison of the third set of substituents from C-3.

(9) J. Brewster, *J. Am. Chem. Soc.*, **81**, 5475 (1959).

(10) J. A. Berson, J. S. Walia, A. Remanick, S. Suzuki, P. Reynolds-Warnhoff, and D. Willner, *ibid.*, **83**, 3986 (1961).

(11) Melting points are reported as observed on a Kofler micro hot stage. The optical rotations at 589 mμ were determined in ethyl acetate at 26 ± 2°, l = 2, on a Zeiss polarimeter. The o.r.d. data were obtained in methanol with a Rudolph recording spectropolarimeter, Model 260-655-850. Ultraviolet spectra were determined in methanol with a Bausch and Lomb spectronic 505 spectrophotometer. The n.m.r. spectra were determined with deuteriochloroform solutions on a Varian A-60 instrument.

(12) N. Zelinsky, *Ber.*, **36**, 208 (1903).