890 cm.$^{-1}$, which was identical with VIb, the 3-hydroxyetiolactone prepared from the synthetic etiolactone (V).

The isolation and characterization of 5α-(4,5)-dihydroaldosterone (Ia) and 3βOH,5α-(4,5)-tetrahydroaldosterone (IIa) indicates that the ring A reduced products with A/B *trans* (5α) in configuration are favored.

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RECEIVED AUGUST 4, 1960

THE KETO-ENOL EQUILIBRIUM OF ETHYL ACETOACETATE UNDER HIGH PRESSURE

Sir:

It has been demonstrated in recent years that studies of the effect of pressure on reaction rates in the liquid phase often permit certain conclusions to be drawn regarding the mechanism involved.[1] For instance, reactions are accelerated if they proceed through a transition state that has a greater separation of charge than the reactant(s) and *vice versa*, since the intense electric field of an ion causes local compression of solvent molecules.[2] In the expression $d \ln k/dp = -\Delta V^*/RT$, the volume of activation is negative in such cases. On the other hand, a reaction is decelerated (ΔV^* is positive) if the formation of the transition state depends on homopolar bond breaking and *vice versa*,[3] since the sum of the van der Waals radii of the fragments exceeds that of the reactant.

It appeared that another feature often of interest in mechanistic studies, *i.e.*, formation of a cyclic transition state, could be subject to a pressure effect.[4] A comparison of the densities of straight chain hydrocarbons shows that the molar volume of n-C_mH_{2m+2} exceeds that of n-$C_{m-6}H_{2m-10}$ by 96 ± 1 ml./mole (m ranging from 11 to 17). This difference is a measure of the volume of hexamethylene, —$(CH_2)_6$—. This value is 12 ml./mole *smaller* than the molar volume of cyclohexane (108 ml./mole). Parachor data[5] on ring structures similarly suggest that ring structures have greater volume requirements than straight chains. Presumably the core of such doughnut-like molecules is too small to be accessible to other molecules.

In this work, the keto–enol equilibrium was studied as an example. If the process of forming a cyclic structure such as the enol form of ethyl acetoacetate[6] does not contribute to the change in molar volume, the equilibrium constant (K keto/enol) should decrease as the pressure is increased, since the molar volume of the group —C(OH)=CH— is smaller than that of the group —$COCH_2$— by about 4.0 ml./mole (estimated from the densities of unsaturated alcohols and isomeric carbonyl compounds); if the internal H-bond is taken into account, this difference would undoubtedly be somewhat greater. If the ring formation has the positive volume requirement described above, the molar volume of the enol form should be *larger* than that of the keto form by about 5 ml./mole. The effect of pressure on this equilibrium was studied by Kabachnik, Yakushkima and Kislyakova,[7] who reported no significant change in K for the pure substance. Since the rate of interconversion is extremely variable (depending on traces of impurities[6]) it appeared desirable to repeat this work. The new data (Table I) show that K in the pure liquid increases with pressure; the molar volume of the enol form exceeds that of the keto form by 1.0–1.5 ml./mole. This would suggest that it may be possible to recognize reactions involving a cyclic transition state by a retarding effect of pressure. An experimental program to test this statement is about to start in this laboratory.

TABLE I

p(atm.)[a]	% enol[b]	K keto/enol	ΔV (ml./mole)[c]
1	7.7	12.0	
1350	7.2	13.0	−1.5
2500	7.0	13.2	−1.0
3700	6.4	14.6	−1.3

[a] The apparatus will be described at a later date. [b] At 25°. Samples of the ester were withdrawn without releasing the pressure, collected in a quartz vessel and analyzed at once in the usual way (K. H. Meyer and P. Kappelmeyer, *Ber.*, **44**, 2718 (1911)). Care was taken to insure the system was at equilibrium and that interconversion during analysis was negligible. [c] Calculated from $(\ln K_p - \ln K_1) = -\Delta V/RT$.

Acknowledgment.—This work was done at the Rohm and Haas Research Laboratories. The author had the benefit of many helpful discussions with Mr. O. H. Loeffler and Drs. C. Huggett and B. Iwanciow.

(1) For an excellent review, see S. D. Hamann, "Physico-Chemical Effects of Pressure," Academic Press, Inc., New York, N. Y., 1957.

(2) H. C. David and S. D. Hamann, *Trans. Far. Soc.*, **50**, 1188 (1952).

(3) A. E. Nicholson and R. G. W. Norrish, *Disc. Far. Soc.*, 97 (1956).

(4) C. Walling and J. Peisach have considered this possibility recently in the dimerization of isoprene to cyclic products (THIS JOURNAL **80**, 5819 (1958)).

(5) S. Sugden, "The Parachor and Valency," Geo. Rutledge & Sons, Ltd., London, 1929.

(6) G. W. Wheland, Ch. XIV, "Advanced Organic Chemistry," 2nd Edition, John Wiley & Sons, Inc., New York, N. Y., 1949.

(7) M. I. Kabachnik, S. E. Yakushkima and N. V. Kislyakova, *Doklady Akad. Nauk., S.S.S.R.*, **96**, 1169 (1954); *cf. C.A.*, **49**, 8815 (1955). The authors stated that the system was allowed 4 hours to reach equilibrium; in this work it was found that at least 20 hours was necessary.

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WILLIAM J. LE NOBLE

RECEIVED AUGUST 23, 1960

THE STEREOCHEMISTRY OF JACOBINE

Sir.

Recent investigations[1] have shown all previous structures proposed for jacobine, jaconecic acid and *iso*jaconecic acid to be incorrect. The structures of these compounds are correctly represented by I, II and III, respectively. We wish now to present evidence which permits assignment of stereochemistry to the above compounds, as shown in Ia, IIa and IIIa.

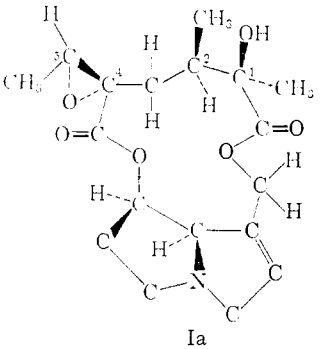
(1) R. B. Bradbury and S. Masamune, THIS JOURNAL, **81**, 5201 (1959), and also see T. A. Geissman, *Aust. J. Chem.*, **12**, 247 (1959).

Earlier we described the formation of optically active β-methyl-γ-carboxy-γ-valerolactone (IV) and optically active β-methyllevulinic acid (V) upon treatment of jaconecic acid (II) with lead tetraacetate in hot aqueous acetic acid.[1] The asymmetric centers C_1 and C_2 of II undoubtedly were unaffected during the reaction that led to IV and V. Therefore, the stereochemistry of these two products can be related directly to that of II.

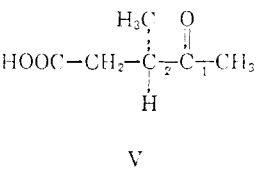
The C_2 Center of II.—The Baeyer–Villiger reaction[2] of the methyl ester of V with perbenzoic acid and then treatment with barium hydroxide, diazomethane and hydrazine afforded levorotatory β-hydroxybutyric acid hydrazide of *known absolute configuration* (43% yield), m.p. 127°, $[\alpha]^{25}D$ −25.1 (EtOH).[2] This correlation establishes the absolute configuration of the C_2 center of II.

The C_1 Center of II.—The two possible stereoisomeric racemates of β-methyl-γ-carboxy-γ-valerolactone (VI and VII, *vide infra*) were synthesized and their stereochemistry was established. Finally each racemate was resolved and compared with IV, a direct degradation product of II.

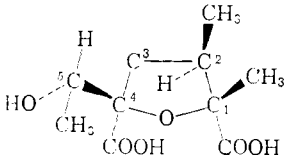
The acid hydrolysis of methyl *dl*-β-methyllevulinate cyanohydrin gave rise to lactone-A (VI), m.p. 151–152°; *p*-bromophenacyl ester, m.p. 86–88°, and the diastereoisomeric lactone-B (VII), m.p. 65.5–67°; *p*-bromophenacyl ester, m.p. 105–106°. Addition of three moles of phenylmagnesium bromide to VI followed by mild acid treatment gave 2,3-dimethyl-5,5-diphenyl-2-hydroxypent-4-enoic acid (VIII), m.p. 129–130°, which was ozonized (oxidative work-up in a neutral medium) to furnish α,β-dimethylmalic acid (IX), m.p. 150–151°.[3] The dimethyl ester of IX was reduced with lithium aluminum hydride to give triol-A, 2,3-dimethylbutane-1,2,4-triol (X); bis-*p*-nitrobenzoate, m.p. 156–157.5°. The lactone-A (VI) is thus correlated with X. The stereochemistry of X was determined by the stereoselective synthesis of the diastereoisomeric triol-B (XI); bis-*p*-nitrobenzoate, m.p. 162–163.5°. Dimethylmaleic anhydride was subjected to a reaction sequence involving reduction with lithium aluminum hydride to the diol, b.p. 81° (0.05 mm.), acetylation to the diacetate, b.p. 132–132.5° (15 mm.), perbenzoic acid treatment to the epoxide, b.p. 95–97° (0.6 mm.), and finally epoxide cleavage with lithium aluminum hydride to yield XI. The two triols, X and XI, proved to be diastereoisomeric, m.m.p. of the two bis-*p*-nitrobenzoates 140–148°. The known stereochemical course[4] of epoxide opening with lithium aluminum hydride establishes the configuration of XI and therefore the diastereoisomer X is shown to be Xa. Consequently the two methyl groups of VI are assigned a *trans* configuration, and since IV, the valerolactone obtained from jaconecic acid, was found to be an optically active isomer of VII,[5] the methyl groups of IV must possess a *cis* configuration.



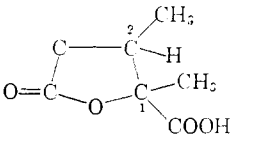
Ia



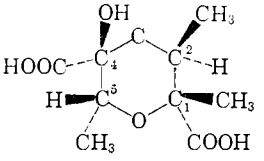
V



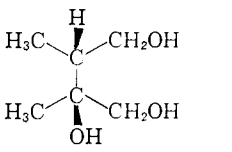
IIa



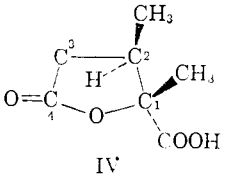
VI Racemate Methyls *trans*
VII Racemate Methyls *cis*



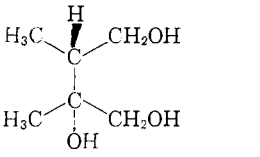
IIIa



Xa



IV



XI

The C_4 Center of II.—That the two carboxylic groups of II are *cis* follows from the previous finding[1] of the facile formation of acetyljaconecic anhydride from II.

The C_5 Center of II.—The action of methylmagnesium iodide on the phenyl glyoxalate ester[6] at C_5 of dimethyl jaconecate and then hydrolysis gave optically active atrolactic acid (60% yield), $[\alpha]^{23}D$ +4.31 (EtOH).[2] The predominance of the *d*-isomer in the product establishes the absolute configuration of the C_5 center of II.

The above findings show that the stereochemistry of jaconecic acid is IIa. Since the stereochemistry of retronecine has been established previously,[7] jacobine and isojaconecic acid may be assigned Ia and IIIa. These assignments are made on the basis of this consideration for the formation of II and III from I: during the alkaline hydrolysis, the epoxide ring of I is cleaved *with inversion* at either C_4 or C_5 by the C_1 hydroxyl group, giving jaconecic acid and isojaconecic acid, respectively.

The known relationship of jacobine with jaconine[1] and jacoline[1] also suggests the stereochemistry of the latter compounds.

(2) W. Klyne, "Progress in Stereochemistry," Butterworths Scientific Publications, London, 1954, Vol. I, chap. 5.

(3) R. B. Bradbury, *Aust. J. Chem.*, **9**, 521 (1956).

(4) W. G. Brown, "Organic Reaction," R. Adams, ed., John Wiley and Son, Inc., New York, N. Y., 1951, Vol. 6, p. 476.

(5) VI was resolved through the cinchonidine salt to afford an enantiomorph, m.p. 181.5–183°, $[\alpha]^{28.5}D$ +3.93 (H_2O); *p*-bromophenacyl ester, m.p. 118°. The resolution of VII was achieved either with brucine or cinchonidine.[1]

(6) This ester was purified by molecular distillation at 130–140° (0.03 mm.), $[\alpha]^{21}D$ +28.5° (MeOH).

(7) For a recent review, see N. J. Leonard, "The Alkaloids," R. H. F. Manske, ed., Academic Press Inc., New York, N. Y., 1960, Vol. 6, chap. 2.

Of some thirty *Senecio* alkaloids of known structures,[7] jacobine is now the first member of the family whose stereochemistry is completely formulated with the absolute configuration also established. The stereochemical correlation of this alkaloid with other members of the *Senecio* family (in particular, seneciphylline,[8] integerrimine[7] and senecionine[7]) will be undertaken.[9,10,11]

(8) S. Masamune, *Chem. and Ind.*, 21 (1959).

(9) Satisfactory analyses and ultraviolet and infrared spectra were obtained for all the new compounds described herein.

(10) The author is deeply indebted to Dr. R. B. Bradbury, Swinburne Technical College, Australia, for his helpful suggestions and generous gifts of natural products, without which this work would not have been completed.

(11) This investigation was supported by a grant (RG-6646) from the National Institute of Health, Public Health Service.

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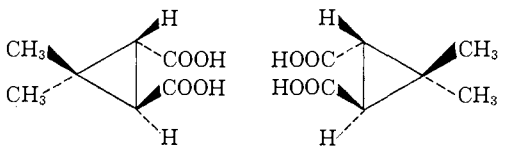
RECEIVED JULY 26, 1960

CYCLOPROPANES. VII. THE ABSOLUTE CONFIGURATION OF *trans*-CARONIC AND *cis* AND *trans*-UMBELLULARIC ACIDS[1]

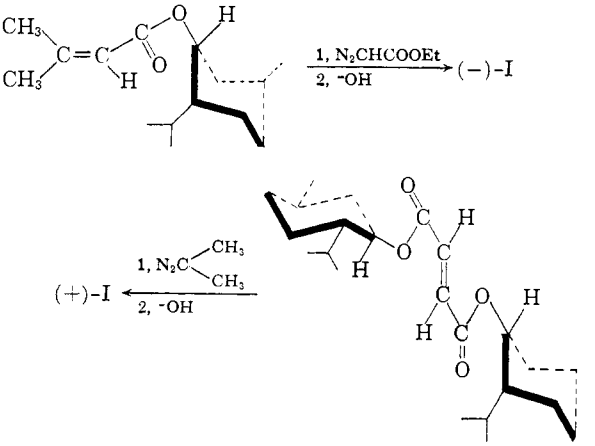
Sir:

It was shown recently that the addition of diazodiphenylmethane to (−)-menthyl acrylate and (−)-menthyl methacrylate resulted in partial asymmetric syntheses.[2] On the basis of the Prelog[3]–Cram[4] model[5] the absolute configurations were assigned tentatively to the 2,2-diphenylcyclopropanecarboxylic acids that were obtained. We wish to report evidence in support of the use of this model, and to assign absolute configurations to *cis* and *trans*-umbellularic acids.



I

The absolute configuration of *trans*-caronic acid has been previously established[6] and has the configuration shown above. This fact provides one with the means of determining whether the Prelog–Cram model can be used for establishing absolute configurations by the addition of diazo derivatives to α,β-unsaturated menthyl esters. Using this model one would predict that the addition of diazodimethylmethane to (−)-dimenthyl fumarate would produce (+)-I in excess, whereas the addition of ethyl diazoacetate to (−)-menthyl β,β-dimethylacrylate should yield (−)-I predominantly. This prediction has been verified experimentally (*vide infra*) and provides cogent support for the use of the Prelog–Cram model.



Ethyl diazoacetate (4.8 g., 0.042 mole) was added slowly to (−)-menthyl β,β-dimethylacrylate[7] (10.0 g., 0.042 mole) at 130–140°. The reaction mixture was distilled to remove unreacted acrylate (7.3 g.) which was treated once more with an equivalent amount of ethyl diazoacetate to yield a total of 2.4 g. (65%) of crude adduct.[8] The adduct was subjected to complete saponification[9a] to yield pure caronic acid (27%),[9b] $[\alpha]^{20}D$ − 5.05° (ethanol), m.p. 205–207°, whose infrared spectrum was identical with an authentic sample.[10] The observed optical rotation corresponds to 15.9% asymmetric synthesis.[10]

To a xylene solution of dimethyldiazomethane[11] was added a solution of (−)-dimethyl fumarate (31.4 g.) in xylene at 0–5° to yield, upon removal of solvent, an oily product. The oil (10.0 g.) was heated with copper powder (1.0 g.) at 160–170° until nitrogen evolution ceased and the product distilled to yield 5.3 g. (56%) of the adduct ester. Complete saponification[9a] yielded *trans*-caronic acid (0.20 g., 25%),[12] m.p. 206–212°, $[\alpha]^{20}D$ + 2.0° (ethanol). This corresponds to 6.3% asymmetric synthesis.

Ethyl diazoacetate (5.0 g.) was added slowly to (−)-menthyl α-isopropylacrylate[13] (11.3 g.) at 80° until nitrogen evolution ceased. The addition product was saponified[9a] and the mixture of *cis* and *trans* acids separated to yield 1.25 g. (14.7%) of *cis*-umbellularic acid, m.p. 107–110°, $[\alpha]^{16}D$ − 5.4° ($CHCl_3$), whose infrared spectrum was identical with that of an authentic sample.[14] This represents 6% asymmetric synthesis.

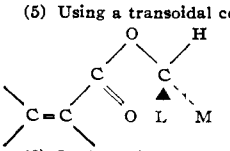
(1) This work was supported, in part, by a grant from the National Science Foundation.

(2) F. J. Impastato, L. Barash and H. M. Walborsky, THIS JOURNAL, **81**, 1514 (1959).

(3) V. Prelog, *et al.*, *Helv. Chim. Acta*, **36**, 308 (1953).

(4) D. J. Cram and F. A. Abd Elhafez, THIS JOURNAL, **74**, 5828 (1952).

(5) Using a transoidal coplanar configuration for the



system and a staggered orientation of the asymmetric center such that two substituents (L and M) or (H and M) flank the carbonyl and the third is in the plane of the coplanarity.

(6) L. Crombie and S. H. Harper, *J. Chem. Soc.*, 470 (1954), established absolute configuration of chrysanthemum-carboxylic acid. Chrysanthemum-carboxylic acid has been degraded to caronic acid (see H. Staudinger and L. Ruzicka, *Helv. Chim. Acta.*, **7**, 201 (1924)).

(7) M.p. 35–36°, $[\alpha]^{15}D$ −80.4° (ethanol); it gave the correct elemental analysis, as did all other new substances reported here.

(8) A fraction b.p. 160–168° at 0.6 mm. was collected. Complete fractionation was avoided. The yield is based on recovered (−)-menthyl β,β-dimethylacrylate.

(9) (a) As evidenced by the absence of carbonyl absorption at 1720 cm.$^{-1}$ in the neutral fraction. (b) The *cis* isomer was not isolated.

(10) A. Fredga and Å. Skiström, *Arkiv. Kemi*, **8**, 433 (1955).

(11) P. C. Guha and D. K. Sankaran, *Ber.*, **70**, 1688 (1937).

(12) The infrared spectrum showed slight contamination by fumaric acid.

(13) B.p. 64–65° at 0.1 mm., $n^{12}D$ 1.4648, $[\alpha]^{16}D$ −81.6° (ethanol).

(14) H. N. Rydon, *J. Chem. Soc.*, 829 (1936).