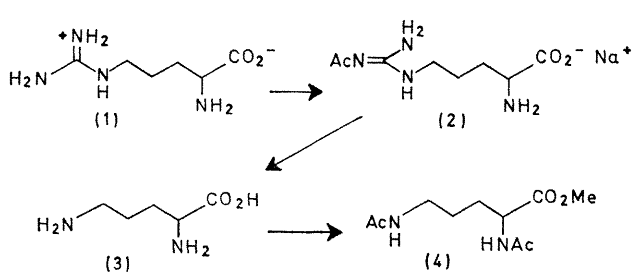
Reductive Cleavage of Acyl-guanidines to Amines

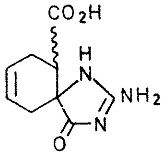
By JEFFREY S. BLAND and JOHN F. W. KEANA*
(*Department of Chemistry, University of Oregon, Eugene, Oregon* 97403)

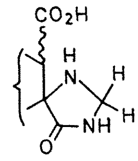
Summary A new mild reductive cleavage of the guanidine moiety is illustrated by the conversion of sodium ω-acetylarginate (**2**) and acyl-guanidine (**5**), respectively, into ornithine (**3**) and amine (**6**) using sodium in ammonia containing acetic acid.

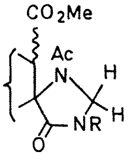
THE guanidine moiety has been hydrolysed under stringent conditions to the corresponding amine.[1,2] The conversion[2] of arginine into ornithine in 75% yield (99% optical purity) by the action of barium hydroxide under reflux (0·5 M) constitutes one of the more mild cleavage procedures previously reported. We report that acyl-guanidines undergo smooth reductive cleavage to the corresponding amine under dissolving metal conditions at −33°.



Treatment of L-arginine (**1**) ([α]$_D$ = 12·1°† with 1 equiv. of sodium methoxide in methanol under reflux followed by addition of ethyl acetate led to sodium ω-acetylarginate (**2**),‡ m.p. 210—220° ([α]$_D$ = 8·5°). Arginate (**2**) could be converted with HCl in methanol into L-arginine hydrochloride which was 98·0% optically pure. Treatment of (**2**) with 10 equiv. of sodium in boiling liquid ammonia containing 10 equiv. of acetic acid led to L-ornithine (**3**) in 67% yield§ (97·6% optically pure) based on starting (**1**). Under these conditions arginine itself was recovered unaltered. In another experiment crude (**3**) was treated with HCl in methanol followed by acetic anhydride, to give the oily ester diacetate (**4**) (molecular ion; calcd., *m/e* 230·126; found, *m/e* 230·125) in 35% yield from (**2**).


(**5**)


(**6**)


(**7**) R = Ac
(**8**) R = H (m.p. 267°)

The versatility of this new mild reductive cleavage reaction was exemplified by the treatment of acyl-guanidine (**5**)[3] with 15 equiv. of sodium in ammonia containing 15 equiv. of acetic acid which led in 70% yield to acid (**6**) (or tautomer). Crude (**6**) was characterized as the amorphous methyl ester diacetate (**7**) (molecular ion: calcd., *m/e* 294·121; found, *m/e* 294·122). Ester (**7**), obtained in 40% overall yield from (**5**), displayed in its 100 MHz ($CDCl_3$)

---

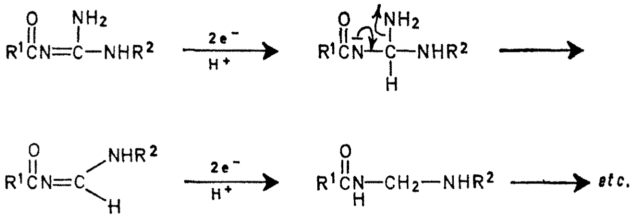
† Rotations were taken at *c* 2·0 in water at 22°.

‡ New substances (**2**), (**4**), (**7**), and (**8**) show i.r., n.m.r., and mass spectra consistent with the assigned structures. Satisfactory elemental analyses were obtained for (**2**) and (**8**): (**8**) was prepared by partial acetylation of crude (**6**) followed by chromatography.

§ No attempt was made to maximize yields for this communication.

spectrum absorptions at δ 2·12 (s, 3H, acetyl), 2·4—2·8 (m, 4H, allylic hydrogens), 2·52 (s, 3H, acetyl), 3·24 (d of d, 1H, methine), 3·75 (s, 3H, methoxy), 5·12 (AB q, J_{AB} 6·5 Hz, 2H, methylene), and 5·8—6·0 (m, 2H, vinyl).

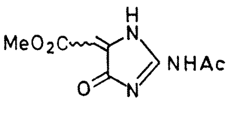
The ability of sodium in ammonia containing acetic acid to effect the conversions (**2**) into (**3**) and (**5**) into (**6**) may be rationalized as shown in the Scheme.



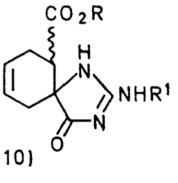
SCHEME

Our new procedure should allow for the first time the selective modification of an arginine residue to an ornithine residue within a polypeptide.

Note added in proof: Recent work of Katner[4] suggests that the dienophile used in the preparation of the adducts in this paper has the imidazoline structure (**9**). The Diels–Alder adduct and its products should therefore possess spiro structures (**10**) rather than the hydroquinazoline structures shown in the paper. We have recently obtained adducts possessing the hydroquinazoline structure from the addition of butadiene and isoprene to 2-acetamido-6-methoxycarbonylpyrimid-4(3H)-one.



(9)



(10)

We thank the National Science Foundation for financial support.

(*Received, March* 16*th,* 1971; *Com.* 313.)

---

[1] D. D. Van Slyke, *J. Biol. Chem.*, 1911, **10**, 15; W. R. Boon and W. Robson, *Biochem. J.*, 1935, **29**, 2684; P. B. Hamilton and R. A. Anderson, *Biochem. Prep.*, 1953, **3**, 96.

[2] D. E. Rivard and H. E. Carter, *J. Amer. Chem. Soc.*, 1955, **77**, 1260.

[3] J. F. W. Keana, F. P. Mason, and J. S. Bland, *J. Org. Chem.*, 1969, **34**, 3705.

[4] A. S. Katner and E. A. Ziege, personal communication.