

alkaloids.<sup>5</sup> It was suggested that the alkaloid is formed from ammonia and the poly- $\beta$ -keto acid I derived from four acetate units.<sup>6</sup> We have now carried out tracer experiments which confirm this hypothesis.

Sodium acetate- $1\text{-C}^{14}$  (41 mg., 1.0 mc.) was fed to two year old hemlock plants *via* a cotton wick. After 8 days the plants were harvested yielding crude alkaloids having a total activity of  $7.8 \times 10^5$  d.p.m. From this mixture coniine and conhydrine (II, R = OH) were isolated having specific activities of  $3.8 \times 10^5$  and  $1.5 \times 10^5$  d.p.m./mmole, respectively. The radioactive coniine was subjected to the following degradation to determine the location of radioactivity. The coniine was refluxed in ethanol with methyl iodide in the presence of sodium bicarbonate yielding N-methylconiine methiodide. The unsaturated amines obtained by a Hofmann degradation on this methiodide were hydrogenated over platinum and then allowed to react with methyl iodide affording a mixture of 1-dimethylaminoctane methiodide (III) and 4-dimethylaminoctane methiodide (IV) which were separated by chromatography on alumina.<sup>7</sup> A Hofmann degradation on the methiodide III afforded 1-octene, which was cleaved with osmium tetroxide followed by sodium metaperiodate, yielding formaldehyde, collected as its dimedone derivative [C-6], and heptanal, which was oxidized with potassium permanganate to heptanoic acid. A Schmidt reaction on this acid yielded carbon dioxide, collected as barium carbonate [C-5], and hexylamine which was converted to 1-dimethylamino-hexane methiodide. This methiodide was degraded in the same way as compound III affording C-4 as formaldehyde and C-3 as barium carbonate. Hofmann degradation of the methiodide IV afforded a mixture of 3- and 4-octene which was oxidized without separation yielding a mixture of pentanoic, butanoic, and propanoic acids. We were unable to obtain enough pure pentanoic acid for further degradation. However, a Schmidt reaction on the butanoic acid afforded carbon dioxide representing the average activity of C-2 and C-3. A Schmidt reaction on the propanoic acid afforded carbon dioxide [C-1']. A Kuhn-Roth oxidation of coniine afforded only acetic acid which was subjected to the Schmidt reaction yielding carbon dioxide [C-2'] and methylamine collected as N-methylbenzamide [C-3'].

The percentage distribution of activity in the radioactive coniine was as follows: C-2, 26; C-3, 1.6; C-4, 22; C-5, 1; C-6, 24; C-1', 1.3; C-2', 22; C-3', 1.6%. Thus almost all the activity is located on the even numbered carbons and, within experimental error, is equally distributed among these four positions.

Our results indicate the danger of drawing conclusions from tracer work involving uniformly labeled compounds. Presumably the uniformly labeled lysine which was fed to the hemlock plants underwent degradation affording acetate which was then utilized for the synthesis of coniine.

Work is in progress to determine whether the eight carbon chain present in coniine is formed by the condensation of one acetylcoenzyme A with three malonylcoenzyme A molecules.<sup>8</sup>

(5) E. Leete, "Biogenesis of Natural Compounds," P. Bernfeld, Ed., Pergamon Press, Oxford, 1963, Chapter 17, p. 751.

(6) A. R. Battersby, *Quart. Rev. (London)*, **15**, 259 (1961), also suggested this hypothesis independently.

(7) These methiodides were first obtained from coniine by M. Mugdan, *Ann.*, **298**, 131 (1897).

(8) C. S. J. Wakil and J. Ganguly, *J. Am. Chem. Soc.*, **81**, 2597 (1959).

(9) Alfred P. Sloan Fellow, 1962-1964.

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## The Synthesis of an Unsaturated $\beta$ -Lactam

Sir:

The present communication describes the preparation and characterization of 1,2-diphenyl-2-azetinone-4 (VI), which is believed to be the first authentic unsaturated  $\beta$ -lactam of established structure. There are in the earlier literature several compounds of questionable structure which have been assigned the azetinone formula,<sup>1</sup> and many unsuccessful attempts to prepare unsaturated  $\beta$ -lactams (including VI) were reported during the wartime cooperative penicillin program.<sup>2</sup> Whereas previous efforts had utilized acyclic compounds, we employed well characterized saturated  $\beta$ -lactams in our synthetic sequences.



- I, R = NH<sub>2</sub>  
II, R = CH<sub>2</sub>COO  
III, R = *p*-ClC<sub>6</sub>H<sub>4</sub>N=NNH  
IV, R = *p*-CH<sub>3</sub>C<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>  
V, R = H

Treatment of an aqueous solution of the known 3-amino-1,4-diphenyl-2-azetidione hydrochloride<sup>3</sup> with one equivalent of sodium hydroxide afforded 3-amino-1,4-diphenyl-2-azetidione (I) in 92% yield, C<sub>15</sub>H<sub>14</sub>N<sub>2</sub>O, m.p. 118°,  $\lambda_{\text{max}}^{\text{Nujol}}$  5.72  $\mu$ . *Anal.* Found: C, 75.37; H, 5.94; N, 11.82. Diazotization of I using sodium nitrite in acetic acid-water at 0°, followed by chromatography over neutral alumina, led to a 67% yield of 3-acetoxy-1,4-diphenyl-2-azetidione (II), C<sub>17</sub>H<sub>15</sub>NO<sub>3</sub>, m.p. 152-154°;  $\lambda_{\text{max}}^{\text{Nujol}}$  5.72, 8.25  $\mu$ . *Anal.* Found: C, 72.74; H, 5.50; N, 4.75. The only isolable product from the pyrolysis of II at 610° was benzaniline (78%).<sup>4</sup> The only other product isolated from the diazotization reaction was an isomer of II (8% yield, m.p. 156-157°, m.m.p. with II 147-150°,  $\lambda_{\text{max}}^{\text{Nujol}}$  5.72, 8.25  $\mu$ ), which on pyrolysis gave a 70% yield of benzaniline.

A deamination procedure developed recently<sup>5</sup> led us to prepare the triazene III; reaction of *p*-chlorobenzene-diazonium hexafluorophosphate with I gave 70% of 3-(*p*-chlorophenyldiazoamino)-1,4-diphenyl-2-azetidione (III), m.p. 138-139°,  $\lambda_{\text{max}}^{\text{Nujol}}$  5.73, 6.1  $\mu$ . An ethereal solution of *p*-toluenesulfonic acid converted III into 3-tosyloxy-1,4-diphenyl-2-azetidione (IV), C<sub>22</sub>H<sub>19</sub>NO<sub>5</sub>S, in 40% yield; m.p. 161-161.5°,  $\lambda_{\text{max}}^{\text{Nujol}}$  5.72, 8.5  $\mu$ . *Anal.* Found: C, 66.97; H, 5.10; S, 8.32. The tosyloxy lactam IV was inert to an attempted elimination-substitution using bromide in acetone<sup>6</sup> and to elimination with *t*-butoxide in dimethyl sulfoxide.<sup>7</sup>

Cleavage of the triazene III with one equivalent of boron trifluoride etherate led to the evolution of the theoretical amount of nitrogen, the precipitation of the boron trifluoride salt of *p*-chloroaniline, and the isolation, after chromatography over neutral alumina and crystallization from acetone-water, of 1,2-diphenyl-2-azetinone-4 (VI), C<sub>15</sub>H<sub>11</sub>NO, in 20% yield; m.p. 121° dec.,  $\lambda_{\text{max}}^{\text{Nujol}}$  5.71, 12.5  $\mu$ ,  $\lambda_{\text{max}}^{\text{EtOH}}$  252, 358 m $\mu$  ( $\epsilon$  11,500, 530).

(1) F. S. Kipping and W. H. Perkin, *J. Chem. Soc.*, **56**, 330 (1889); A. Kotz and B. Merkel, *J. prakt. Chem.*, **79**, 102 (1909); P. Bruylants, *Bull. acad. roy. M $\acute{e}$ d. Belg.*, [5] **7**, 252 (1921).

(2) S. A. Ballard, D. S. Melstrom, and C. W. Smith, "The Chemistry of Penicillin," H. T. Clarke, J. R. Johnson, and R. Robinson, Ed., Princeton University Press, Princeton, N. J., 1949, pp. 980-982.

(3) J. C. Sheehan and J. J. Ryan, *J. Am. Chem. Soc.*, **73**, 1204 (1951).

(4) Ring cleavages have been observed in the pyrolysis of 1,2-di-(acetoxy-methyl)-cyclobutane by W. J. Bailey, C. H. Cunov, and L. Nicholas, *ibid.*, **77**, 2787 (1955).

(5) E. H. White and H. Scherrer, *Tetrahedron Letters*, 758 (1961).

(6) S. Winstein, D. Darwish, and N. J. Holness, *J. Am. Chem. Soc.*, **78**, 2915 (1956).

(7) C. H. Snyder, *Chem. Ind. (London)*, 121 (1963).

The corresponding saturated  $\beta$ -lactam V showed an ultraviolet absorption at 248  $\mu$  ( $\epsilon$  1300). *Anal.* Found: C, 81.25; H, 5.25, N, 6.60. The n.m.r. spectrum (in  $\text{CDCl}_3$ , chemical shifts in p.p.m. from tetramethylsilane) shows a broad multiplet at 7.0–7.5  $\delta$  (10 H) and a multiplet at 5.0  $\delta$  (1 H) which could be assigned to the aromatic hydrogens and the vinyl hydrogen, respectively.

Hydrogenation of VI over platinum catalyst proceeded with the uptake of one equivalent of hydrogen and yielded 1,4-diphenyl-2-azetidione (V), m.p. 154–156°. An authentic sample of V was prepared as described by Gilman and Speeter,<sup>8</sup> m.p. 154–155.5° (lit.<sup>8</sup> 153–154°), undepressed upon admixture with the sample of V obtained by hydrogenation of VI and having an identical infrared spectrum (potassium bromide).

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(8) H. Gilman and C. Speeter, *J. Am. Chem. Soc.*, **65**, 2255 (1943).

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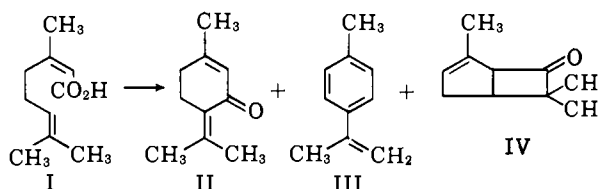
### The Cyclization of Geranic Acids. Preparation of a Cyclobutanone

Sir:

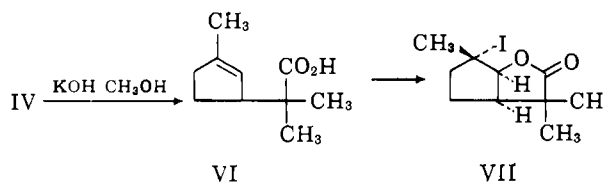
In a series of papers describing the self-condensation products of unsaturated acids, Schinz<sup>1</sup> treated the geranic acids (I) with acetic anhydride and sodium acetate and obtained piperitenone (II). We have repeated this work using the mixture of geranic acids obtained by the silver oxide oxidation of citral<sup>2,3</sup> and find that the neutral fraction of the reaction product is composed of three compounds. By fractional distillation one of the three was separated and was shown to be II [b.p. 118–120° (2 mm.); dinitrophenylhydrazone, m.p. 184–185°].<sup>4</sup> The other two components were easily separated by g.l.c. The first of these was an aromatic hydrocarbon  $\text{C}_{10}\text{H}_{12}$  (III); n.m.r. (all in  $\text{CDCl}_3$ ; chemical shifts in p.p.m. from  $\text{Me}_4\text{Si}$ ) 2.13  $\delta$  (3 H, multiplet), 2.33  $\delta$  (3 H, singlet), 5.04  $\delta$  (1 H, multiplet), 5.35  $\delta$  (1 H, multiplet), 7.15 and 7.33  $\delta$  (4 H in an  $\text{A}_2\text{B}_2$  pattern);  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  247, 283, and 294  $\mu$  ( $\epsilon$  12,500, 5100, 2000), which established the structure of III as 4-methyl- $\alpha$ -methylstyrene.<sup>5</sup>

The third compound,  $\text{C}_{10}\text{H}_{14}\text{O}^6$  (IV), b.p. 86–88° (20 mm.) ( $\lambda_{\text{max}}^{\text{CCl}_4}$  3.28, 5.62, 12.49  $\mu$ ), was a cyclobutanone or a highly strained cyclopentanone; 2,4-dinitrophenylhydrazone, m.p. 120–122°. IV, with hydrogen and platinum catalyst formed a dihydro derivative V [b.p. 124–126° (150 mm.);  $\lambda_{\text{max}}^{\text{CCl}_4}$  5.62  $\mu$ ;  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  309  $\mu$  ( $\epsilon$  53); 2,4-dinitrophenylhydrazone, m.p. 103–104°] indicating a single double bond in a bicyclic ring system in IV. The ultraviolet spectrum of IV ( $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  310  $\mu$  ( $\epsilon$  260)) suggested that the double bond was located  $\beta, \gamma$  to the carbonyl group with some  $\pi$ -bond overlap.<sup>7</sup> The n.m.r. spectrum of IV [1.12  $\delta$  (3 H, singlet), 1.19  $\delta$  (3 H, singlet), 1.75  $\delta$  (3 H, multiplet), 2.55  $\delta$  (3 H, broad multiplet), 4.03  $\delta$  (1 H,

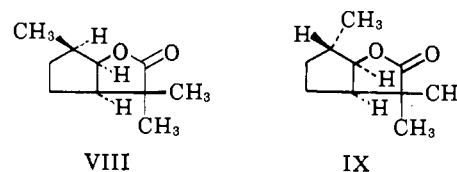
broad multiplet), 5.46  $\delta$  (1 H, multiplet)] indicated the presence of a dimethyl group next to the carbonyl, a third methyl group attached to a trisubstituted double bond, and a single hydrogen located on the carbon between the carbonyl and the double bond. The mass spectrum<sup>8</sup> of IV confirmed the molecular weight of the compound and also showed very intense peaks at  $m/e$  80 and  $m/e$  70, indicative of a methylcyclopentadiene and dimethyl ketene ions. On the basis of these data we propose that IV is 2,6,6-trimethyl[3.2.0]-bicyclo-2-heptene-7-one.



Refluxing methanolic potassium hydroxide converted IV to  $\alpha$ -fencholenic acid (VI), m.p. 45–46°. The structure of VI was established by comparison of its infrared spectrum with that of an authentic sample of  $\alpha$ -fencholenic acid prepared by the hydrolysis of fenchone oxime.<sup>9</sup> The position of the double bond of  $\alpha$ -fencholenic acid was established by conversion to the iodolactone VII; m.p. 74–75°;  $\lambda_{\text{max}}^{\text{CCl}_4}$  5.61  $\mu$ ; n.m.r. 2.20  $\delta$  (3 H, singlet), 5.10  $\delta$  (1 H, doublet,  $J = 5.0$  c.p.s.).



Aqueous acid degradation of IV led to a mixture of 3-methyl-2-cyclohexenone,<sup>10</sup> 2,4-dinitrophenylhydrazone, m.p. 177–178°, and two isomeric lactones (VIII and IX) ( $\lambda_{\text{max}}^{\text{CCl}_4}$  5.63  $\mu$ ) that were difficultly separable even by g.l.c. While the n.m.r. spectrum of VIII had a low field triplet (4.80  $\delta$ ,  $J = 6$  c.p.s.), in contrast the spectrum of IX showed a pair of doublets (4.48  $\delta$ ,  $J = 6$  and 2.5 c.p.s.). The mixture of  $\gamma$ -lactones VIII and IX could also be prepared from methyl  $\alpha$ -fencholenate<sup>11</sup> by refluxing in benzene with *p*-toluenesulfonic acid monohydrate.



Refluxing IV in toluene with *p*-toluenesulfonic acid monohydrate caused a series of rearrangements to X (b.p. 68–71° (1 mm.);  $\lambda_{\text{max}}^{\text{CCl}_4}$  5.72  $\mu$ ,  $\lambda_{\text{max}}^{\text{CH}_3\text{OH}}$  301  $\mu$ , ( $\epsilon$  323); 2,4-dinitrophenylhydrazone, m.p. 185–187°; n.m.r. 1.03  $\delta$  (3 H, singlet), 1.13  $\delta$  (3 H, singlet), 1.75  $\delta$  (1 H, doublet,  $J = 11$  c.p.s.), 2.04  $\delta$  (1 H, doublet,  $J = 11$  c.p.s.), 2.40  $\delta$  (3 H, multiplet), 3.13  $\delta$  (1 H, multiplet), 4.92  $\delta$  (1 H, multiplet), 5.16  $\delta$  (1 H, multiplet). Upon catalytic reduction X was converted only to a dihydro derivative XI [b.p. 100° (10 mm.);  $\lambda_{\text{max}}^{\text{CCl}_4}$  5.73  $\mu$ ; 2,4-dinitrophenylhydrazone, m.p. 144–146°] so X must be bicyclic.  $\text{NaIO}_4$  and  $\text{KMnO}_4$  oxidation

(8) We are indebted to Professor K. Biemann for the mass spectrum of IV.

(1) C. Balant, C. A. Vodoz, H. Kappeler, and H. Schinz, *Helv. Chim. Acta*, **34**, 722 (1951).

(2) K. Bernhauer and R. Forster, *J. Prakt. Chem.*, **147**, 199 (1936).

(3) G. A. Howard and R. Stevens, *J. Chem. Soc.*, 161 (1960).

(4) Y. R. Naves and G. Papazian, *Helv. Chim. Acta*, **25**, 1028 (1942).

(5) M. J. Murray and W. S. Galloway, *J. Am. Chem. Soc.*, **70**, 3867 (1948).

(6) Satisfactory elementary analyses were obtained for all new compounds reported herein.

(7) R. C. Cookson and N. S. Wariyar, *J. Chem. Soc.*, 2302 (1956).

(9) G. B. Cockburn, *J. Chem. Soc.*, **75**, 501 (1899); O. Wallach, *Ann.*, **379**, 182 (1911).

(10) L. I. Smith and J. F. Rouault, *J. Am. Chem. Soc.*, **65**, 631 (1943).

(11) Prepared by  $\text{CH}_2\text{N}_2$  treatment of VI or by refluxing IV in methanolic hydrogen chloride.