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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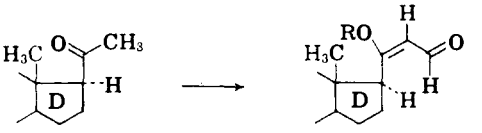
RECEIVED JULY 20, 1964

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]

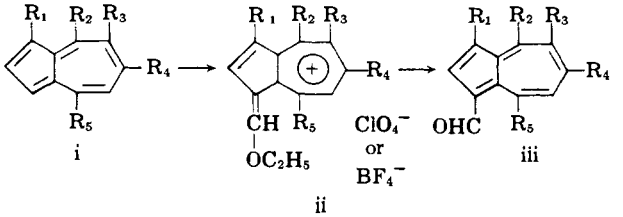


When 3β-acetoxypregn-5-en-20-one in excess triethyl orthoformate was treated briefly (2–5 min.) with 72%

(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).

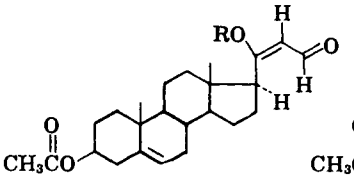
(2) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New Hork, N. Y., 1940, pp. 218–221, 305; S. Winstein and R. E. Buckles, *J. Am. Chem. Soc.*, **65**, 613 (1943); J. H. DeWolfe and J. L. Jensen, *ibid.*, **85**, 3264 (1963).

(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.

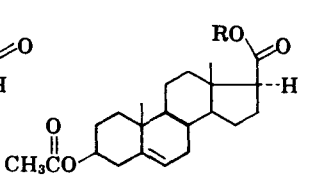


(4) The transformation illustrated should be compared with the Vilsmeier reaction [(a) Houben–Weyl, "Methoden der Organischen Chemie," Vol. 7, Georg Thieme Verlag, Stuttgart, 1954, Part 1, p. 30; (b) M. Maheas, *Bull. soc. chim. France*, 1989 (1962)]. The Vilsmeier reaction involving ketones [(c) Z.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

perchloric acid (2.1 equiv.) an intensely colored red-brown solution was observed. Addition of base decolorized the reaction mixture and isolation afforded a crystalline compound (Ia), m.p. 175–178°, λ_{max} 261 mμ (ε 19,300), ν_{max} 1660 and 1600 cm.$^{-1}$, $[\alpha]_D$ −163°,[5] in about 80% yield. An equivalent reaction could be demonstrated with trimethyl orthoformate yielding Ib, m.p. 187–189°, λ_{max} 260 mμ (ε 18,800), ν_{max} 1660 and 1597 cm.$^{-1}$, $[\alpha]_D$ −178°. The p.m.r. spectra[6] of these compounds indicated an aldehydic proton (589 c.p.s.) coupled to an olefinic proton (328 c.p.s., J_{AB} = 8 c.p.s.). Also indicated was the presence of an alkoxyl group and a single proton, as a triplet, centered at 193 c.p.s. The precise arrangement of these functional groups[7] was indicated by potassium permanganate oxidation of Ia and Ib which gave, respectively, ethyl 3β-acetoxyandrost-5-ene-17β-carboxylate (IIa), m.p. 130–132°, $[\alpha]_D$ −29°, and methyl 3β-acetoxyandrost-5-ene-17β-carboxylate (IIb), m.p. 155–156°.[8]

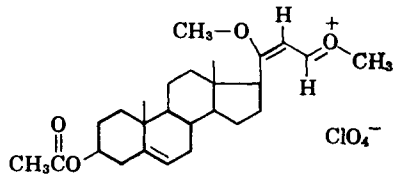


Ia, R = C_2H_5
b, R = CH_3



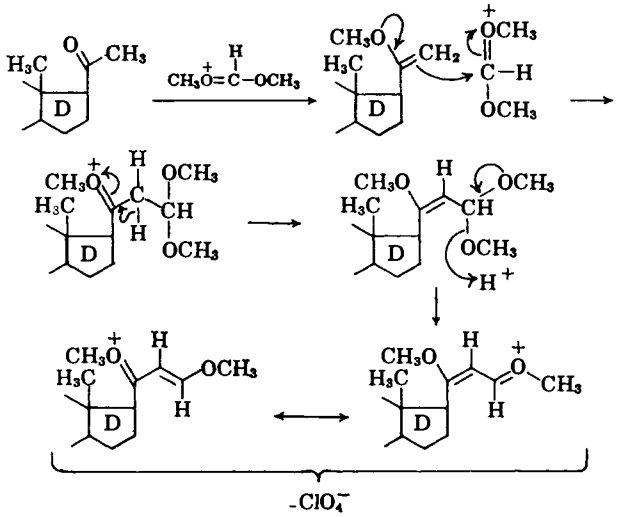
IIa, R = C_2H_5
b, R = CH_3

An insight to the mechanism of the reaction was obtained by the following observations. During the course of the reaction leading to Ib, a precipitate was formed which on isolation and characterization proved to be a perchlorate salt (strong infrared band at 1082 cm.$^{-1}$, Nujol).[9] The isolated salt[10] was decomposed with pyridine–water to aldehyde Ib, and, moreover, could be regenerated by subjecting Ib itself to the original reaction conditions. The p.m.r. spectrum of the salt in deuteriochloroform showed signals for two methoxyl groups (270 and 279 c.p.s.) and two vinylic protons (397 and 550 c.p.s., J_{AB} = 12 c.p.s.) in addition to the C-6 proton (323 c.p.s.). On the basis of these observations, the perchlorate salt has been assigned structure III,[11] [21-(3β-acetoxy-20-methoxypregna-5,-



III

20-dienyl)]methylcarboxonium perchlorate.[12] A mechanism illustrating its formation can be depicted as



We have studied the reaction of carboxonium ions with a variety of steroidal ketones and will shortly report these results. In addition we have also investigated the reactions of these aldehydes with a variety of reagents and find them to be versatile compounds for further transformations.

acraldehydes. When applied to acetals [(d) D. Bertin, L. Nedelec, and J. Mathieu, *Compt. rend.*, **253**, 1219 (1961)] or ketals and enol ethers [(e) Z. Arnold and J. Zemlicka, *Collection Czech. Chem. Commun.*, **24**, 786 (1959); (f) D. Burn, G. Cooley, J. W. Ducker, B. Ellis, D. N. Kirk, and V. Petrow, *Tetrahedron Letters*, 733 (1964); (g) D. Burn, G. Cooley, M. T. Davies, J. W. Ducker, B. Ellis, P. Feather, A. K. Hiscock, D. N. Kirk, A. P. Leftwick, V. Petrow, and D. M. Williamson, *Tetrahedron*, **20**, 597 (1964)], β-alkoxyacraldehydes are obtained.

(5) All new compounds gave satisfactory analyses. Ultraviolet spectra were determined in methanol. Optical rotations were measured in chloroform. Infrared data are for potassium bromide disks or as otherwise stated.

(6) The p.m.r. data were obtained on a Varian A-60 spectrometer using TMS as an internal standard and deuteriochloroform as solvent. We wish to acknowledge the helpful assistance of Messrs. George Morton and Van Canaday with the interpretation of these spectra.

(7) We favor the *trans* orientation of the alkoxyl and formyl groups in the condensation products based on spectroscopic evidence to be discussed in the full publication on this work.

(8) This compound proved identical with an authentic sample of the etienic ester as shown by infrared and n.m.r. analyses. M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 1164 (1939), report a melting point of 153–154° for this compound.

(9) R. N. Jones and C. Sandorfy, "Chemical Applications of Spectroscopy," Interscience Publishers, Inc., New York, N. Y., 1956, p. 417, cite an intense maximum at 1090 cm.$^{-1}$ as characteristic of the perchlorate ion in organic compounds.

(10) The perchlorate salt (indefinite m.p. 80–125° dec.) exhibited a limited stability. At room temperature, exposed to the atmosphere for several hours, the sample considerably darkened from its initial very pale yellow appearance.

(11) Alkylalkylideneoxonium perchlorates have previously not been reported as isolable salts although fluoroborates and hexachloroantimonates are known.[1c,d] The stability of III may be rationalized through resonance stabilization involving the enol ether function.

(12) The problem of naming oxonium salts of this type, with a consistent nomenclature, presents certain difficulties, since the expressions "carbonium," "carboxonium," and "oxonium" may be used interchangeably for the same ion. Therefore, we have arbitrarily decided to name the compound III as a carboxonium ion prototype, R_1R_2—$\overset{+}{C}$=O—R_3, thus avoiding certain nomenclature difficulties for this resonance contributor.

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