Studies on the Synthesis of Corrins and Related Ligands. A Simple Synthesis of γ-Substituted Butyrolactams *via* the Conjugate Addition of Cyanide to αβ-Unsaturated Ketones

By R. V. STEVENS* and MORRIS KAPLAN

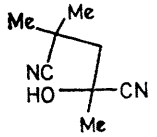
(*Department of Chemistry, Rice University, Houston, Texas*, 77001)

Summary A simple synthesis of γ-substituted butyrolactams involving a hydrolysis of β-cyano-ketones and their conversion into semicorrinoid-like substances is outlined.

THE conjugate addition of an excess of cyanide in warm aqueous alcohol to mesityl oxide was reported by Lapworth[1] to yield a compound of m.p. 165—166° which was assigned structure (**1**) on the basis of its nitrogen analysis and solubility in cold aqueous base and the fact that a hot alkaline solution liberated HCN. Repetition of this experiment yielded two crystalline compounds in variable amounts depending upon the conditions. One of these had m.p. 168—169° and behaved like Lapworth's compound. However, its spectral features were inconsistent with the assigned structure. We now re-formulate this compound as the γ-cyano-butyrolactam (**2**) on the basis of the following evidence: C, H, N analysis agree with the assigned structure [(**1**) and (**2**) have the same empirical formula]; i.r. (Nujol) ν_{max} 3180, 3090, 2245, and 1750 cm^{-1}; n.m.r. ($CDCl_3$) δ 1·22 (s,3H), 1·38 (s,3H), 1·68 (s,3H), and 2·25 (ABq,2H). The other crystalline compound was the known[2] carbinolamide (**3**) and its isolation from the same reaction mixture clarified the origin of (**2**) and provided the means for its rational synthesis. Thus, exposure of (**3**) to a basic cyanide solution provided the cyano-lactam (**2**) in high yield. The formation of (**3**) *via* the conjugate addition product (**4**) was not particularly surprising, since such solutions become strongly basic as the reaction proceeds. However, the additional observation that simply warming an aqueous alcoholic solution of (**4**) (prepared in 55% yield from mesityl oxide and "Et_2AlCN"[3]) in pH 10 $Na_2CO_3/NaHCO_3$ buffer also afforded (**3**) in 84% yield was of special interest. This unusually mild basic hydrolysis of a nitrile is no doubt assisted by the neighbouring carbonyl function. To test these observations further we also prepared the cyano-ketone (**5**),† b.p. 73—74°/0·2 mm, *via* the Nagata[3] procedure. Warming this compound in the same buffer solution also yielded the carbinolamide (**6**), m.p. 117·5—118·5° (60%). Pyrolytic dehydration of (**3**) to a mixture of enamides (**7**) and (**8**) in the presence of $MgSO_4$ proceeded quantitatively.

With a practically unlimited supply of intermediate (**2**) in hand, it became of interest to see if base-induced elimination of HCN might be followed by double-bond equilibration to the exocyclic position as in (**9**). Provided the base was a hindered one, such a proposition appeared both sterically

† Each intermediate reported in this communication has been subjected to i.r., n.m.r., and, wherever applicable, u.v. analysis. Supporting data were obtained from mass spectral and/or combustion analysis.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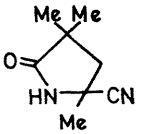
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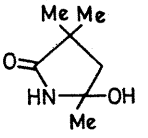
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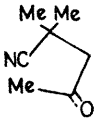
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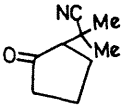
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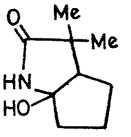
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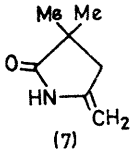
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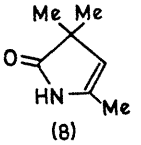
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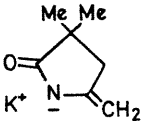
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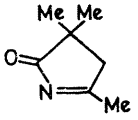
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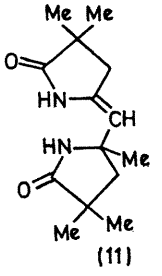
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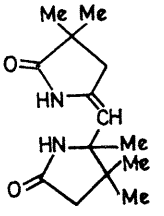
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attractive and electronically favourable. Furthermore, such an anion could then serve as a nucleophilic agent towards its own precursor (**10**) in much the same manner as cyanide had in the (**3**) → (**2**) transformation. When (**2**) [or the isomeric mixture (**7**) + (**8**)] was exposed to slightly more than 1-equiv. of $KOBu^t$ in warm Bu^tOH a mixture of two crystalline substances was obtained. The dimeric nature of these two materials was established from combustion and mass-spectrometric data. Except for the rather delicate question of the geometry of its double bond, one of the dimers, m.p. 192—194°, was assigned structure (**11**) on the basis of its i.r. maxima 3200 and 3090 (NH), 1720 and 1670 (C=O); and its n.m.r. spectrum ($CDCl_3$) δ 9·0 and 7·95 (broad s, 1 H each), 4·49 (t, 1H, *J* 1·3 Hz), 2·46 (d, 2H, *J* 1·3), 2·00 (broad s, 2H), 1·40 (s, 3H), and *ca.* 1·2 (broad s, 12H). The exocyclic enamide chromophore, λ_{max} (95% EtOH) 232 nm (ε 11,600), compares favourably with that found in the related known‡ dimeric compound (**12**), *i.e.* 229 (12,900). The structure of the other crystalline dimer, m.p. 183—184°, remains less certain although the spectral evidence is suggestive of the corresponding endocyclic double-bond isomer. Catalytic hydrogenation of each of the dimeric compounds provided the same two stereoisomeric reduction products, confirming the isomeric nature of these compounds.

We thank the Public Health Service, the Robert A. Welch Foundation, and Eli Lilly Company for support of this work. The n.m.r. and mass spectrometers were purchased with funds provided by the National Science Foundation. R.V.S. is grateful to the Sloan Foundation for a fellowship.

(*Received, May* 11*th*, 1970; *Com.* 723.)

‡ R. Scheffold, Eidg. Technische Hochschule, Zürich, Ph.D. dissertation (1963). We thank Professor Eschenmoser for supplying us with the spectral data for this compound, *cf.* ref. 4.

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