Kinetics of the Decarboxylation of Some 1,1-Cycloalkanedicarboxylic Acids

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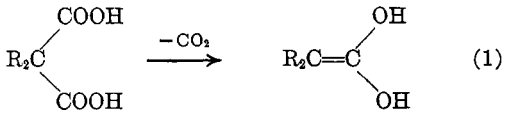
The kinetics of decarboxylation of the 1,1-cycloalkanedicarboxylic acids of the three-, four-, five-, and six-membered rings have been studied in collidine, diethylene glycol, 98% sulfuric acid, and 85% phosphoric acid and in the molten state. No simple correlation between rate and ring size or solvent is evident, but rather ΔH^* and ΔS^* tend to balance each other out to confine the rates to a rather limited range. The linear relationship between ΔH^* and ΔS^* is discussed.

The mechanism of decarboxylation of malonic acid (and presumably the α-substituted malonic acids) probably follows a two-step process involving loss of carbon dioxide as the first step, followed by ketonization of the intermediate enol.[1] The solvent may serve both to assist in the loss of carbon dioxide by solvation and as a protonating agent toward the intermediate enol. Loss of carbon dioxide begins to take place at



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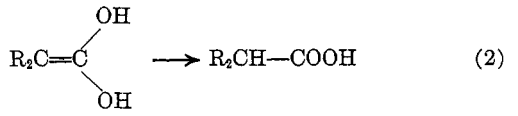


(2)

about the melting point of the acid, and the reaction rate has a marked temperature coefficient. In all of the kinetic experiments described in the literature, the rate has been followed by evolution of the carbon dioxide. The kinetic importance of the ketonization reaction is not known.

Clark[2] has published a very extensive series of papers on the influence of the solvent on the kinetics of the decarboxylation of substituted malonic acids. His results indicate that there is a linear relationship between ΔH^* and ΔS^*. All his rate data fit a series of very closely spaced parallel lines on the ΔH^* *vs.* ΔS^* plot, and, consequently, the observed rates are a result of a fairly close compensation by ΔH^* for changes in ΔS^*.

The influence of ring size on this reaction has not previously been explored, except that ring size and solvent have a substantial effect on stereochemistry in the decarboxylation of 1,1,2-cycloalkanetricarboxylic acids.[3] The influence of ring size and solvent were so pronounced that it was considered very much worthwhile to look at the kinetics of the reaction, using the simpler 1,1-cycloalkanedicarboxylic acids, however, in order to ascertain whether ring size or solvent may have been altering the fundamental mechanism.

Results and Discussion

The 1,1-cycloalkanedicarboxylic acids of cyclopropane, cyclobutane, cyclopentane, and cyclohexane were prepared and purified by conventional procedures. They were decarboxylated in quantities of sufficient size to give about 25 cc. of carbon dioxide when completely converted to the monocarboxylic acids. The rates were followed by measurement of the rate of evolution of carbon dioxide. The decarboxylation solvents employed were 98% sulfuric acid, 85% phosphoric acid, diethylene glycol, and collidine. Decarboxylations were also carried out without a solvent. The solvents were chosen to give as wide a spread to the kinetic and activation energy data as possible.

The reaction kinetics were cleanly first order virtually to completion of the reaction (Figure 1, where the last

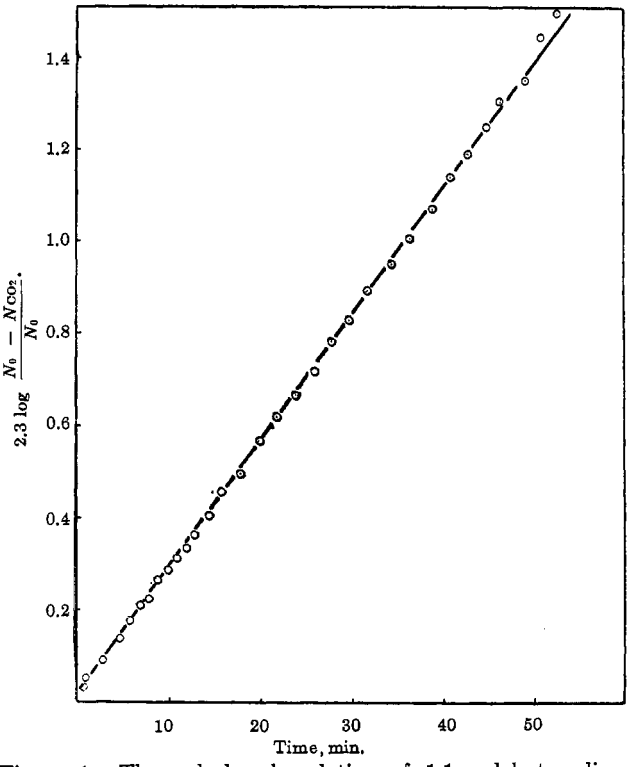


Figure 1.—Thermal decarboxylation of 1,1-cyclobutanedicarboxylic acid without solvent at 165°.

point in the upper right corner corresponds to 86% completion). The reactions were carried out over a range of temperatures convenient for measuring the rate of carbon dioxide evolution. Satisfactory Arrhenius plots were obtained (Figures 2–5) from which the enthalpies and entropies of activation were computed. The low solubility of the 1,1-cyclohexanedicarboxylic acid in sulfuric acid, and the fact that the evolution of carbon dioxide from this compound in sulfuric acid was much greater than theoretical, makes the data for that point quite unreliable, but for the rest of the compounds in

(1) G. Fraenkel, R. L. Belford, and P. E. Yankwich, *J. Am. Chem. Soc.*, **76**, 15 (1954).
(2) L. W. Clark, *J. Phys. Chem.*, **68**, 3048 (1964), and papers cited therein.
(3) P. I. Abell and D. J. J. Lennon, *J. Org. Chem.*, **30**, 1206 (1965).

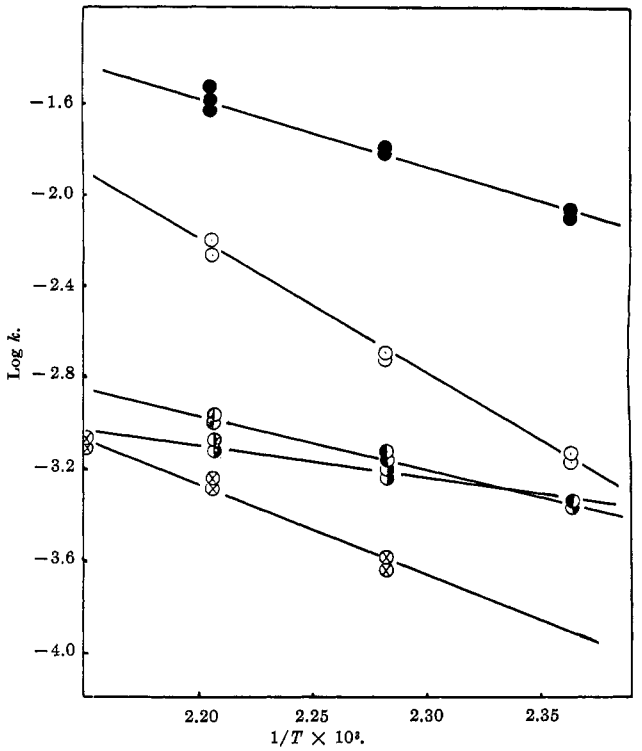


Figure 2.—Arrhenius plot for the decarboxylation of 1,1-cyclopropanedicarboxylic acid: ◑, collidine; ⊗, diethylene glycol; ●, sulfuric acid; O, phosphoric acid; and ◐, no solvent.

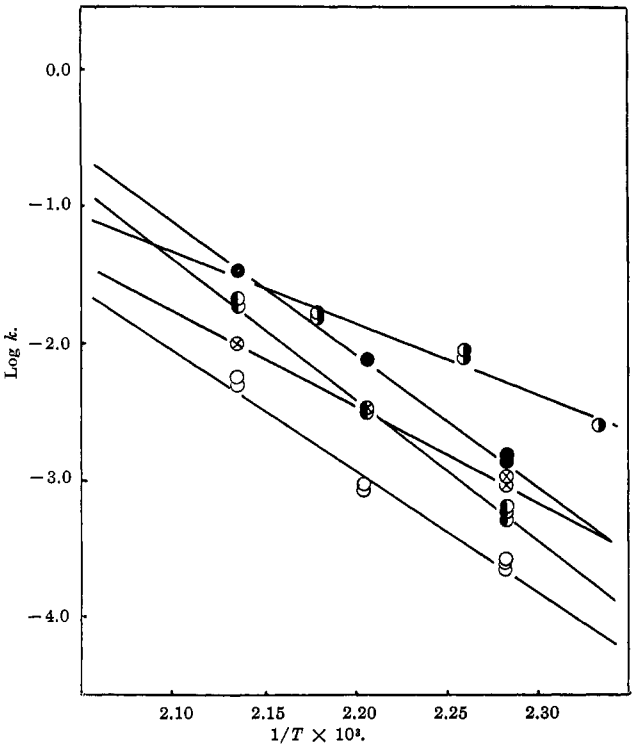


Figure 3.—Arrhenius plot for the decarboxylation of 1,1-cyclobutanedicarboxylic acid. The symbols for solvent are the same as those in Figure 2.

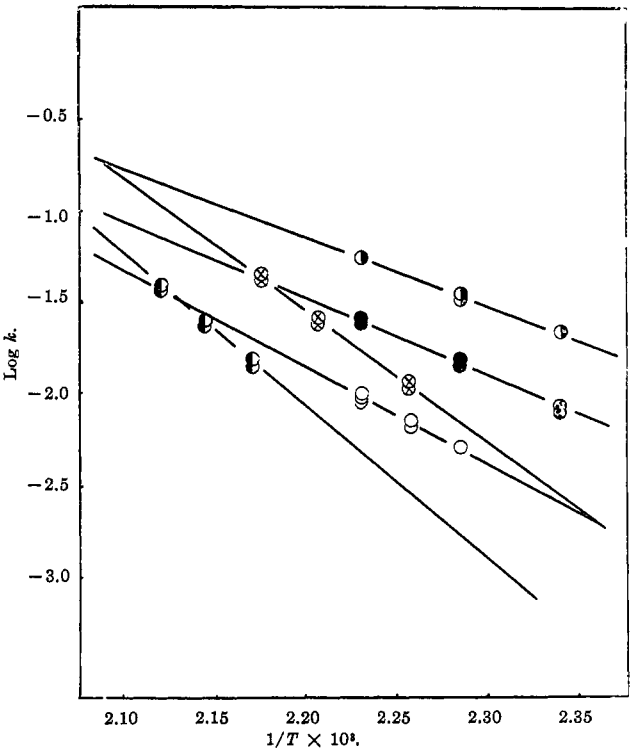


Figure 4.—Arrhenius plot for the decarboxylation of 1,1-cyclopentanedicarboxylic acid. The symbols for solvent are the same as those in Figure 2.

TABLE I

KINETIC DATA

1,1-Cycloalkanedicarboxylic acid	Solvent	$k \times 10^5$, sec.$^{-1}$[a]	ΔH^*, kcal./mole[b]	ΔS^*, e.u.
Cyclopropane	H_2SO_4	30.05	13.13 ± 0.365	−37.68 ± 0.835
	H_3PO_4	4.97	25.61 ± 0.244	−17.36 ± 0.559
	Molten	1.21	14.66 ± 0.438	−40.11 ± 0.100
	Collidine	1.11	6.65 ± 0.331	−58.81 ± 0.757
	Diethylene glycol	0.63	17.12 ± 0.437	−36.63 ± 0.97
Cyclobutane	H_2SO_4	7.25	41.01 ± 0.233	21.42 ± 0.515
	H_3PO_4	1.13	39.99 ± 0.531	15.61 ± 0.117
	Molten	3.29	48.92 ± 0.257	37.18 ± 0.568
	Collidine	13.50	23.17 ± 0.765	−16.80 ± 0.172
	Diethylene glycol	3.30	30.80 ± 0.640	−2.755 ± 0.141
Cyclopentane	H_2SO_4	37.45	21.15 ± 0.359	−19.42 ± 0.821
	H_3PO_4	15.35	18.66 ± 0.167	−27.06 ± 0.378
	Molten	8.95	37.35 ± 0.822	13.16 ± 0.176
	Collidine	72.90	17.47 ± 0.210	−26.14 ± 0.482
	Diethylene glycol	28.60	18.55 ± 0.170	−25.52 ± 0.377
Cyclohexane	H_2SO_4	1746	47.30 ± 0.156	44.34 ± 0.372
	H_3PO_4	6.31	25.27 ± 0.337	−13.69 ± 0.746
	Molten	6.26	34.38 + 0.454	6.70 ± 0.100
	Collidine	29.9	11.87 ± 0.905	−39.96 ± 0.207
	Diethylene glycol	26.0	25.45 ± 0.101	−10.77 ± 0.223

[a] At 180°. Values extrapolated or interpolated from best least squares) through experimental data. [b] Error estimate is 95% certainty in ±2 standard deviations.

the other solvents the kinetics are believed to be valid. These rates and associated thermodynamic quantities are collected in Table I, while samples of the decarboxylation rate constants for 1,1-cyclobutanedicarboxylic acid at a variety of temperatures and in the various solvents are shown in Table II.

A plot of the enthalpies *vs.* entropies of activation for the various dicarboxylic acids in the selected solvents is shown in Figure 6, in which a moderately good linear relationship is observable. The majority of the points fall on a single straight line, except that the points for the 1,1-cyclopropanedicarboxylic acid give a parallel line, with only the sulfuric acid solvent falling off this second line and onto the line for the other acids. The slopes of these lines, by a least-squares treatment, are 485 and 459, and the intercepts are 31,216 and 33,564 for the general and cyclopropyl acid lines, re-

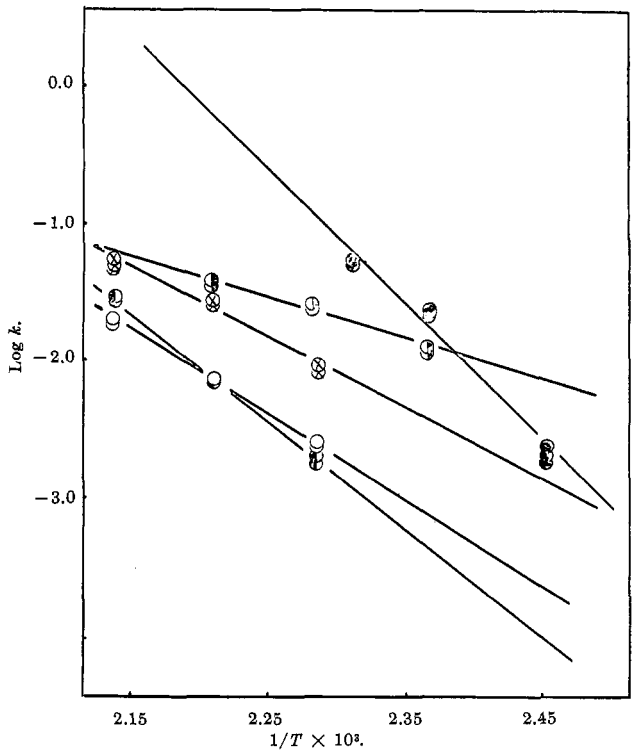


Figure 5.—Arrhenius plot for the decarboxylation of 1,1-cyclohexanedicarboxylic acid. The symbols for solvent are the same as those in Figure 2.

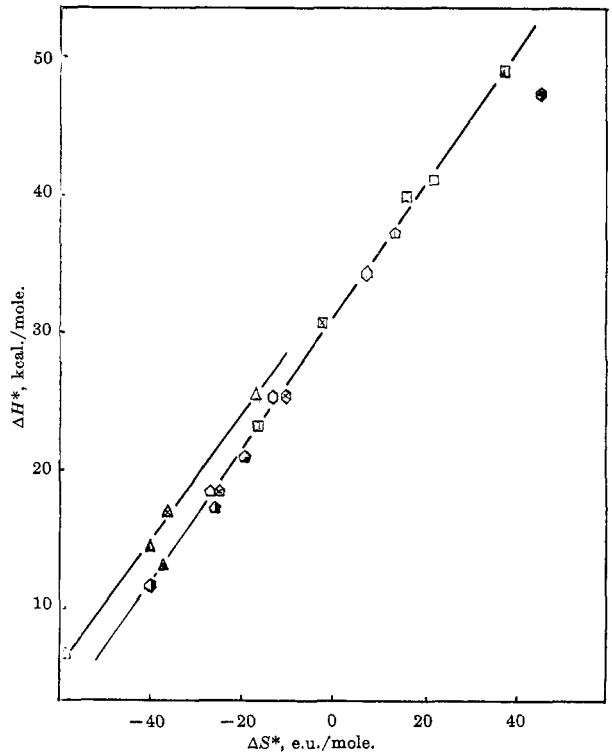


Figure 6.—Enthalpy of activation *vs.* entropy of activation for 1,1-cycloalkanedicarboxylic acids; the size of the ring is indicated by the shape of the symbol. The symbols correspond to those in Figure 2.

TABLE II

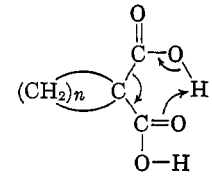
RATE CONSTANTS FOR DECARBOXYLATION OF 1,1-CYCLOBUTANEDICARBOXYLIC ACID

Solvent	$k \times 10^3$, sec.$^{-1}$ 155°	165°	170°	180°	185°	195°
H_2SO_4		0.156		7.25		325
H_3PO_4		0.266		1.13		5.54
Molten		0.478		3.29		18.8
Collidine	2.38		7.96		15.60	
Diethylene glycol		1.12		3.30		9.74

spectively. The slope has the units of absolute temperature and is referred to as the isokinetic temperature, while the intercepts have the units of calories. These values compare with similar decarboxylation data from Clark[2] where the slope had the value of 422, and the intercept 31,000. There are several points relative to Figure 6 which bear examination and discussion. (1) The points for the 1,1-cyclopropanedicarboxylic acid decarboxylation are confined to the lower left, with low values of ΔH^* and quite negative ΔS^* values, while the points for the cyclobutyl compound are found toward the upper right. (2) The data for the five- and six-membered rings are spread out over the entire line. (3) Only the points for the three-membered ring are not included in the straight line through the majority of the points. (4) The values of ΔS^* are generally at or near the maximum when collidine is used as solvent, regardless of ring size.

Leffler and Grunwald[4] have discussed the linear relationship between enthalpies and entropies of activation in a given reaction series at considerable length. They point out that, where such a relationship has clear validity (*i.e.*, where the isokinetic temperature obtained as the slope of the ΔH^*–Δ^* line is significantly displaced from the temperature at which the data is collected), a straight-line relationship indicates a probable continuity of mechanism and the presence of only one variable interaction mechanism. Where more than one interaction mechanism (*e.g.*, steric effects as well as inductive effects) is present, then parallel lines result. While our isokinetic temperature, as calculated from the slope of the ΔH^*–ΔS^* plot, falls in the midst of the temperature range at which data were collected (and might therefore be suspect), the test for confidence suggested by Petersen, *et al.*,[5] indicates a substantial reliability in the linearity of the relationship. Our values for reliability, $d\Delta H^*/2\delta$, where δ is the maximum fractional error in ΔH^*, range from 4.23 to 17.60. Values greater than unity indicate validity in the linearity of the relationship.

The interpretation of these results is not so straightforward as had been hoped when the work was initiated. While it might be expected that steric effects would be of prime importance in the decarboxylation process, there are several distinct ways in which these effects might enter the picture. One is the strain involved in forming an exocyclic double bond as the enol is formed, and certainly the cyclopropanedicarboxylic acid is going to resist formation of such a bond more than the larger rings. A second steric problem is the achievement of the presumed cyclic transition state



(4) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1963.

(5) R. C. Petersen, J. H. Markgraf, and S. D. Ross, *J. Am. Chem. Soc.*, **83**, 3819 (1961).

where the ring strain may spread the angle between the two carboxyl groups to a point where intramolecular hydrogen transfer is seriously impeded. It is this strain and the greater entropy requirements involved that might be presumed to displace the cyclopropanedicarboxylic acid points from the general linear relationship of ΔH^* *vs.* ΔS^* for the other acids, although the failure of the point for sulfuric acid to fall with the other four solvents is not readily interpretable.

A third steric factor is the bulk of the solvent as it solvates the acid and/or the departing carbon dioxide. Entropy terms ought to show up markedly here, and the consistently negative values of ΔS^* for collidine compared with the other solvents indicates that it is indeed involved in solvation. However, while the entropy requirements are high, the ability to solvate carbon dioxide[1] compensates, and the enthalpy of activation is considerably lower in this solvent. Certainly no real base catalysis is observed, however.

The fact that the points for the three larger rings yield a single ΔH^* *vs.* ΔS^* line indicates a good compensation of these two factors and the probability that there is only one important "interaction mechanism" involved. That this is not ring strain seems clear; thus the best alternative is solvent action on a cyclic transition state. Some reinforcement for this notion comes from the positioning of the cyclobutanedicarboxylic acid points on the upper right portion of the enthalpy–entropy diagram (Figure 6), since the small ring would be expected to pull back the methylene groups to permit easy access of solvent.

The summation of these ideas would suggest that the transition state must lie closer to starting materials than enol in decarboxylation and that in general the entropies and enthalpies of activation compensate each other to produce only a small range of rates through the ring series investigated.

Experimental Section

The 1,1-cycloalkanedicarboxylic acids of the three-, four-, five-, and six-membered rings were prepared by the method of Vogel,[6] as originally worked out for the four-membered ring acid in which a polymethylene dibromide is condensed with sodium malonic ester. The acids were purified by recrystallization.

The products, prepared by using the apporpriate polymethylene dibromide, are described in Table III.

TABLE III

1,1-Cycloalkanedicarboxylic acid	M.p., °C. This work	M.p., °C. Lit.[a]	% yield[b]
Cyclopropane	139–141	140–141	12
Cyclobutane	156–157	157	27
Cyclopentane	183–184	184–186	29
Cyclohexane	174–176	179.5	32

[a] From ref. 6. [b] Calculated on the basis of polymethylene dibromide.

Decarboxylation of the Acids.—Weighed samples of the dicarboxylic acids (0.001 mole) were introduced into a small reaction flask together with 1.5 ml. of solvent and heated in mineral oil under constant temperature conditions. The volume of carbon dioxide generated in the reaction vessel was measured in a gas buret over saturated sodium chloride solution, and the volume observed was corrected to standard conditions. The decarboxylations without solvent were carried out by heating the reaction flask to temperatures in excess of the melting points of the acids until carbon dioxide evolution was complete. The decarboxylations in collidine, concentrated H_2SO_4, 85% H_3PO_4, and diethylene glycol were carried out by heating also, again until gas evolution was complete. In a typical example, 0.1440 g. (0.001 mole) of 1,1-cyclobutanedicarboxylic acid was introduced into a small reaction flask together with 1.50 ml. of solvent and heated in the constant-temperature oil bath. In a series of three such runs, the gas evolution was 21.82, 21.70, and 22.20 cc. at STP (22.40 cc. at STP theoretical). The reaction was carried out at three tempratures between 155 and 195° for this acid, in triplicate for each temperature. The gas volumes, corrected to standard conditions, were used to prepare Arrhenius plots, and from these the rate constants were obtained from the slopes. See Figures 2–5. The rate constants for the four-membered ring acid are collected in Table II.

From absolute reaction rate theory, ΔH^* and ΔS^* were computed by solving the following equation as simultaneous expressions at two different temperatures, and ΔH^* was plotted against ΔS^* in Figure 6.

$$k_1 = \frac{kT}{h} e^{\frac{-\Delta H^*}{RT}} e^{\frac{\Delta S^*}{R}}$$

Acknowledgment.—We are indebted to Dr. Scott MacKenzie and the University of Rhode Island Computer Laboratory for the least-squares treatment of the data.

(6) A. I. Vogel, *J. Chem. Soc.*, 1487 (1929).

Microbiological Hydroxylation of Alkaloids from *Funtumia latifolia*

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The two steroidal alkaloids funtumine and funtumidine are both monohydroxylated by the fungus *Aspergillus ochraceus* in the 11α and 12β positions. The structures of the hydroxylated products were established by infrared and n.m.r. spectra, optical rotation, and conversion to the respective 5α-pregnane-3,11,20-trione and 5α-pregnane-3,12,20-trione.

Steroidal alkaloids from the leaves of *Funtumia latifolia* have been subjected to chemical modication but not, reportedly, to microbiological transformation. Our findings on the fungal alterations of funtumidine (Ia) and funtumine (IIa)[1] are presented here. Microbiological modification of other steroidal alkaloids (conessine,[2] solasodine,[3] and tomatidine[3a,4]) has recently been reported.

Funtumidine (Ia) and funtumine (IIa) are both

(1) M.-M. Janot, Q. Khuong-Huu, and R. Goutarel, *Compt. rend.*, **246**, 3076 (1958); **248**, 982 (1959).

(2) (a) J. de Flines, A. R. Marx, W. F. van der Waard, and D. van der Sijde, *Tetrahedron Letters*, **No. 26**, 1257 (1962); (b) S. M. Kupchan, C. J. Sih, S. Kubota, and A. M. Rahim, *ibid.*, **No. 26**, 1767 (1963); (c) E. L. Patterson, W. W. Andres, and R. E. Hartman, *Experientia*, **20**, 256 (1964).