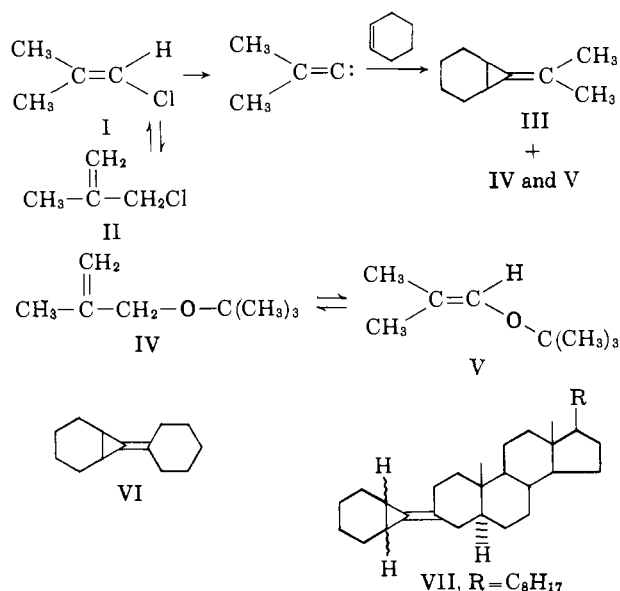


(0.30 mole) in 370 ml. of boiling tetrahydrofuran for 16 hr. in the presence of an excess of cyclohexene (0.95 mole), 7-isopropylidenenorcaradiene (III) was isolated (8%),³ indicating the intermediate formation of isopropylidenecarbene.



The carbene adduct III in the n.m.r. spectrum shows the allylic methyl group signals at 8.25 τ ,⁴ mol. wt. 136 (mass spec.), infrared 5.63 μ ($>C=C<$), n^{25}_D 1.4753.

In addition to the isopropylidene carbene adduct III, a mixture of isomeric *t*-butyl ethers, 1-*t*-butoxy-2-methylpropene-2 (IV) and 1-*t*-butoxy-2-methylpropene-1 (V), was isolated. This mixture of ethers could not be adequately resolved by gas chromatography, but an n.m.r. spectrum of the mixture indicated the composition of IV to V as (3:1).

Reaction of the isomeric allylic chloride 1-chloro-2-methylpropene-2 (II) with potassium *t*-butoxide in tetrahydrofuran in the presence of excess cyclohexene led unexpectedly to the same 7-isopropylidenenorcaradiene adduct (III) (20%) and about the same composition of isomeric ethers IV and V was isolated as obtained from the vinylic isomer 1-chloro-2-methylpropene-1 (I).

These results indicate that interconversion of the allylic and vinylic chlorides occurs under these reaction conditions and the isopropylidenecarbene is generated by 1,1 elimination from the vinylic chloride. The origin of the isomeric *t*-butoxy ethers is through the displacement reaction on the allylic chloride by *t*-butoxide ion. The allylic *t*-butyl ether formed in this manner is then isomerized to the vinylic *t*-butyl ether with potassium *t*-butoxide.⁵

In accord with this supposition, rapid quenching of a reaction mixture of 1-chloro-2-methylpropene-2 (II) and potassium *t*-butoxide in boiling toluene led to an isomeric chloride mixture of I and II of (1:1.25) by analysis of the n.m.r. spectrum.

Other alkylidenecarbenes were generated by treatment of the appropriate chloride and captured as the

(3) Satisfactory analyses have been obtained for all new compounds reported herein. Rotations are reported in chloroform.

(4) Splitting of the methyl groups signals is apparent in the n.m.r. spectrum of III, this effect is either due to the nonequivalence of the methyl groups in different conformational environments or a long-range spin-spin coupling effect. This problem is under further study.

(5) (a) T. J. Prosser, *J. Am. Chem. Soc.*, **83**, 1701 (1961); (b) C. C. Price and W. H. Snyder, *ibid.*, **83**, 1773 (1961). The facile isomerization of allyl ethers to vinyl ethers in the presence of potassium *t*-butoxide is reported by these authors.

cyclohexene adduct. Chloromethylenecyclohexane⁶ yielded the cyclohexylidenecarbene adduct VI, mol. wt. 176 (mass spec.), infrared 5.62 μ ($>C=C<$), n^{25}_D 1.5070. This carbene adduct VI was accompanied by *t*-butoxymethylenecyclohexane.⁷

A steroidal vinylic chloride, 3-chloromethylenecolestane, m.p. 80–81°, $[\alpha]_D +21^\circ$, yielded the carbene adduct VII (25%),⁸ m.p. 160–163°, $[\alpha]_D +27^\circ$, mol. wt., 482, infrared 5.62 μ ($>C=C<$). Also isolated from the reaction was 3-*t*-butoxymethylenecolestane, m.p. 104–106°, $[\alpha]_D +26^\circ$.

(6) These chloromethylene derivatives are conveniently prepared by the Wittig reaction of chloromethyltriphenylphosphonium chloride and ketones by the method of D. Seyferth, S. O. Grim, and T. O. Read, *ibid.*, **83**, 1617 (1961).

(7) It is of interest that treatment of chloromethylenecyclopentane with potassium *t*-butoxide in toluene in the presence of cyclohexene yielded no products of cyclopentylidenecarbene addition to cyclohexene. The only product isolated was 1-*t*-butoxymethylcyclopentane. This finding is in accord with the report [A. Schriesheim, R. J. Muller, and C. A. Rowe, Jr., *ibid.*, **84**, 3164 (1962)] that methylenecyclopentane is more rapidly converted to the endocyclic isomer than methylenecyclohexane. The rapid isomerization of chloromethylenecyclopentane to the endocyclic allylic chloride followed by chloride displacement with *t*-butoxide ion seems to be a plausible explanation for the apparent absence of carbene product in this reaction.

(8) Thin layer chromatography of this material showed the persistent presence of two closely migrating spots. This material is presumably a mixture of α - and β -isomers of the norcaradiene ring system.

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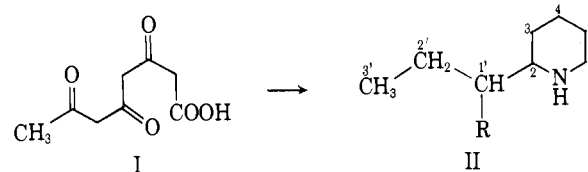
RECEIVED SEPTEMBER 9, 1963

The Biosynthesis of Coniine from Four Acetate Units¹

Sir:

It has been generally accepted that coniine (II, R = H), one of the alkaloids found in hemlock (*Conium maculatum*), is produced in the plant by a condensation between Δ^1 -piperidine (derived from lysine) and acetoacetic acid followed by unexceptional decarboxylation and reduction.² Some tracer work has been reported³ which apparently substantiated this hypothesis. Uniformly labeled L-lysine- C^{14} was fed to *C. maculatum* and radioactive coniine isolated from the plants several days later. However the alkaloid was not degraded to determine the distribution of activity.

Some seven years ago we fed DL-lysine- $2-C^{14}$ to hemlock plants by adding the tracer to a hydroponic solution in which the roots were growing. The crude alkaloids isolated from the plant had very low activity. A similar result was obtained when cadaverine- $1,5-C^{14}$



was fed to the plants.⁴ More recently a solution of lysine- $2-C^{14}$ was administered to hemlock plants, growing in soil, by means of a cotton wick inserted into the stem. Again, alkaloids of very low activity were obtained. We therefore proposed an alternate hypothesis for the biosynthesis of coniine and related piperidine

(1) This investigation was supported by research grant GB-363 from the National Science Foundation.

(2) R. Robinson, "The Structural Relations of Natural Products," Clarendon Press, Oxford, 1955.

(3) U. Schiedt and H. G. Höss, *Z. Naturforsch.*, **13b**, 691 (1958); *Z. physiol. Chem.*, **330**, 74 (1962).

(4) Cadaverine- $1,5-C^{14}$ was a much more efficient precursor of the piperidine ring of anabasine than lysine- $2-C^{14}$; E. Leete, *J. Am. Chem. Soc.*, **80**, 4393 (1958).

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

Sodium acetate- 1-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 7.8×10^5 d.p.m. From this mixture coniine and conhydrine (II, R = OH) were isolated having specific activities of 3.8×10^5 and 1.5×10^5 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.⁷ 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.⁸

(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) Cf. 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 β -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 β -lactam of established structure. There are in the earlier literature several compounds of questionable structure which have been assigned the azetinone formula,¹ and many unsuccessful attempts to prepare unsaturated β -lactams (including VI) were reported during the wartime cooperative penicillin program.² Whereas previous efforts had utilized acyclic compounds, we employed well characterized saturated β -lactams in our synthetic sequences.



- I, R = NH₂
II, R = CH₂COO
III, R = *p*-ClC₆H₄N=NNH
IV, R = *p*-CH₃C₆H₄SO₃
V, R = H

Treatment of an aqueous solution of the known 3-amino-1,4-diphenyl-2-azetidione hydrochloride³ with one equivalent of sodium hydroxide afforded 3-amino-1,4-diphenyl-2-azetidione (I) in 92% yield, C₁₅H₁₄N₂O, m.p. 118°, $\lambda_{\text{max}}^{\text{Nujol}}$ 5.72 μ . *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), C₁₇H₁₅NO₃, m.p. 152-154°; $\lambda_{\text{max}}^{\text{Nujol}}$ 5.72, 8.25 μ . *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%).⁴ 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 μ), which on pyrolysis gave a 70% yield of benzaniline.

A deamination procedure developed recently⁵ 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 μ . An ethereal solution of *p*-toluenesulfonic acid converted III into 3-tosyloxy-1,4-diphenyl-2-azetidione (IV), C₂₂H₁₉NO₅S, in 40% yield; m.p. 161-161.5°, $\lambda_{\text{max}}^{\text{Nujol}}$ 5.72, 8.5 μ . *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 acetone⁶ and to elimination with *t*-butoxide in dimethyl sulfoxide.⁷

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), C₁₅H₁₁NO, in 20% yield; m.p. 121° dec., $\lambda_{\text{max}}^{\text{Nujol}}$ 5.71, 12.5 μ , $\lambda_{\text{max}}^{\text{EtOH}}$ 252, 358 m μ (ϵ 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} l. 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).