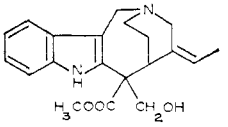
Iboga alkaloids.[2] Furthermore, it was encouraging that stemmadenine (**3**) has been shown to coexist with apparicine (**1**), being present in the fruits of *Aspidosperma pyricollum*.[3] If the biosynthesis of apparicine (**1**) were to proceed through the intermediacy of stemmadenine (**3**), then clearly the degradation of the two-carbon bridge to the one-carbon unit present in this alkaloid, with loss of the original C-2 of tryptophan, much occur as one of the very *last* steps in the biosynthetic pathway. In direct contrast to this, it was possible that this carbon atom was lost as one of the *first* transformations from tryptophan. Indeed, our results showing loss of C-2 and retention of C-3 are highly reminiscent of the results of the elegant experiments of Leete and Marion[4,5] regarding the biosynthesis of the alkaloid gramine (**5**), in which compound **4** is presumably the penultimate precursor. Regarding **4** as "nortryptamine," it was attractive to envisage an alternative biosynthetic route to the apparicine family of alkaloids as paralleling the biosynthesis of other indole alkaloids except that they originated from this "nortryptamine" compound instead of from tryptamine (or tryptophan) itself.

In order to test these hypotheses, stemmadenine (**3**), 3-aminomethylindole (**4**) (prepared as reported previously by the reduction of indole-3-carboxaldehyde oxime),[6] and vallesamine (**6**),[7] an alkaloid with structural featues intermediate between stemmadenine (**3**) and apparicine (**1**), were labeled with tritium in the aromatic portion of the molecule and fed to the roots of



6

Aspidosperma pyricollum. A summary of the results of the various experiments is presented in Table I.

Table I. Results of Incorporation into Apparicine and Uleine of Various Intermediates under Identical Conditions in *Aspidosperma pyricollum* Roots

Expt	Compound fed	% incorporation Apparicine	Uleine
1	[*ar*-^{3}H]DL-Tryptophan (**2**)	0.02	<0.0001
2	[*ar*-^{3}H]Stemmadenine (**3**)	0.55	<0.0007
3	[*ar*-^{3}H]Vallesamine (**6**)	0.01	<0.003
4	[*ar*-^{3}H]3-Aminomethylindole (**4**)	<0.001	<0.0001

The most striking feature of the results was the astonishingly high incorporation of stemmadenine (**3**), strongly indicating that this alkaloid, which plays such an important role in the biosynthesis of other indole alkaloids, is also of crucial importance in the biosynthesis of apparicine (**1**). This result, together with the failure of **4** to be incorporated, demonstrates that fragmentation of the tryptophan moiety and loss of C-2 occur as *one of the final steps* in the biosynthesis. Since initial evidence bearing on the biosynthesis of stemmadenine (**3**) is already available,[2] interest in the present instances is immediately directed toward the way in which stemmadenine (**3**) is converted to apparicine (**1**). In this conversion, essentially two distinct changes are required—loss of C-8 of stemmadenine (**3**) and decarboxylation of the ester function at C-3 to the exocyclic methylene group. Clearly these two changes can be considered *a priori* to occur in one of three ways: (1) loss of C-8 preceding decarboxylation, (2) decarboxylation preceding loss of C-8, and (3) both changes occurring simultaneously. In this regard, the very low incorporation of vallesamine (**6**) (with respect to that of stemmadenine (**3**)) would tend to rule out consideration 1, since vallesamine (**6**) can be regarded as that structure in which loss of C-8 of stemmadenine (**3**) has occurred without decarboxylation. That some incorporation (0.01%) is observed is perhaps not very surprising in view of the very close structural relationship between vallesamine (**6**) and apparicine (**1**), but if vallesamine (**6**) were on the true biosynthetic pathway, an incorporation comparable to, or even higher than, that observed for stemmadenine would have been expected. We wish to emphasize that these experiments were conducted on roots of the same plant so as to completely minimize any differences between them.

The present data do not allow distinction between choices 2 and 3, and one can envisage mechanisms by which either choice could be involved. Experiments designed to distinguish between these possibilities are now in progress.

As expected, none of the above compounds was incorporated into uleine. These results are consistent with the negative incorporation of tryptophan as noted in the accompanying communication.

Acknowledgment. Financial aid from the National Research Council of Canada is gratefully acknowledged. We are very grateful to Dr. C. Djerassi, Stanford University, and Dr. A. Hofmann and Dr. D. Stauffacher, Sandoz, Ltd., Basle, for samples of stemmadenine and vallesamine.

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(2) A. A. Qureshi and A. I. Scott, *Chem. Commun.*, 948 (1968).
(3) R. R. Arndt, S. H. Brown, N. C. Ling, P. Roller, C. Djerassi, J. M. Ferreira, B. Gilbert, E. C. Miranda, S. E. Flores, A. P. Duarte, and E. P. Carrazzoni, *Phytochemistry*, **6**, 1653 (1967).
(4) E. Leete and L. Marion, *Can. J. Chem.*, **31**, 1195 (1953).
(5) D. O'Donovan and E. Leete, *J. Am. Chem. Soc.*, **85**, 461 (1963).
(6) N. Putochin, *Ber.*, **59B**, 1987 (1926).
(7) A. Walser and C. Djerassi, *Helv. Chim. Acta*, **47**, 2072 (1964).

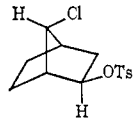
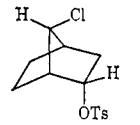
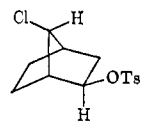
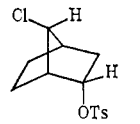
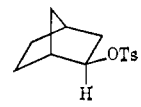
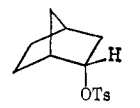
The Acetolysis of the 7-Chloro-2-tosyloxynorbornanes

Sir:

The anomalous results obtained in our laboratory in relation to the acetolysis of 7-oxygenated 2-norbornyl tosylates have demonstrated the complexity of utilizing electron-withdrawing functions containing oxygen to destabilize the norbornyl cation.[1] In order to test whether a nonoxygenated electron-withdrawing function could be used to determine the effect of an electron deficiency on the developing 2-norbornyl cation, we have investigated the solvolysis of the four epimeric 7-chloro-2-tosyloxynorbornanes.[2] We wish to report at

(1) P. G. Gassman and J. L. Marshall, *J. Am. Chem. Soc.*, **88**, 2822 (1966); P. G. Gassman and J. L. Marshall, *Tetrahedron Letters*, 2429, 2433 (1968); P. G. Gassman and J. G. Macmillan, *J. Am. Chem. Soc.*, in press.
(2) *syn*-7-Chloro-*exo*-2-tosyloxynorbornane (**1**) and *anti*-7-chloro-*exo*-2-tosyloxynorbornane (**3**) have been studied previously.[3] However, these studies only provided rate data on the *exo*-tosylates and product studies were based on infrared comparisons of reaction mixtures.

Table I. Acetolysis Rates of 7-Chloro-2-tosyloxynorbornanes

Compound	Temp, °C	Rate, sec^{-1}	$\Delta H^{\ddagger}$, kcal/mole	$\Delta S^{\ddagger}$, eu	k_{rel}, 25°
 1	100.0 ± 0.02	(6.68 ± 0.08) × 10^{-4}			
	90.0 ± 0.02	(1.99 ± 0.01) × 10^{-4}	26.4	−2.9	
	80.0 ± 0.02	(8.37 ± 0.04) × 10^{-5}			
	(25)[a]	6.62 × 10^{-8}			246
	78.2[b]	6.6 × 10^{-5}			
 2	130.0 ± 0.02	(1.24 ± 0.02) × 10^{-4}			
	120.0 ± 0.02	(5.04 ± 0.03) × 10^{-5}	29.1	−4.7	
	110.0 ± 0.02	(1.77 ± 0.01) × 10^{-5}			
	(25)[a]	2.69 × 10^{-10}			1
 3	100.0 ± 0.02	(5.40 ± 0.04) × 10^{-4}			
	90.0 ± 0.02	(1.73 ± 0.00) × 10^{-4}	26.9	−2.0	
	80.0 ± 0.02	(6.58 ± 0.03) × 10^{-5}			
	(25)[a]	4.29 × 10^{-8}			160
	78.2[b]	5.2 × 10^{-5}			
 4	130.0 ± 0.02	(2.71 ± 0.03) × 10^{-4}			
	120.0 ± 0.02	(1.08 ± 0.01) × 10^{-4}	29.3	−2.7	
	110.0 ± 0.02	(3.81 ± 0.00) × 10^{-5}			
	(25)[a]	5.38 × 10^{-10}			2
 5	(25)[c]	2.33 × 10^{-5}			85,000
 6	(25)[c]	8.28 × 10^{-8}			310

[a] Extrapolated from higher temperatures. [b] See ref 3. [c] P. von R. Schleyer, M. M. Donaldson, and W. E. Watts, *J. Am. Chem. Soc.*, **87**, 375 (1965).

this time the results of this study and to discuss the mechanistic implications of these results on the classical–nonclassical norbornyl cation controversy.

Table I lists the rates of solvolysis of **1–4**, and *exo*- and *endo*-2-norbornyl tosylate (**5** and **6**). It should be noted that the presence of a chloro group in the 7 position causes a rate decrease for both the *exo*- and *endo*-tosylates of approximately 300 relative to **5** and **6**, respectively. This rate deceleration is roughly what would be predicted on the basis of the electron-withdrawing ability of chlorine. The most important aspect of this rate comparison is that *even though the rates of the 7-chloro-2-norbornyl tosylates are dramatically slower owing to the inductive effect of the chlorine group, the exo/endo rate ratio remains high*, being 246 for the *syn* chloro compounds and 80 for the *anti* isomers. If the high *exo/endo* rate ratios, usually observed in the solvolysis of 2-norbornyl tosylates, were due to acceleration of the *exo* isomer *via* neighboring group participation by the σ electrons of the C_1–C_6 bond, it would be anticipated that the electron-withdrawing effect of the 7-substitutent should decrease such participation by destabilizing the partial positive charge which would develop at C_1.[1] We do not observe any such predicted decrease in the *exo/endo* rate ratios when we have a chlorine in the 7 position. These findings complement those of Brown and coworkers,[4] who have shown that carbonium ion *stabilizing* groups have relatively little effect on the *exo/endo* rate ratio.

In order to ascertain that the 7-chloro groups were not having some unexpected type of influence on the solvolysis of **1–4**, we carefully analyzed the product mixtures from the solvolyses. Table II shows the product analysis for the four tosylates. Let us first consider the epimeric pair in which the chlorine was *anti* to the leaving tosylate function. Since vpc analyses were probably good to ±2%, to a first approximation both **3** and **4** gave the same product mixture.[5] Two aspects of this identity are important. First, neither **3** nor **4** gave detectable amounts of either **11** or **12**.[6] Secondly,

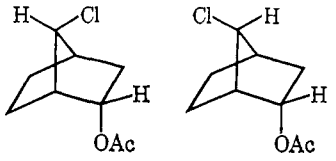
(3) W. G. Woods, R. A. Carboni, and J. D. Roberts, *J. Am. Chem. Soc.*, **78**, 5653 (1956).

(4) H. C. Brown and M.-H. Rei, *ibid.*, **86**, 5004 (1964); H. C. Brown and K. Takeuchi, *ibid.*, **90**, 5268 (1968); H. C. Brown, F. J. Chloupek, and M.-H. Rei, *ibid.*, **86**, 1248 (1964). It should be noted that the effects of carbonium ion stabilizing groups were determined on *tertiary* norbornyl derivatives where the stability of the carbonium ion would be maximized.

(5) In addition to having identical vpc retention times with authentic samples of **7–10** on three different vpc columns, the components of the reaction mixture were partially separated by preparative vpc and **7** and **8** were shown to have identical infrared spectra with authentic samples of **7** and **8**. Details of the synthesis of **7–10** will be furnished in a full paper on this topic. Satisfactory elemental analyses were obtained on all new compounds.

(6) Several very minor products were present in the reaction mixture. These are collectively listed under the heading "other" with the percentage being calculated on the assumption that the vpc response to these components would be similar to those of **7–10**. Two very minor components (*ca.* 0.5% each) had retention times similar to **11** and **12** on several vpc columns, but on other columns no peaks were detected from the product mixture which could correspond to either **11** or **12**.

since both **3** and **4** gave the same reaction mixture it could be assumed that both **3** and **4** were yielding the



11 **12**

same intermediate. This behavior is clearly different from that observed for 7-oxygenated norbornanes[1] but similar to that noted for the parent norbornyl system. This indicates to us that **3** and **4** may be satisfactory compounds for the generation of an electron-deficient norbornyl cation.

Table II. Products from the Acetolysis of 7-Chloro-2-tosyloxynorbornanes

	Percentage composition of the product mixture[a]				
Starting tosylate[b]	7	8	9	10	Other
3[c]	14	70	9	4	3
4	11	69	8	7	5
1[c]	45	42	9	2	2
2	24	42	8	16	9

[a] Product analyses were carried out by vpc after *ca.* 10% reaction since considerable decomposition occurred on prolonged reaction time. [b] Structures in Table I. [c] Roberts and coworkers previously published a product study on **1** and **3**. On the basis of infrared spectra they estimated that both **1** and **3** gave a 50:50 mixture of **7** and **8** (ref 3).

In the epimeric pair **1** and **2** the chlorine was *syn* to the leaving tosylate group and might be expected to have some interaction with the leaving group. Although the rate comparison indicated very little influence of the stereochemistry of the chlorine, product studies showed that **1** and **2**, although they produced the same products, gave different product mixtures with the predominant path for **2** involving an initial hydride shift. Thus **1** and **2** are less satisfactory models than **3** and **4**.

The high *exo/endo* rate ratio, the formation of the same products, and the absence of *endo* products in the solvolysis of the 7-chloro-2-tosyloxynorbornanes indicate that norbornanes in which the formation of a partial positive charge in the 1 position is electronically unfavorable can still behave in a manner very similar to the parent norbornyl system. It would appear that this similarity is most consistent with the theory that there is very little delocalization of charge in the ionization of **5** and **6**.

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(8) National Science Foundation Trainee, 1965–1968.

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Substituent Effects on the Acetolysis of *exo*- and *endo*-2-Norbornyl Tosylates

Sir:

A crucial point of discussion in relation to the classical–nonclassical norbornyl cation controversy has been the meaning of the *exo/endo* rate ratios observed in the solvolysis of 2-norbornyl arenesulfonates.[1] The classical carbonium ion school of thought suggests that *exo*-2-norbornyl tosylate (**1**) solvolyzes at a "normal" rate while *endo*-2-norbornyl tosylate (**2**) solvolyzes abnormally slow for steric reasons.[1b,2] In contrast the nonclassical theory would have **2** solvolyzing at a "normal" rate while **1** is proposed to be abnormally fast owing to neighboring group participation by the 1,6 σ electrons.[1d] Our studies on the effect of electron-withdrawing substituents on the *exo/endo* rate ratio of 2-norbornyl tosylates have shown that certain 7-oxygenated *exo–endo* pairs behave anomalously, and thus have meaningless *exo/endo* rate ratios,[3] while the *anti*-7-chloro-2-tosyloxynorbornanes appear to solvolyze in an uncomplicated fashion and hence should have a meaningful *exo/endo* rate ratio.[4] In order to gain an insight into the over-all effects of substituents on the rates of solvolysis of norbornane derivatives, we have collected and correlated the rates of eight different *exo–endo* pairs of 7-substituted 2-norbornyl tosylates. We wish to report at this time on the results of this correlation and on the mechanistic implications of these results.

Table I lists the rates of acetolysis at 25° for eight 7-substituted *exo*-2-tosyloxynorbornanes.[5–9] A $\rho\sigma^*$ plot of the data is shown in Figure 1. For the eight 7-substituted *exo*-2-tosyloxynorbornanes ρ was -2.33 (correlation coefficient -0.979). Considering the approximations involved, this correlation was unusually good. Although the plot covers a rate spread of *ca.* 18,000 (the rate difference between **3** and **9**), all points fall within a rate factor of 3 of being on the least-squares slope.

In contrast to the unexpectedly good correlation of the reaction rates of *exo*-2-tosyloxynorbornanes with the inductive effect of various 7-substituents, a similar correlation for the corresponding *endo* isomers listed in Table II can best be described as giving an almost

(1) For recent reviews which discuss this point, see: (a) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 111–232; (b) H. C. Brown, *Chem. Brit.*, **2**, 199 (1966); *Chem. Eng. News*, **45**, 87 (Feb 13, 1967); Special Publication No. 16, The Chemical Society, London 1962, p 140; (c) G. D. Sargent, *Quart. Rev.* (London), **20**, 301 (1966); (d) S. Winstein, *J. Am. Chem. Soc.*, **87**, 381 (1965); (e) G. E. Gream, *Rev. Pure Appl. Chem.*, **16**, 25 (1966); see also P. D. Bartlett, "Nonclassical Ions," W. A. Benjamin, New York, N. Y., 1966.

(2) H. C. Brown, I. Rothberg, P. von R. Schleyer, M. M. Donaldson, and J. J. Harper, *Proc. Natl. Acad. Sci. U. S.*, **56**, 1653 (1966).

(3) P. G. Gassman and J. G. Macmillan, *J. Am. Chem. Soc.*, in press, and references contained therein.

(4) P. G. Gassman and J. M. Hornback, *ibid.*, **91**, 4280 (1969).

(5) A. Colter, E. C. Friedrich, N. J. Holness, and S. Winstein, *ibid.*, **87**, 378 (1965).

(6) S. Winstein and D. Trifan, *ibid.*, 74, 1154 (1952); S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *ibid.*, **74**, 1127 (1952); P. von R. Schleyer, M. M. Donaldson, and W. E. Watts, *ibid.*, **87**, 375 (1965).

(7) P. J. Stang and P. von R. Schleyer, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., March 31–April 5, 1968, No. P-192. We wish to thank Professor Schleyer for providing us with the rates of **4** and **11** prior to publication.

(8) P. G. Gassman and J. L. Marshall, *Tetrahedron Letters*, 2433 (1968).

(9) P. G. Gassman and J. L. Marshall, *J. Am. Chem. Soc.*, **88**, 2822 (1966).