limit; while the other phase (β) is present alone wherever this limit is exceeded. They also make plain the migration of the phase boundary with continued diffusion. Finally they show that the higher order diffraction lines from the β phase are much less intense than those of the α phase, a fact probably due to the severe cold working which occurs as β is formed from α by a sudden expansion of over 3% (linear) at the advancing phase boundary.

METALS RESEARCH LABORATORY
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RECEIVED JUNE 8, 1940

COMMUNICATIONS TO THE EDITOR

STRUCTURE OF CANNABIDIOL. VIII. POSITION OF THE DOUBLE BONDS IN CANNABIDIOL. MARIHUANA ACTIVITY OF TETRAHYDROCANNABINOLS

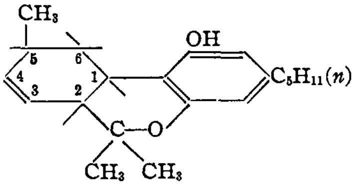
Sir:

Certain mild reagents (previous papers V, VI) convert cannabidiol into a tetrahydrocannabinol $[\alpha]^{32}\mathrm{D}$ $-165 \pm 7°$; more vigorous reagents to one with $[\alpha]^{32}\mathrm{D}$ $-240 \pm 10°$. It is obvious from the rotations that these forms are not absolutely pure and each is probably contaminated with the other.

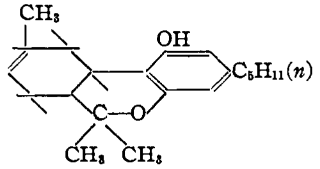
The lower-rotating tetrahydrocannabinol can be converted to the higher-rotating by the same reagents and under the same conditions which convert cannabidiol to the higher-rotating form; thus the lower-rotating form is presumably the initial reaction product in the isomerization of cannabidiol and the higher-rotating form a secondary product. Therefore, the lower-rotating form probably has the double bond in the same position as the corresponding double bond in cannabidiol.

Cannabidiol has been shown to have no double bond conjugated to the benzene ring; that its two double bonds are not conjugated to each other is indicated by the very close values of the absorption spectrum of cannabidiol (maximum log ϵ, 3.18), and that of tetrahydrocannabidiol (3.05) and confirmed experimentally by failure of repeated attempts to condense cannabidiol dimethyl ether with maleic anhydride. The double bond in each of the tetrahydrocannabinols has been shown not to be conjugated to the aromatic nucleus by comparison of their physical constants with that of a synthetic tetrahydrocannabinol of unequivocal constitution with the double bond conjugated (see paper VII). Positions 1,2 or 1,6 or 2,3 for the ring double bond in cannabidiol or in the tetrahydrocannabinols are thus excluded.

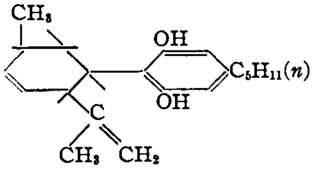
The migration of the double bond in the tetrahydrocannabinol, if 2,3 or 5,6, should proceed to the most favored position, in conjugation with the benzene ring. As this does not occur, positions 3,4 and 4,5 remain and are considered the most probable. The 3,4 is assigned to the lower-rotating tetrahydrocannabinol (I) and the 4,5 to the higher-rotating (II), for migration from the 3,4 to the 4,5 position (which has the methyl substitution) is more likely than *vice versa.* Through its relationship to the lower-rotating tetrahydrocannabinol, cannabidiol may be postulated as having structure III.



I



II



III

The tetrahydrocannabinols have a very potent marihuana activity which is markedly greater than that of the synthetic optically inactive form with the double bond conjugated to the benzene ring. The hexahydrocannabinols have less marihuana activity. Comparative pharmacological values with that of a highly potent product obtained by Dr. J. C. Matchett through fractionation of purified red oil in a molecular still and used as a standard by Dr. S. Loewe at the Cornell Medical School in tests according to his procedure of "Bioassay by Approximation" (*J. Am. Pharm. Assoc.*, **28**, 427 (1939); *J. Pharm. Exptl. Therap.*, **66**, 23 (1939)) are shown in Table I.

TABLE I

BIOASSAY OF TETRAHYDRO AND HEXAHYDRO CANNABINOLS

Substance	Min. Potency above	Max. Potency below	Mean value potency max. deviation
Standard red oil	....	....	1.00
Cannabidiol	....	....	0.00
Tetrahydrocannabinol, −165°	1.50	2.80	2.15 ± 0.66
Tetrahydrocannabinol, −240°	1.50	2.00	1.75 ± .25
Hexahydrocannabinol, −70°	0.60	0.80	0.70 ± .10
Tetrahydrocannabinol (syn.)	.13	.27	.20 ± .07
Hexahydrocannabinol (syn.)	.10	.20	.15 ± .05

The acetates and methyl ethers of the two tetrahydrocannabinols were colorless, highly viscous oils. Tetrahydrocannabinol $[\alpha]^{34}\text{D}$ −164° gave an acetate $[\alpha]^{34}\text{D}$ −167° and methyl ether $[\alpha]^{32}\text{D}$ −166°; tetrahydrocannabinol $[\alpha]^{30}\text{D}$ −240° gave an acetate $[\alpha]^{34}\text{D}$ −229° and methyl ether $[\alpha]^{32}\text{D}$ −226°.

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RECEIVED AUGUST 13, 1940

HINDERED INTERNAL ROTATION OF METHYL GROUPS: THE ENTROPY OF SILICON TETRAMETHYL

Sir:

We have recently completed an investigation which indicates that the potential hindering internal rotation of methyl groups is probably due to hydrogen repulsions.

A study of the entropy of gaseous silicon tetramethyl yields a potential of 1280 calories, compared to 4800 calories for tetramethylmethane. If the potential were mainly due to lack of cylindrical symmetry in the bond orbitals caused by electron interactions, a higher potential than 4800 calories might be predicted for silicon tetramethyl, due to the large number of electrons. Conclusion of complete calorimetric measurements in this Laboratory down to 12°K. on silicon tetramethyl permits an accurate estimate of the hindering potential. The entropy has been calculated using the following frequencies and distances[1]:

Carbon skeleton: ${}^{1}\omega_1 = 598$, ${}^{2}\omega_2 = 202$, ${}^{3}\omega_{4,5,6} = 239$, ${}^{3}\omega_{7,8,9} = 800$ cm.$^{-1}$.
CH_3 internal: ${}^{4}\delta(\pi) = 1264$, ${}^{8}\delta(\sigma) = 1427$, ${}^{4}\nu(\pi) = 2905$, ${}^{8}\nu(\sigma) = 2963$ cm.$^{-1}$.
CH_3 rocking: ${}^{8}\delta = 950$ cm.$^{-1}$.
Distances: Si–C = 1.93 Å., C–H = 1.09 Å.

The frequency ${}^{3}\omega_{7,8,9}$ is estimated from the frequencies 696 and 831 cm.$^{-1}$ which are apparently a result of resonance degeneracy. The rocking frequencies are estimated by analogy with ethane. The calculation of the entropy at 227.00°K. and at 299.8°K. (the normal boiling point) is summarized in Table I along with the corresponding calorimetric values.

TABLE I

THE ENTROPY OF SILICON TETRAMETHYL IN THE IDEAL GAS STATE FROM MOLECULAR AND SPECTROSCOPIC DATA

	227.0°K., e. u.	299.8°K., e. u.
Translational and rotational (free)	72.40	75.73
Vibrational (${}^{3}\omega_{7,8,9}$)	0.23 ± 0.08	0.64 ± 0.1
Vibrational (${}^{8}\delta = 950$)	.28 ± .08	.85 ± .2
Vibrational (other modes)	7.59	10.59
Total	80.50 ± 0.16	87.81 ± 0.3
Calorimetric	77.94 ± .30	86.33 ± .6
$(S_f - S) \times 4$ (experimental)	2.56 ± 0.46	1.48 ± 0.9
$(S - S) \times 4$ ($V = 1280$, $I = 5.3 \times 10^{-40}$)	2.56	1.73

The heat of vaporization was obtained temporarily from the measured vapor pressure equation and approximate state data. Hence the larger error at the higher temperature where the correction to the gas volume is larger. The potential of 1280 ± 160 calories was obtained from Pitzer's tables[2] to fit the experimental discrepancy, $(S_f - S) \times 4$. At the lower temperature if the 950 frequency were in error by 200 cm.$^{-1}$, and if $\omega_{7,8,9}$ should really be at 696 cm.$^{-1}$, the entropy would only be raised by 0.7 e. u. and the potential would then be 1600 calories.

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[1] Rank and Bordner, *J. Chem. Phys.*, **3**, 248 (1935).

[2] Pitzer, *ibid.*, **5**, 469 (1937).