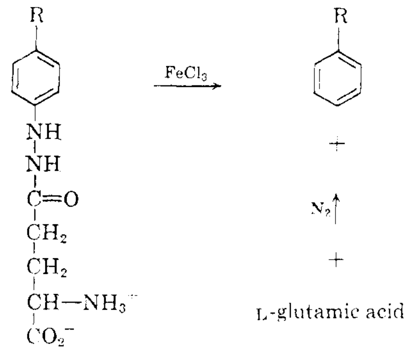
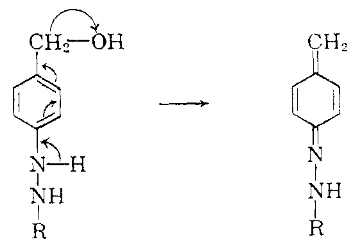


I

ml.) at 4–10° for one minute in a large Waring Blendor. After filtration, the methanol was evaporated *in vacuo*. The aqueous concentrate (2 l.) was passed through a 7.5 × 43 cm. column of Dowex-2 (Ac^-), at the rate of 500–600 ml./hr. The column was eluted with deionized water and the effluent between 1350 and 3700 ml. was passed through a 4″ × 24″ column of Dowex-50 (NH_4^+) at a rate of 800 ml./hr. The column was eluted with deionized water and effluent volume from 8.4 to 10.4 l. was concentrated *in vacuo* to 50 ml. An equal volume of ethanol and 200 ml. of 1-butanol were added and the solution was evaporated *in vacuo* until it became hazy. After standing at 4° for two days 351 mg. of glistening white crystals was obtained; m.p. (dec.) 205–209°, (calcd. for $C_{12}H_{17}N_3O_4$: C, 53.9; H, 6.43; N, 15.7; O, 23.9; —NH_2, 5.2. Found: C, 53.9; H, 6.48; N, 15.5; O, 24.4; —NH_2, 5.5) pK_as in water: 3.4 and 8.86; λ_{max} 237 mμ (ϵ 12,000) and 280 mμ (ϵ 1400); $[\alpha]^{25}_D + 7°$ (*c*, 0.8 in water).

N.m.r. spectral analysis indicated the presence of a *p*-disubstituted benzene ring and the possibility of the —CH_2OH group in the ring. Degradation of agaritine with ferric chloride[3] yielded glutamic acid, nitrogen and benzyl alcohol.

The synthesis of substituted phenylhydrazides of glutamic acid (I) including agaritine (R = CH_2OH) was achieved by condensation of the γ-azide of N-carbobenzoxy-L-glutamic acid[4] with the appropriate hydrazine in ether solution. In the case of analogs such as I where R = H and CH_3 no particular difficulty was encountered and yields of *ca.* 60% were obtained. The protective group was removed by hydrogenolysis. However, the synthesis of agaritine itself presented special problems because of the instability of α-hydroxy-*p*-tolylhydrazine (II, R = H) and its derivatives. Apparently oxygen is eliminated readily in either acid or alkaline medium to yield reactive species III (R = γ-glutamyl or H) which can undergo various side reactions. For this reason it was necessary to devise experimental conditions whereby all steps were carried out under essentially neutral conditions. The α-hydroxy-*p*-tolylhydrazine required for the synthesis of agaritine was prepared by lithium aluminum hydride reduction of *p*-carboxymethylphenylhydrazine in boiling ether. A considerable portion of the ester was reduced to *p*-tolylhydrazine under these mild conditions. This was considered evidence for the elimination reaction (II → III).



II III

Since no satisfactory method was found to isolate and purify α-hydroxy-*p*-tolylhydrazine, aqueous sodium chloride solution was added to the reduction mixture, the inorganic salts were removed by filtration and the γ-azide of carbobenzoxy-L-glutamic acid was added with stirring to the ether solution at 0°. The solvent was evaporated, the protecting group was removed by mild hydrogenolysis[5] and the product was purified by chromatography over Dowex-50 to provide a 6% yield of crystalline agaritine. On the basis of color reactions, R_f values, ultraviolet and infrared spectra, elemental analyses, m.p. and specific rotation the synthetic material was identical with that isolated from *A. bisporus*.

We are grateful to Dr. Bruce Levenberg, Department of Biological Chemistry, University of Michigan, for introducing this problem to us and for his handling of the biochemical aspects of it, to Wm. A. Struck and associates for analytical data, to Dr. George Slomp for the n.m.r. work and to John Woltersom for technical assistance.

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(3) H. B. Milne, J. E. Halven, D. S. Ho and M. S. Mason, *J. Am. Chem. Soc.*, **79**, 637 (1957).

(4) S. G. Waley, *J. Chem. Soc.*, 517 (1955).

(5) Using 10% palladium-charcoal catalyst at 1 atm. at room temperature for one hour. However, using 10% palladium-barium sulfate catalyst at 1 atm. for 7 hours at room temperature, agaritine was converted quantitatively to the *p*-tolyl analog.

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OPTICAL ROTATORY DISPERSION STUDIES. LVII.[1] THE OCTANT RULE AND THE *t*-BUTYL GROUP. EVIDENCE FOR A TWIST FORM IN *cis*-2-*t*-BUTYL-5-METHYLCYCLOHEXANONE[2]

Sir:

From a consideration of the rotatory dispersion curves of (−)-menthone (I)[3] and (+)-isomenthone (II) it was suggested[4] that the energy difference between the axial and equatorial forms of 2-isopropylcyclohexanone is unexpectedly small (less than 0.9 kcal.). This was confirmed by direct

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(1) Paper LVI, C. Djerassi and D. Herbst, *J. Org. Chem.*, in press.

(2) Supported by grant No. CRTY-5061 from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service. A portion of the experimental work was performed in 1959 at Wayne State University.

(3) All structural formulas in this communication represent correct absolute configurations according to the steroid notation.

(4) C. Djerassi, "Optical Rotatory Dispersion," McGraw-Hill Book Co., New York, N. Y., 1960, pp. 106, 187.

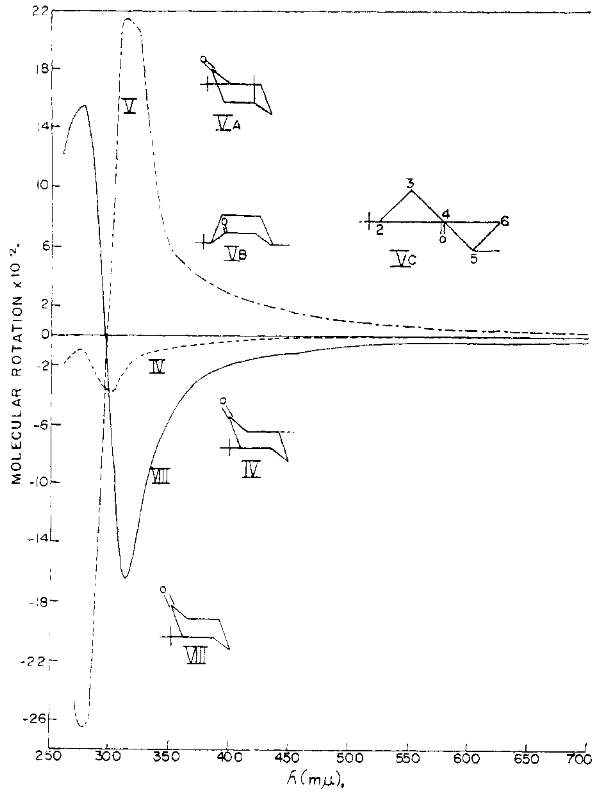

Fig. 1.—Optical rotatory dispersion curves (methanol) of (−)-*trans*-2-*t*-butyl-5-methylcyclohexanone (IV), (+)-*cis*-2-*t*-butyl-5-methylcyclohexanone (V) and (−)-2-*t*-butylcyclohexanone (VIII).

measurements by Allinger and Blatter,[5] who also have studied the role of a *t*-butyl substituent. In connection with our interest in the rotatory dispersion behavior of conformationally flexible cyclohexanones,[6] we have synthesized certain optically active 2-*t*-butylcyclohexanones and these have led to interesting conclusions in the light of the octant rule.[4,7,8]

Addition[9] of methylmagnesium iodide to (+)-pulegone (III) in tetrahydrofuran in the presence of cuprous chloride afforded a mixture of *trans*- and *cis*-2-*t*-butyl-5-methylcyclohexanone (IV, V). The predominant *trans* isomer IV was isolated in pure form by preparative gas phase chromatography on an Ucon Polar-Chromosorb column, while the *cis* ketone V was obtained most conveniently by Jones oxidation (−3°) of the pure all-*cis*-2-*t*-butyl-5-methylcyclohexanol (VI)[10] of m.p. 45–46°, the purity of the two ketones being confirmed by analytical gas phase chromatography on a phenyldiethanolamine succinate–firebrick column. Heating (2 hr. reflux) of either pure IV or V with 5% methanolic potassium hydroxide gave the same equilibrium mixture, whose composition (80% IV *vs.* 20% V) was determined from its rotatory dispersion curve by comparison with the curves (Fig. 1) of the two pure isomers.

According to the tenets of the octant rule,[8] an equatorial α-alkyl substituent in a cyclohexanone should produce a negligible rotational contribution, whereupon one would predict for the chair conformer IV of *trans*-2-*t*-butyl-5-methylcyclohexanone a positive Cotton effect of molecular amplitude similar to that (+2500°) observed[4] for (+)-3-methylcyclohexanone (VII), the dominant factor being the methyl substituent. In actual fact, IV exhibited a weak negative Cotton effect (Fig. 1), which can only be interpreted in terms of an unlikely conformational deformation of IV or to an unexpected rotational contribution of an equatorial *t*-butyl group. In order to settle this question, *trans*-2-*t*-butylcyclohexanol[11] was resolved *via* the two pure 3β-acetoxy-Δ^5-etienic esters,[12] m.p. 181–182°, $[\alpha]^{28}_{\mathrm{D}}$ −45° (all rotations in chloroform) and m.p. 172–174°, $[\alpha]^{28}_{\mathrm{D}}$ −9°, cleavage (lithium aluminum hydride) of which yielded the pure antipodes of $[\alpha]^{28}_{\mathrm{D}}$ −44.4° and $[\alpha]^{28}_{\mathrm{D}}$ +44.2°. Jones oxidation of the former gave (−)-2-*t*-butylcyclohexanone (VIII) with a rather strong negative Cotton effect (Fig. 1) of molecular amplitude −3200°. Combination of the molecular amplitudes of VII and VIII leads to a *calculated negative Cotton effect* of molecular amplitude −700°, which is in very reasonable agreement[13] with the observed one (IV, Fig. 1) of −500°. We conclude that the anticipated chair conformation IV of the *trans* isomer is indeed the correct one and that the unexpectedly large rotational contribution of an α-*t*-butyl group in a cyclohexanone probably reflects the presence of those *t*-butyl rotomers (around C-2 in VIII) which depart from the perfect staggered ethane arrangement.[14] The same explanation can now be offered for the hitherto unrationalized small molecular amplitude (new value +800°) of (−)-menthone (I).[4]

With this information at hand, it now can be stated categorically that the chair conformation VA of *cis*-2-*t*-butyl-5-methylcyclohexanone *cannot* represent the exclusive constituent of its conformer equilibrium in solution. The equatorial *t*-butyl

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[5] N. L. Allinger and H. M. Blatter, *J. Am. Chem. Soc.*, **83**, 994 (1961).

[6] See C. Djerassi, J. Osiecki and E. J. Eisenbraun, *ibid.*, **83**, November (1961).

[7] W. Klyne in "Advances in Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1961, Vol. I, pp. 333–341.

[8] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Am. Chem. Soc.*, **83**, Sept. (1961).

[9] For earlier attempts see V. Grignard and J. Savard, *Compt. Rend.*, **179**, 1573 (1924); H. Rupe, H. Schobel and E. Abegg, *Ber.*, **45**, 1529 (1912).

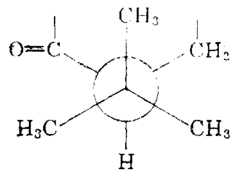
[10] Three of the four possible isomeric cyclohexanols (derivable by lithium aluminum hydride reduction of IV and V) were obtained in pure form and their stereochemistry determined by quantitative chromium trioxide oxidations (J. Schreiber and A. Eschenmoser, *Helv. Chim. Acta*, **38**, 1529 (1955)) for which we are indebted to Prof. A. Eschenmoser.

[11] H. L. Goering, R. L. Reeves and H. H. Espy, *J. Am. Chem. Soc.*, **78**, 4926 (1956).

[12] For preparation of acid see C. Djerassi and J. Staunton, *ibid.*, **83**, 736 (1961); for other resolutions with this acid see R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70, (1959); C. Djerassi, E. J. Warawa, R. E. Wolff and E. J. Eisenbraun, *J. Org. Chem.*, **25**, 917 (1960).

[13] This agreement, *ipso facto*, establishes the absolute configuration of VIII and its precursor alcohol, whose negative rotation is in accord with the alcohol rule of W. Klyne and W. M. Stokes, *J. Chem. Soc.*, 1979 (1954).

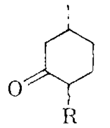
[14] According to the octant rule (ref. 8), in the completely staggered rotomer (i) the *t*-butyl group should make a negligible contribution to the Cotton effect because one of the methyl groups lies practically in the carbonyl plane, while the other two are nearly bisected by that plane.

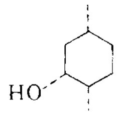


i

group of VA would have to make a molecular amplitude contribution of +3200° (opposite to that of VIII), but the axial methyl group would lower[3] this value appreciably because of its situation in a negative octant. Experimentally (Fig. 1), a positive Cotton effect of +4800° was obtained, which requires that another conformation play an important or exclusive role. If the twist form[15] (of the boat VB) is written as in VC, it will be seen that two of the ring carbons (C-3 and C-5) now make positive contributions,[16] as does the C-5 methyl group, thus being in qualitative agreement with the observed curve. The driving force for this conformational change from VA toward VC is almost certainly the relief of the buttressing to which the axial C-3 hydrogen in VA is exposed on the part of the C-5 methyl function *as well as* one of the equidistant methyl groups of the *t*-butyl moiety.

I R = $-CH(CH_3)_2$
II R = $\ldots CH(CH_3)_2$
III R = $=C(CH_3)_2$
IV R = $-C(CH_3)_3$
V R = $\ldots C(CH_3)_3$
VII R = H
IX R = $-C(CH_3)_2CO_2H$
X R = $\ldots C(CH_3)_2CO_2H$





VI

Addition[17] of cyanide to (+)-pulegone (III) and then hydrolysis gives two isomeric acids, m.p. 92 and m.p. 121°. Rotatory dispersion measurements on these acids and their methyl esters together with equilibration experiments yielded results very similar to those reported above, thus demonstrating that the lower melting isomer should be represented by IX and the higher one by X.

All of the new substances in this communication were fully characterized and gave satisfactory analyses.

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RECEIVED JUNE 29, 1961

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(15) See W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Drieger and W. N. Hubbard, *J. Am. Chem. Soc.*, **83**, 606 (1961).

(16) Consideration of such "asymmetric" ring forms in applications of the octant rule to stereochemical problems concerning six-membered rings—similar to W. Klyne's treatment (*Bull. Soc. Chim. France*, 1396 (1960)) of cyclopentanones—will be covered in a forthcoming paper with Prof. Klyne.

(17) A. Lapworth and R. W. L. Clarke, *J. Chem. Soc.*, **89**, 1869 (1906), isolated only one acid (m.p. 121°).

A NEW PYROLYTIC OLEFIN SYNTHESIS[1]

Sir:

Michaelis and v. Gimborn[2] found that $(C_6H_5)_3$-P^+-CH_2-$CO_2C_2H_5Cl^-$ decomposes slowly at 100° to give triphenylmethylphosphonium chloride. In a somewhat similar experiment Piaux[3] reported that $C_6H_5(CH_3)_2N^+$-$CH_2CO_2C_2H_5I^-$ yields phenyltrimethylammonium iodide on heating. Neither authors reported the isolation of any other products. It seemed reasonable to suspect, as was suggested by Michaelis and v. Gimborn,[2] that carbon dioxide and ethylene were formed.

With this in mind a series of phosphonium and ammonium salts, R_3Z^+-$CH_2CO_2R'X^-$; Z = P,N; X = Br,Cl; R = C_6H_5,C_4H_9, have been prepared and pyrolyzed at temperatures ranging from 136–200°. In all cases an olefin, carbon dioxide and the appropriate onium salt were formed. The best yields and mildest reaction conditions were found with salts, $(C_4H_9)_3P^+$-$CH_2CO_2R'X^-$. Several representative yields of olefins are: R', cyclohexyl (57%); 2-octyl (76%); 1-octyl (62%); 2-heptyl (76%); 1-decyl (67%); cyclohexylcarbinyl (54%); 1-menthyl (43%); *d*-neomenthyl (45%); *trans* - 2 - phenylcyclohexyl (73%); *cis*-2-phenylcyclohexyl (85%) and *trans*-stilbene (90%).

A quantitative study of the isomer distributions obtained with R' = 1-butyl, 1-octyl, 2-butyl, *t*-amyl revealed that both 1-butyl and 1-octyl give 1-butene and 1-octene of high purity (>95%) and high yield. Isomerization of the initially formed terminal olefin can occur if it is not removed from the reaction mixture as it is formed. For example the 1-octyl salt gave 60% 1-octene and 40% isomers when the decomposition was conducted at 170° and the olefin was distilled at atmospheric pressure. Under the same conditions except for reduced pressure (110 mm.) the olefin was > 95% 1-octene. Pyrolysis of the 2-butyl salt at 170° yielded a mixture of butenes; 1-butene (33%), *trans*-2-butene (48%) and *cis*-2-butene (19%). Decomposition of the *t*-amyl salt proceeded smoothly at *ca.* 140° to give a mixture of methylbutenes; 2-methyl-1-butene (32%) and 2-methyl-2-butene (68%).

This synthetic procedure has the advantage over the more conventional ester pyrolysis in the lower temperature required for olefin formation. This is particularly the case for the formation of terminal olefins from primary alcohols.[4] The drastic reduction in temperatures required for effective synthesis suggests a mechanistic change from that for the usual ester pyrolysis.[4] An intriguing possibility involves a transition state in which hydrogen is being transferred to carbon rather than oxygen. Work on this aspect of the reaction and its synthetic extension is being continued.

A typical procedure is given: 2-octyl bromoacetate, 23.0 g., 0.10 mole, and tributylphosphine, 20.0 g., 0.10 mole, were mixed with cooling. The mixture was heated to 190° (bath) and maintained

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(1) Research supported by the National Science Foundation.

(2) A. Michaelis and H. V. Gimborn, *Ber.*, **27**, 272 (1894).

(3) L. Piaux, *Compt. rend.*, **190**, 645 (1930).

(4) C. H. DePuy and R. W. King, *Chem. Revs.*, **60**, 431 (1960).