Tetrahedron, 1966, Vol. 22, pp. 3011 to 3020. Pergamon Press Ltd. Printed in Northern Ireland

PHOTODIMERS OF PIPERITONE

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(*Received in U.S.A.* 12 *March* 1966; *accepted for publication* 2 *May* 1966)

Abstract—The photodimerization of (−)-piperitone has been re-investigated and the previously described three photodimers have been isolated. From a study of the dipole moments and natural abundance C^{13}—H NMR spectra, it has been established conclusively that the three dimers are cyclobutane derivatives formed by head to head combinations. In two of the dimers the stereochemistry at both ring junctions of the six and four membered rings is *cis*, while the third dimer contains at least one *trans* junction. The relative and absolute stereochemistry of the most abundant photodimer has been completely established from consideration of its ORD curve.

SEVERAL laboratories have recently[1–3] reported on the photo-dimerization of α,β-unsaturated carbonyl compounds to yield cyclobutane derivatives. Although the reaction is quite general,[4] only in a few isolated cases has it heen established whether this type of photodimerization occurs head-to-head (h–h) or head-to-tail (h–t). Eaton[2] has described the irradiation of 2-cyclopentenone, in which two dimers, I and II, were isolated. In both dimers the carbonyl groups were anti (on opposite sides of the plane of the cyclobutane ring); however, in one case the fusion was h–h and in the other h–t. Thus, both h–h and h–t fusions are possible within the same system and therefore each dimer requires individual experimental investigation.

With this in mind we have re-examined the irradiation of (−)-piperitone (III). The photolysis of this α,β-unsaturated ketone was first investigated by Treibs,[5] who obtained one photodimer when the photolysis was conducted in sunlight, and the same compound with two additional photodimers when a mercury arc was employed. In our hands the three photodimers reported by Treibs were obtained on irradiation of an aqueous alcoholic solution of III with a high pressure mercury lamp (Hanovia 450 W) and separated by fractional recrystallization of the reaction mixture.

To simplify the discussion of these compounds we shall represent the dimer m.p. 169–170° (corresponding to Treib's compound, m.p. 163°) by A; the dimer m.p. 157–159° by B; and that m.p. 142–144° by C.

The three dimers A, B, and C each show only weak absorption at 302 mμ ($\varepsilon = 85$), indicative of a saturated carbonyl group: the absorption in the IR of the carbonyl groups at 1700 cm^{-1} eliminates the possibility of a ring contraction to a cyclopentanone derivative.[6] These facts also preclude the α,β-unsaturated ketone features of the α- and β-dipiperitones.[7] Further, the formation of photo-addition products such as IV,

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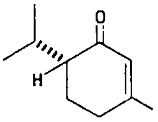
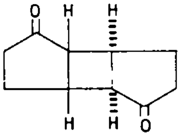
[1] P. Yates and M. J. Jorgenson, *J. Amer. Chem. Soc.* **85**, 2956 (1963).
[2] P. E. Eaton, *J. Amer. Chem. Soc.* **84**, 2344 (1962).
[3] G. M. Blackburn and R. L. H. Davies, *Chem. Comm.* 215 (1965).
[4] A. Mustafa, *Chem. Revs.* **51**, 1 (1951).
[5] W. Treibs, *Ber. Dtsch. Chem. bis* **63**, 2738 (1930).
[6] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* p. 128. Methuen, London (1954).
[7] W. I. Taylor, *Chem. & Ind.* 252 (1954).

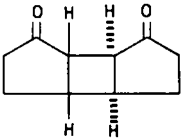
which has been observed[8] in the case of other unsaturated aldehydes and ketones, was eliminated by consideration of the NMR spectra. None of the three compounds shows any absorption downfield from $\delta = 2{\cdot}79$, demonstrating the absence of olefinic protons. The above information is compatible only with the dimer containing a cyclobutane ring,[9] of which many examples have been reported.[4]



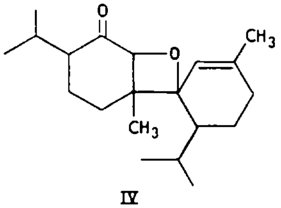
III



I



II



IV

It now remains to determine which of the many structural and configurational isomers correspond to the three compounds isolated.

Corey *et al.*[10] have demonstrated that both *cis* and *trans* ring junctions between six and four membered rings may be obtained in a photochemical reaction. The investigators have also shown that a *trans* junction, adjacent to a carbonyl group, is less stable than a *cis* junction, and that on treatment with dilute alkali such *trans*-joined compounds isomerize to the more stable *cis* isomers. Dimer A, on treatment with dilute alkali or dilute acid, was recovered in good yield and unchanged, as shown by the comparison of its IR spectrum (in CS_2), NMR spectrum, and ORD curve with those of the untreated material. When the treatment was conducted in D_2O, the presence of dilute alkali led to the disappearance of the singlet at $\delta = 2{\cdot}79$ in the NMR spectrum, which we assign to the protons of the cyclobutane ring. These results demonstrate that in alkaline conditions the bridgehead protons exchange without change in stereochemistry; it is therefore clear that both ring junctions in A are *cis*.

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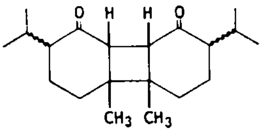
[8] N. C. Yang, M. Nussim, M. J. Jorgenson and S. Murov, *Tetrahedron Letters* 3657 (1964).

[9] Evidence for the presence of a cyclobutane ring from C^{13}—H NMR spectra will be presented below.

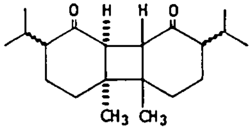
[10] E. J. Corey, R. B. Mitra and H. Uda, *J. Amer. Chem. Soc.* **85**, 362 (1963).

Under similar conditions B was transformed into C. Thus, B must contain at least one *trans* junction, while both junctions must be *cis* in the case of C. Since A was obtained in highest yield, it was used for most of the experiments. Its structure will be considered first, and those of B and C will become apparent once that of A has been established.

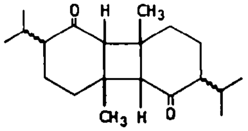
It is possible, from knowledge of the dipole moments, to distinguish between the h–h dimers (V and VI) and the h–t dimers (VII and VIII). Compounds such as VII and VIII are expected to have only very small dipole moments, whereas V and VI should have dipole moments equal to about *twice* that of the bond moment of the carbonyl group (2 × $\sim$2·4 D)[11] As a preliminary control to such application of dipole moment data in the differentiation between h–h and h–t dimers, the compounds I and II, of known structure, were prepared and their dipole moments were measured in benzene. They were found to be 1·3D[12] and 5·0D, respectively. The dipole moments of A and C, also determined in benzene, were both found to be 4·8 Debye. A careful examination of the Dreiding models of the h–h and h–t photodimers indicates that only an extreme conformation of the h–t compound, in which the carbonyl groups are quite close to one another and in which the substituted cyclohexanone rings are syn (VII), could account for a dipole moment of such magnitude.[13] The h–h dimers, in contrast, can easily have dipole moments of such size.



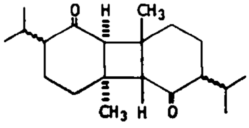
V



VI



VII



VIII

Conformation of the assignment of A as a h–h dimer was obtained from the natural abundance C^{13}—H satellite proton NMR spectrum. Recently Anet[14] has used this technique in her study of the photodimer of thymine. As mentioned earlier, the lowest field absorption in the NMR spectrum at $\delta = 2{\cdot}79$ has been assigned to the cyclobutane protons. It was therefore possible to observe the lower field C^{13}—H satellite of the cyclobutane hydrogens as shown in Fig. 1. The C^{13}—H coupling constant,

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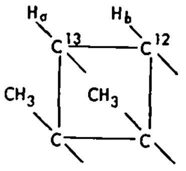
[11] L. F. Sutton, in *Determination of Organic Structures by Physical Methods* (Edited by E. A. Braude and F. C. Nachod) Vol. 1; p. 390. Academic Press, New York (1955).

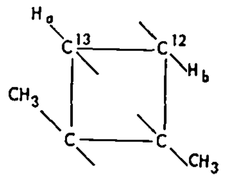
[12] It is not known at this time whether the value results from incomplete cancellation of the moments of the carbonyl group or from a large contribution from atomic polarization. The dipole moments were determined on a Sargent Model V Oscillometer.

[13] The non-polar solvent, benzene, favors charge dispersal, i.e. the location of carbonyl groups as far from each other as possible, rather than a situation in which the polar carbonyls are in close proximity, as would be required in the conformation of the h-t dimer necessary for a large dipole moment.

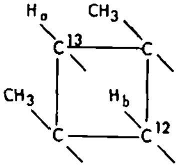
[14] R. Anet, *Tetrahedron Letters* 3713 (1965).



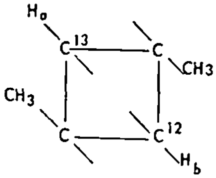
IX a



IX b



X a



X b

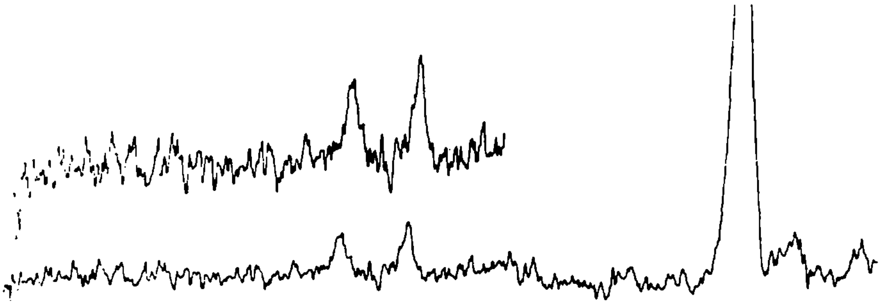


FIG. 1. C^{13}—H satellite proton NMR spectrum of A Time Averaging Computer sum of 100 scans.

J = 140 ± 1 c/s is between the 136 c/s value for cyclobutane reported by Foote[15] and the value of 153 ± 2 c/s reported by Anet,[14] and thus provides additional evidence for the presence of a cyclobutane ring.[15] The observed C^{13}—H satellite was a doublet, with J = 7·6 ± 0·2 c/s. This latter coupling constant can be used to differentiate between the h–h and h–t dimers. The cyclobutane protons H_a and H_b which are no longer magnetically equivalent in the C^{13}—H satellite spectrum (see partial structures IXa and IXb), would be expected to have a coupling constant of this magnitude, whereas J_{HaHb} in Xa and Xb would be < 1 c/s.[16]

Thus, having been established as an h–h dimer with *cis* ring junctions, it remains necessary to determine whether the carbonyl groups are syn (XIa) or anti (XII or XIII). The Ha–Hb coupling constant of 7·6 ± 0·2 c/s does not permit a distinction between these two possibilities.[17] We therefore took advantage of the fact that piperitone is optically active; (—)-piperitone used in this work has the absolute configuration shown by III. Inspection of the Dreiding models of XI, XII and XIII

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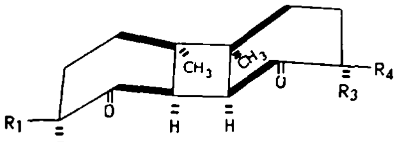
[15] C. S. Foote, *Tetrahedron Letters* 579 (1963 has reported that the C^{13}—H coupling constant for cyclobutane is 136 c/s, while those for cyclopentane and cyclohexane lie in the range 124–128 c/s.

[16] A 0·5 c/s coupling constant was noted in Ref. 17.

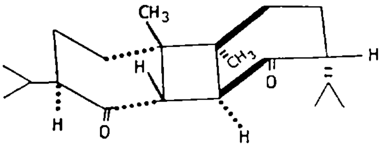
[17] V. Georgian, L. Georgian and A. V. Robertson, *Tetrahedron* **19**, 1219 (1963) has shown that the *trans* and *cis* coupling constants of adjacent hydrogens in 3,4-dibromocyclobutane-1,2-dicarboxylic acid vary from 8·7–9·2 c/s.

shows that XIb has a plane of symmetry perpendicular to the plane of the four-membered ring. Since the configuration of the isopropyl group is not likely to change during the photolysis (XIa) this compound would be optically active, but treatment with dilute alkali should lead to partial epimerization of one of the isopropyl groups. Although epimerization is not an absolute requirement, since conformations of each cyclohexanone ring are possible in which the isopropyl groups are quasi equitorial, the Cotton effect associated with the carbonyls of compound XIa cannot be large because of its nearly symmetrical nature.

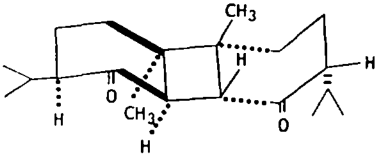


XI

(a) $R_1 = R_3 = -CH(CH_3)_2$; $R_2 = R_4 = H$
(b) $R_1 = R_4 = -CH(CH_3)_2$; $R_2 = R_3 = H$



XII



XIII

The situation is quite different for XII and XIII since for these molecules epimerization of the isopropyl groups of cyclobutane hydrogens does not yield a symmetric and optically inactive molecule. Furthermore, by application of the octant rule[18] it can be shown that the ORD curves associated with each carbonyl group in XII and XIII add, whereas they almost cancel in XI. The application of the octant rule to XII will be discussed in some detail since the analysis for XI and XIII was essentially identical. If one considers only the substituted cyclohexanone of XII on the left one finds that in all its conformations (i.e. twist and boat) the bulky cyclobutane with its fused substituted cyclohexanone falls either in the lower right or upper left quadrants both of which make *positive* contributions to the ORD curve. The other substituents (i.e. methylene, methyl and isopropyl groups) contribute *much less* to the asymmetry about the carbonyl group and essentially balance in opposing quadrants. If one now views the situation from the carbonyl in the cyclohexanone ring on the right one finds that in all the possible conformation the bulky substituents are again in the lower right or upper left quadrants (positive). In view of the many possible conformations one cannot make a quantitative prediction, however, qualitatively a large positive Cotton effect can be predicted for XII. A similar analysis for the Cotton effect expected from XIII leads to the conclusion that it should be large and *negative*. Since a large positive effect is observed the relative and absolute stereochemistry assigned to

[18] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* 83, 4013 (1961).

compound A is shown in XII. (The assumption that each carbonyl contributes one half of the observed rotation was confirmed by the ORD curve of the monoethylene thioketal of A, also shown in Fig. 2.)

Neither B or C were found to have any optical activity between 600 mμ and 250 mμ. A comparison of the IR and NMR spectra (60 Mc and 100 Mc) of A, B and C indicates that the spectra of A and C are indistinguishable from each other but that B differs from both A and C (Fig. 3). Since the NMR spectrum is quite sensitive to changes in conformation and geometry of a molecule, it appears unlikely that the spectra of A and C would be identical if the stereochemistry differed about the cyclobutane ring. That the stereochemistry is in fact identical was shown by the C^{13}—H satellite spectrum of C, which showed the C^{13}—H coupling constant to be 140 ± 1 c/s with $J_{H_a-H_b} = 7{\cdot}6 \pm 0{\cdot}2$ c/s, identical with the values from A. The principal difference between C and A is thus one of optical activity,[19] and two structures for C can be envisaged. In the first, C would be derived from one molecule each of (+)- and (—)-pipertone, instead of the two (—)-piperitone molecules that form A, and the second possibility is that of a racemate of A in which one member was composed of two (+) piperitone, while the other was composed of two (—)-piperitones. Each of these possibilities requires both optical isomers of piperitone. As a test of these possibilities synthetic racemic piperitone was photolysed as before and the sole product isolated was indeed C. It has not been possible to differentiate between these two alternatives.

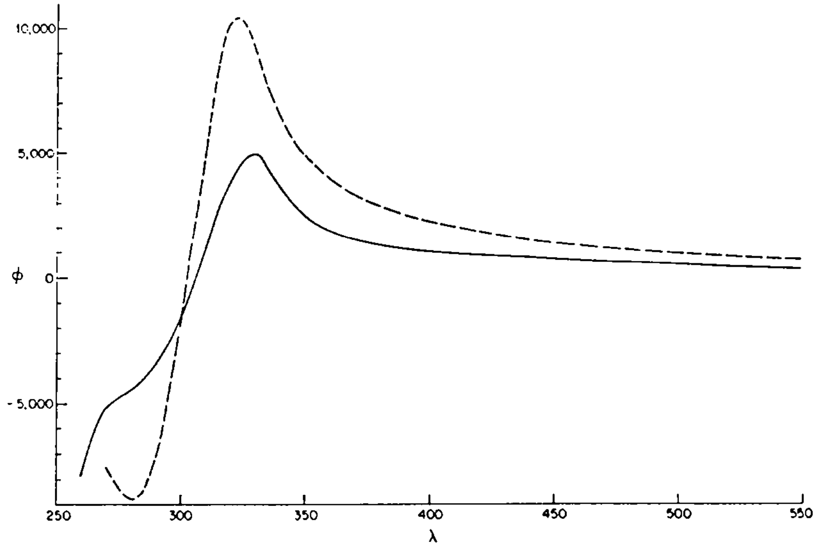


Fig. 2. ORD curves of A - - - - and its monoethylenethioketal ———.

Since B can be converted to C, its structure as a h–h dimer has been established. Its instability to alkali further establishes the presence of at least one *trans* six-four ring junction. The singlet nature of the hydrogens and methyl groups on the cyclobutane ring suggests that each pair of groups has an identical environment. This is most easily rationalized if both six-four ring junctions in C are *trans*.

[19] The optical purity of the starting material is approximately 50%; $[\alpha]_D^{20}$ −24° observed, reported for d(+)-piperitone +49°.

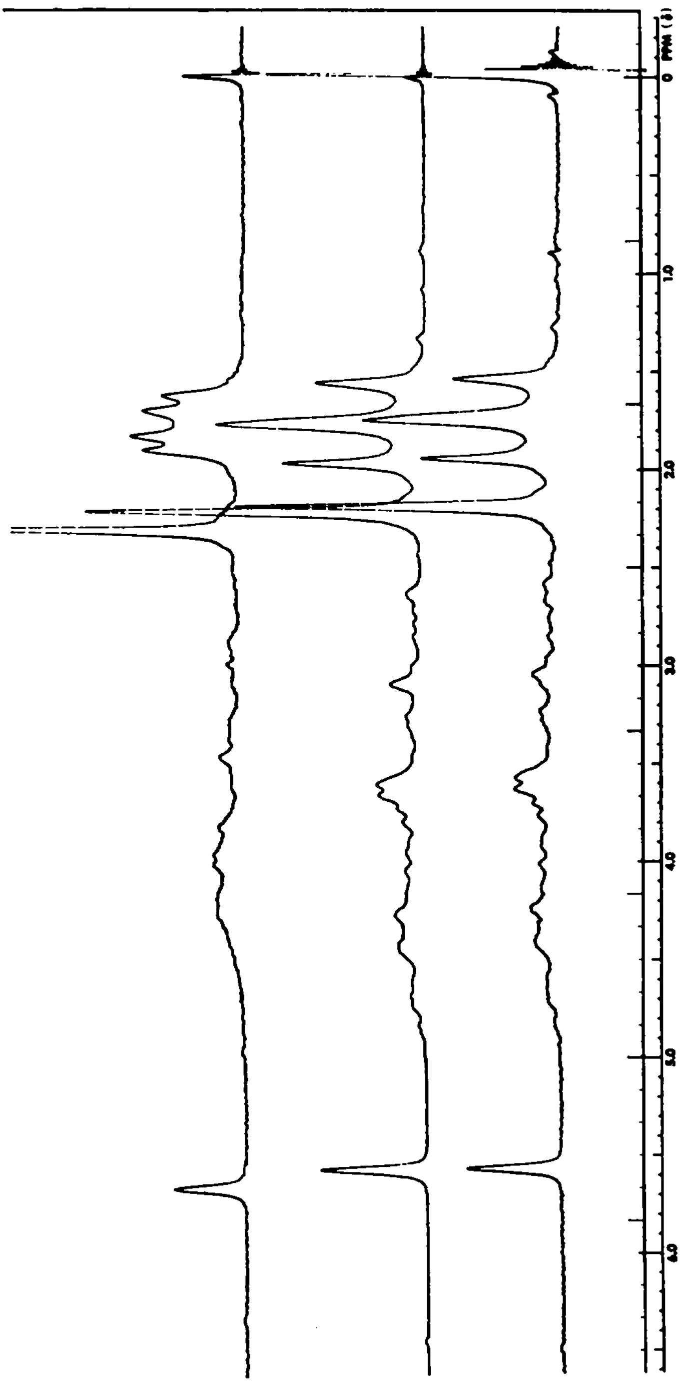


FIG. 3. A comparison of the NMR (60 Mc) spectra of B (top); A (middle); and C (bottom).

The low yield of the three photodimers has thus far precluded the determination of the quantum yield for the reaction; nor is much information available regarding the multiplicity of the excited state. Finally, the possibility of dimer A being a secondary photoproduct, derived from an unstable *trans*-fused dimer has not been excluded. The photodimerization of piperitone is remarkable, however, for the stereoselectivity with which the process takes place.

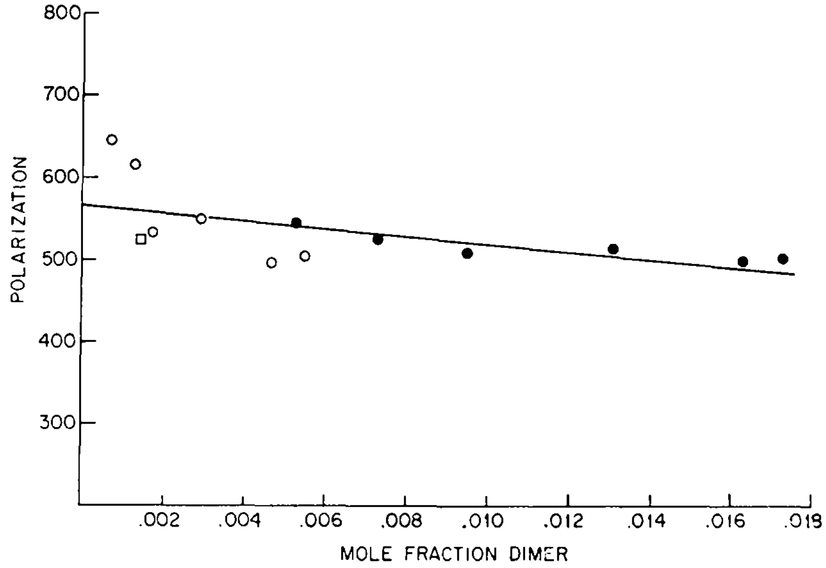


FIG. 4. Extrapolation in determination of limiting polarization in dipole moment determination, A ●; B □; and C ○.

TABLE 1. PIPERITONE PHOTODIMERS

Dimer	Mole Fraction f_2	Molar Polarization P_2
A.	0·00526	544
	0·00730	526
	0·00955	508
	0·00960	509
	0·01318	514
	0·01634	497
	0·01731	502
C.	0·00074	645
	0·00132	615
	0·00176	533
	0·00294	549
	0·00461	498
	0·00551	505
B.	0·00146	528

See Figure 4 for extrapolated molar polarization.

TABLE 2. CYCLOPENTENONE PHOTODIMERS

Dimer	Mole Fraction f_2	Molar Polarization P_2
I	0·00590	96
	0·01920	95
	0·02626	100
	0·02607	98
	0·01289	98
	0·02228	96
	0·01219	87
	0·00365	78
	0·02998	93
II	0·00781	569
	0·01250	540
	0·002634	558
	0·02114	520
	0·02000	530
	0·00862	555

EXPERIMENTAL

Photolysis of piperitone. A solution of piperitone (14·5 g; K & K Laboratories, Inc., $[\alpha]_D^{25}$ −24°) in EtOH (175 ml) and water (100 ml) was irradiated with a water-cooled Hanovia 450 watt high press Hg immersion lamp using a Pyrex filter. The solution was irradiated for 10 hr, during which time N_2 was bubbled through the solution. The precipitate (~1 gm) was filtered, washed with a small amount of cold MeOH, and dried. Repeated recrystallizations from aqueous EtOH or MeOH yielded A, m.p. 169–170° (fine white needles). Concentration of the mother liquors from the recrystallizations yielded a white solid (needles) from which C was obtained by repeated recrystallizations from aqueous MeOH or EtOH. These mother liquors from several batches were combined and concentrated. Compound B was isolated by recrystallization of these residues as plates; m.p. 157–159°. (Found:* Dimer A: C, 78·72; H, 10·60; mol. wt. 317; Dimer B: C, 78·70; H, 10·46; mol. wt. 318; Dimer C: C, 79·02; H, 10·64; mol. wt. 312; Calc. for $C_{20}H_{32}O_2$: C, 78·89; H, 10·59%; mol. wt.: Calc. 304.)

The ORD curve (Cary 60 Spectropolarimeter) for 170° dimer in MeOH conc. 0·015 g/100 ml, $[\alpha]_D = +192°$, $\Phi_{325} = +10{,}700°$ and $\Phi_{280} = -8800°$.

Monoethylenethioketal of compound A. Employing a modification of the Fieser[10] procedure, to 0·100 gm of compound A in 5 ml AcOH was added 0·0347 gm of ethanedithiol in 2·6 ml AcOH and 4 drops BF_3-etherate. The solution was allowed to stand for 2 days at room temp, poured into water, extracted with benzene, washed with water and dil. aq, $NaHCO_3$ dried and concentrated. The oil was chromatographed on Silica Gel H (Merck AG, Darmstadt). The benzene fraction on concentration yielded a solid m.p. 128–130°. Mass spectra analysis using a MS-9 double focussing mass spectrometer gave an empirical formula $C_{22}H_{36}S_2O$, the mol. wt. of which is calculated to be 380·219; found 380·221. The principal mass peaks at 227, 228 and 153 indicate cleavage of the cyclobutane ring. An unequivocal analysis of the NMR spectrum of the thioketal was not possible. Raney Nickel desulfurization of the thioketal resulted in cleavage of the cyclobutane ring yielding a waxy, olefinic ketone (unconjugated) whose structure was not completely determined. ORD curve in MeOH conc. 0·1156 g/100 ml, $[\alpha]_D = 92·3°$, $\Phi_{330} = +4912°$ and $\Phi_{270} = -5144°$.

The data for the dipole moment measurements on compounds I, II, A, B and C are summarized in Tables 1 and 2 below.

Base catalysed deuterium exchange of A. To a solution of 70 mg of compound A in 7 ml THF was added 3 ml of 0·1N NaOD in D_2O. After standing for 3 days at room temp the solvent was

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* Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich.

[10] L. F. Fieser, *J. Amer. Chem. Soc.* **76,** 1945 (1954).

[11] H. Henecka, *Chem. Ber.* **81,** 201 (1948); *Ibid.* **82,** 112 (1949).

removed under reduced press and the solid dissolved in benzene, dried and concentrated. Preparative TLC on Silica Gel H using 5% AcOEt in benzene separated A from some isomerized lower melting photodimer. The absence of the absorption band at $\delta = 2{\cdot}79$ in the NMR spectrum showed that the cyclobutane hydrogens had been exchanged for deuterium. When the reaction was carried out with NaOH in H_2O the recovered A was identical in all respects: NMR, IR and ORD, with untreated A. Although the isomerized photodimer was not obtained completely pure, the ORD curve of this material indicated that it has essentially the same rotation as A. The NMR spectrum indicated changes ascribable to the isomerization of an axial isopropyl group to an equatorial one.

Acknowledgment—One of us (R. O. K.) gratefully acknowledges the financial support from the Research Corporation.