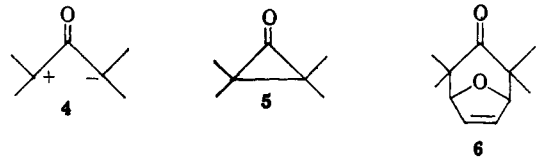
Photolysis of **1** must form an acyclic intermediate, perhaps **4** (only one resonance structure is shown), a type of intermediate which has been considered for Favorskii rearrangements and other reactions.[2] The intermediate can cyclize to tetramethylcyclopropanone (**5**) which in ethanol solution forms **2**. Adduct **6**, isolated by g.l.c. in 35% yield from a similar photolysis of **1** in refluxing furan, is formed most probably from addition of the same intermediate to furan. This

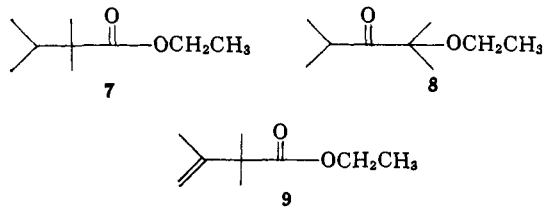


4 **5** **6**

adduct was also obtained recently by Cookson, Nye, and Subrahmanyam.[3] Ethyl isobutyrate must arise from addition of ethanol to dimethylketene formed from an alternate photolytic cleavage of **1**.

The structure proof for **2**[4] is based on spectral evidence and on the preparation of a *p*-nitrobenzoate derivative,[4] m.p. 117–118°. The highest nonisotopic peak in the mass spectrum of **2** was the parent peak, $m/e = 158$. The n.m.r. spectrum[5] of a carbon tetrachloride solution of **2** exhibited absorptions at 6.38 (quartet, $J = 7$, 2 protons) and 8.83 p.p.m. (triplet, $J = 7$, 3 protons) for the ethyl hydrogens, at 7.08 p.p.m. (singlet, 1 proton) for the hydroxyl hydrogen, and at 8.98 p.p.m. (singlet, 12 protons) for the methyl hydrogens. In dimethyl sulfoxide solution, **2** absorbed at 9.03 (6 protons) and 9.05 p.p.m. (6 protons), indicating that there are two types of methyl groups, and at 4.00 p.p.m. (1 proton), within the range characteristic[6] for hydrogens of hemiketal hydroxyls. A dichloromethane solution of the *p*-nitrobenzoate ester had absorptions at 1.68 (singlet, 4 protons), 6.28 (quartet, $J = 7$, 2 protons), 8.82 (triplet, $J = 7$, 3 protons), 8.80 (singlet, 6 protons), and 8.90 p.p.m. (singlet, 6 protons).

Isolation by g.l.c. also furnished combined yields of 10–15% of ethyl 2,2,3-trimethylbutyrate (**7**), 2-ethoxy-2,4-dimethyl-3-pentanone[4] (**8**), and ethyl 2,2,3-trimethyl-3-butenoate (**9**); distillation of photolysis solutions furnished combined yields of about 30% of the same components. It is possible that these are not initial products of photolysis but instead artifacts formed from **2**. In fact, formation of these compounds was observed from the partial decomposition of **2** during its isolation by g.l.c. and by refluxing **2** in ethanol. The structure of **8**, not previously reported, is consistent with the n.m.r. and infrared spectra; **8** formed a 2,4-dinitrophenylhydrazone derivative,[4] m.p. 110–112°, and was reduced with lithium aluminum hydride to an alcohol[4] which was reoxidized to **8** with chromic anhydride–pyridine. It was reported recently that photolysis of **1** in methanol and 2-propanol gave esters corresponding to **3** and **7** as the major products.[7]



7 **8** **9**

Further investigations of the formation and reactions of intermediates such as **4** and of the reactions of cyclopropanone derivatives are in progress.[8]

Acknowledgment.—We are indebted to Eastman Chemical Products, Inc., for a generous sample of **1** and to Professor P. S. Skell for helpful discussions. We are also pleased to acknowledge the assistance of the National Science Foundation in providing funds to aid in the purchase of the Varian A-60 n.m.r. spectrometer and the Bendix time-of-flight mass spectrometer used in this research.

(2) J. G. Aston and J. D. Newkirk, *J. Am. Chem. Soc.*, **73**, 3900 (1951); J. G. Burr, Jr., and M. J. S. Dewar, *J. Chem. Soc.*, 1201 (1954); E. F. Ullman, *J. Am. Chem. Soc.*, **82**, 505 (1960); H. O. House and W. F. Gilmore, *ibid.*, **83**, 3972, 3980 (1961); A. W. Fort, *ibid.*, **84**, 2620, 2625, 4979 (1962); R. C. Cookson and M. J. Nye, *Proc. Chem. Soc.*, 129 (1963).

(3) R. C. Cookson, M. J. Nye, and G. Subrahmanyam, *ibid.*, 144 (1964).

(4) Satisfactory analyses were obtained for all new compounds.

(5) Chemical shifts are in p.p.m. relative to tetramethylsilane as 10.00.

(6) O. L. Chapman and R. W. King, *J. Am. Chem. Soc.*, **86**, 1256 (1964).

(7) N. J. Turro, G. W. Byers, and P. A. Leermakers, *ibid.*, **86**, 955 (1964).

(8) Carbon tetrachloride solutions of **2** after heating and concentration have sometimes exhibited strong absorption at 1800 cm.$^{-1}$ that may be due to **5**.

(9) Alfred P. Sloan Research Fellow.

(10) Part of this work was done by D. C. C. in partial fulfillment of the requirements for a B.S. degree, The Pennsylvania State University, 1961.

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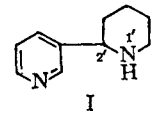
RECEIVED JUNE 24, 1964

The Biosynthesis of Anabasine. Origin of the Nitrogen of the Piperidine Ring[1]

Sir:

In the past decade much information has been obtained on the biosynthesis of alkaloids by administering isotopically labeled compounds, especially α-amino acids, to alkaloid-producing plants. However, in most of these investigations the tracer used has been carbon-14, and there is very little direct knowledge concerning the origin of the nitrogen in alkaloids.[2]

The biosynthesis of anabasine (I), a major alkaloid of *Nicotiana glauca*, has now been investigated using N^{15}-labeled precursors. We have previously shown that the administration of lysine-2-C^{14} to intact *N. glauca* plants leads to the formation of anabasine labeled



I

solely at C-2′ of the piperidine ring.[3] A similar result was obtained when lysine-C^{14} was fed to a sterile culture of excised roots.[4] In the present work we fed a mixture of lysine-2-C^{14} and lysine-ε-N^{15} to sterile cultures of excised *N. glauca* roots cultivated by the method of Dawson and co-workers.[4] In a second experiment a mixture of lysine-2-C^{14} and lysine-α-N^{15} was administered. One month after feeding the tracers the roots were harvested and extracted with chloro-

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

(2) A notable exception was the formation of ephedrine-N^{15} from phenylalanine-N^{15}: S. Shibata and I. Imaseki, *Pharm. Bull.* (Tokyo), **4**, 277 (1956).

(3) E. Leete, *J. Am. Chem. Soc.*, **78**, 3520 (1956).

(4) M. L. Solt, R. F. Dawson, and D. R. Christman, *Plant Physiol.*, **35**, 887 (1960).

form, affording nicotine and anabasine, which were separated by chromatography on alumina. The anabasine was degraded to determine the distribution of C^{14} and N^{15} in the molecule. Oxidation of the alkaloid with potassium permanganate yielded nicotinic acid, assayed as its methyl ester. Decarboxylation of the nicotinic acid by heating with calcium oxide afforded pyridine, collected as its oxalate. The activities of the alkaloids and their degradation products are recorded in Table I.

The results indicate that essentially all the C^{14} in the anabasine was located at C-2′ in agreement with our previous findings.[3] It is also clear that the ϵ-, but not the α-, amino group of lysine is incorporated directly into the piperidine ring of anabasine. In experiment 1 the specific incorporation of the N^{15} (24.8%) into the piperidine ring was a little lower than the specific incorporation of C^{14} (31.1%). However

TABLE I

	Wt., mg. Precursor fed	% excess N^{15}[c]	Spec. act.,[d] d.p.m./mmole
Experiment 1			
DL-Lysine-2-C^{14}·HCl[a]	5.07	91 (in Nϵ)	1.40×10^8
DL-Lysine-ϵ-N^{15}·HCl[b]	100.12		
Anabasine	33.0	11.354[e]	4.42×10^7
Methyl nicotinate		0	4.35×10^7
Pyridine oxalate		...	$<0.01 \times 10^7$
Specific incorporation of C^{14} into C-2′ = 31.1%			
Specific incorporation of N^{15} into N-1′ = 24.8%			
Nicotine	13.5	1.217[f]	1.03×10^6
Specific incorporation of C^{14} into nicotine = 0.074%			
Specific incorporation of N^{15} into nicotine = 2.6%[g]			
Experiment 2			
DL-Lysine-2-C^{14}·HCl	4.84	90 (in Nα)	1.77×10^8
DL-Lysine-α-N^{15}·HCl[h]	72.55		
Anabasine	21.75	1.024[e]	7.05×10^7
Methyl nicotinate		0	6.83×10^7
Pyridine oxalate		...	$<0.01 \times 10^7$
Specific incorporation of C^{14} into C-2′ = 38.6%			
Specific incorporation of N^{15} into N-1′ = 2.27%			
Nicotine	7.5	0.054[f]	5.05×10^6
Specific incorporation of C^{14} into nicotine = 0.29%			
Specific incorporation of N^{15} into nicotine = 0.11%			

[a] Purchased from Tracerlab, Inc., Waltham, Mass. [b] Purchased from Volk Radiochemical Co., Skokie, Ill., who purchased it from Merck Sharpe and Dohme of Canada, Ltd., Montreal, Canada. [c] We thank Adrian Swanson of the Mass Spectrometry Laboratory, University of Minnesota, for the N^{15} analyses. [d] Radioactivities were determined in a Nuclear Chicago Model 720 liquid scintillation spectrometer. [e] Average of the pyridine and piperidine nitrogen. [f] Average of the pyridine and pyrrolidine nitrogen. [g] Degradation indicated that there was no excess N^{15} in the pyridine ring of nicotine. [h] Prepared according to the method of V. I. Maimind, K. M Ermolaev, and M. M. Shemyakin, *J. Gen. Chem. USSR*, **26**, 2313 (1956).

this result may be rationalized by postulating that some ϵ-transamination occurs leading to α-aminoadipic-δ-semialdehyde followed by resynthesis of lysine from unenriched nitrogen. Some transamination of the ϵ-amino group certainly occurs since a significant amount of N^{15} (2.6%) was found in the pyrrolidine ring of the nicotine which was isolated from the same roots. As expected, the incorporation of C^{14} into the nicotine was quite low (0.074%) since the established precursors of this alkaloid are nicotinic acid and ornithine.[5] In the second experiment, involving lysine-2-C^{14}-α-N^{15}, the specific incorporation of N^{15} (2.27%) was much less than that of the C^{14} (38.6%).

Our results are therefore consistent with the hypothesis[3] that the piperidine ring of anabasine is formed from lysine *via* α-keto-ϵ-aminocaproic acid. Our recent observation[6] that only the δ-amino group of ornithine is incorporated into the pyrrolidine ring of nicotine is complementary with the present work.

(5) E. Leete, E. G. Gros, and T. J. Gilbertson, *Tetrahedron Letters*, 587 (1964).

(6) Alfred P. Sloan Foundation Fellow, 1962–1965.

(7) Fellow of the Consejo de Investigaciones Cientificas y Técnicas, Argentina.

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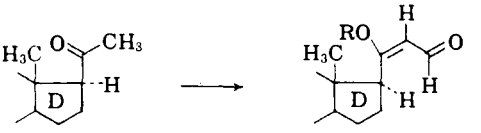
RECEIVED JULY 20, 1964

Steroid Synthesis Based on Oxonium Intermediates. I. Application to 20-Ketosteroids

Sir:

The synthesis, isolation, and chemical properties of simple dialkoxycarbonium salts have been studied intensively by Meerwein and co-workers.[1] Apart from the isolated salts, dialkoxycarbonium ions have been generally accepted as the intermediates in reactions involving orthoesters and strong acids.[2] This communication describes the reaction of 20-ketosteroids with *in situ* generated dialkoxycarbonium ions leading to an unusual formylation reaction.[3] The reaction can be generally illustrated in the following manner.[4]

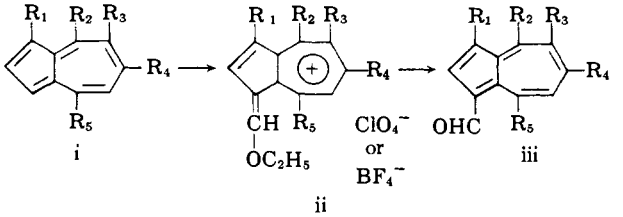


When 3β-acetoxypregn-5-en-20-one in excess triethyl orthoformate was treated briefly (2–5 min.) with 72%

(1) (a) H. Meerwein, P. Borner, O. Fuchs, H. J. Sasse, H. Schrodt, and J. Spille, *Chem. Ber.*, **89**, 2060 (1956); (b) H. Meerwin, K. Bodenbenner, P. Borner, F. Kunert, and K. Wunderlich, *Ann.*, **632**, 38 (1960); (c) H. Meerwein, V. Hederich, H. Morschel, and K. Wunderlich, *ibid.*, **635**, 1 (1960); (d) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *ibid.*, **641**, 1 (1961). For a recent review of these and other ambident ions see S. Hunig, *Angew. Chem.*, **76**, 400 (1964).

(2) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New Hork, N. Y., 1940, pp. 218–221, 305; S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, **65**, 613 (1943); J. H. DeWolfe and J. L. Jensen, *ibid.*, **85**, 3264 (1963).

(3) A broad analogy for the orthoester reaction is known in the azulene series: E. C. Kirby and D. H. Reid, *J. Chem. Soc.*, 1724 (1961); K. Hafner, H. Pelster, and J. Schneider, *Ann.*, **650**, 62 (1961), report the reaction of an azulene (i) with $(C_2H_5O)_3CH$–HBF_4 or $HClO_4$ to yield a stable azulinium salt (ii). Hydrolysis of the salt gave the formylated azulene derivative iii.



(4) The transformation illustrated should be compared with the Vilsmeier reaction [(a) Houben–Weyl, "Methoden der Organischen Chemie," Vol. 7, Georg Thieme Verlag, Stuttgart, 1954, Part 1, p. 30; (b) M. Maheas, *Bull. soc. chim. France*, 1989 (1962)]. The Vilsmeier reaction involving ketones [(c) Z. Arnold and J. Zemlicka, *Proc. Chem. Soc.*, 227 (1958); *Collection Czech. Chem. Commun.*, **24**, 2385 (1959)] leads to a synthesis of β-chloro-