

## THE RITTER REACTION OF 4-METHYLPENT-3-ENONITRILE\*

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Conflicting reports exist regarding the participation of olefinic nitriles in the Ritter reaction.<sup>1</sup> Although Nentwig<sup>2</sup> has reported that pent-4-enitrile undergoes such a reaction to yield 5-methylpyrrolidone, Hill and Conley<sup>3</sup> conclude that the carbonium ion and nitrile groups involved must be separated by a longer carbon chain than that present in the pentenitrile. Examination of molecular models confirms this latter view, and shows that separation of the reaction centres by a chain of at least four methylene groups is necessary to permit their mutual interaction.

Readily available<sup>4</sup> 4-methylpent-3-enitrile (I) was considered a suitable substrate for an initial examination of the reaction. Protonation of (I) gives a tertiary carbonium ion, and if an intramolecular reaction were to occur the expected product, 5,5-dimethyl-2-pyrrolidone (II), is well authenticated.<sup>5</sup>

Treatment of (I) with concentrated sulphuric acid gave, after dilution with water and basification, two crystalline products, (A) and (B), in 4% and 23% yield respectively, neither of which proved to be the pyrrolidone (II).

Compound (A),  $C_{12}H_{22}N_2O_2$ , was insoluble in water and organic solvents and was shown by i.r. spectroscopy to be a secondary amide. Acid hydrolysis gave 4-amino-4-methylpentanoic acid<sup>6</sup> thus indicating that (A) is the diazacyclodecane-dione (IV), formed by a double intermolecular Ritter reaction possibly involving an intermediate such as (III). The low solubility of (IV) in organic solvents is paralleled by similar macrocyclic diamides.<sup>7</sup>

Compound (B),  $C_{12}H_{20}N_2O$ , was obtained from the chloroform extract of the aqueous mother liquors of the original reaction mixture. The i.r. spectrum of (B) showed no N-H stretching vibrations and a single carbonyl band at  $1680\text{ cm}^{-1}$ . The n.m.r. spectrum of (B) showed two methyl singlets at  $\delta\ 1.21$  and  $\delta\ 1.48$ , both integrating for six protons: four-proton  $CH_2-CH_2$  multiplets at  $\delta\ 1.70-1.90$  and  $\delta\ 2.35-2.63$  were also present. Hydrogenation of compound (B) gave a dihydro derivative whose i.r. spectrum revealed the presence of an NH group, thus indicating the presence of a C=N group in (B). The n.m.r. spectrum of dihydro-B showed two *gem*-dimethyl doublets at  $\delta\ 1.08$  ( $J\ 2\text{ c/s}$ ) and  $\delta\ 1.37$  ( $J\ 7\text{ c/s}$ ), a complex eight-proton

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<sup>1</sup> Ritter, J. J., and Minieri, P. P., *J. Am. chem. Soc.*, 1948, **70**, 4045.

<sup>2</sup> Nentwig, J., Diss. Marburg 1953, p. 22, quoted in Houben-Weyl, "Methoden der organischen Chemie." Vol. 11(2), p. 561. (Georg Thieme: Stuttgart 1958.)

<sup>3</sup> Hill, R. K., and Conley, R. T., *J. Am. chem. Soc.*, 1960, **82**, 645.

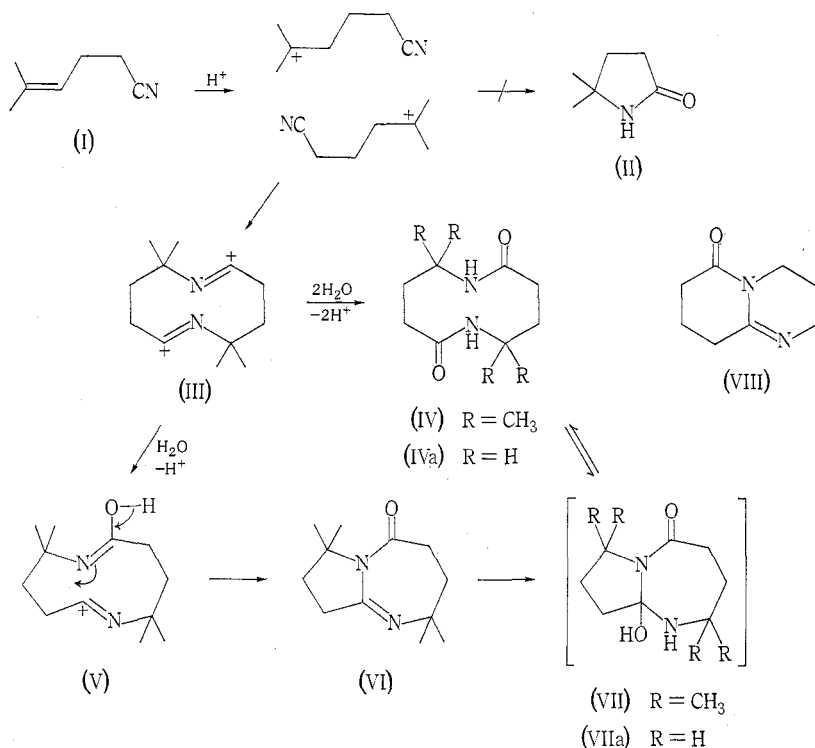
<sup>4</sup> Letch, R. A., and Linstead, R. P., *J. chem. Soc.*, 1932, 443.

<sup>5</sup> Moffet, R. B., *Org. Synth.*, 1963, Coll. Vol. IV, 357.

<sup>6</sup> Schumann, E. L., Paquette, L. A., Heinzelman, R. V., Wallach, D. P., DaVanzo, J. P., and Greig, M. E., *J. mednl pharm. Chem.*, 1962, **5**, 464.

<sup>7</sup> Dale, J., and Conlon, R., *J. chem. Soc.*, 1964, 182.

multiplet at  $\delta$  1.50–2.88 and a two-proton triplet at  $\delta$  4.72 ( $J$  5 c/s): on exchange with deuterium oxide this latter signal became a one-proton triplet. On this evidence we concluded that compound (B) was the diazabicyclodecenone (VI).



It is of interest that in contrast to the facile hydrogenation of (B), Dale and Conlon<sup>8</sup> found that the closely related compound (VIII) was resistant to hydrogenation. They also reported that reduction of (VIII) with lithium aluminium hydride in refluxing tetrahydrofuran led to complete disruption of the molecule giving only volatile products; compound (B) behaved in a like manner.

Confirmation of structure (VI) came from treatment of (B) with aqueous silver oxide when (IV) was obtained in good yield. Examples of this latter transformation, which involves initial hydration of the imine followed by ring opening, have been reported by Shemyakin *et al.*<sup>9</sup> These workers also found that certain cyclic diamides underwent the reverse process of transannular amide–amide interaction and subsequent dehydration, when boiled in xylene. Glover *et al.*<sup>10</sup> achieved cyclization of (IVa) on heating with dilute hydrochloric acid. Compound (IV) however was inert to both these procedures even with longer reaction periods. We ascribe this unreactivity of (IV) to its extreme insolubility in the reaction media.

<sup>8</sup> Dale, J., and Conlon, R., *J. chem. Soc.*, 1965, 3487.

<sup>9</sup> Shemyakin, M. M., Antonov, V. K., Shkrob, A. M., Shehelokov, V. I., and Agadzhanian, Z. E., *Tetrahedron*, 1965, **21**, 3537.

<sup>10</sup> Glover, G. I., Smith, R. B., and Rapoport, H., *J. Am. chem. Soc.*, 1965, **87**, 2003.

We were also unable to effect the conversion of (IV) into (VI) under conditions duplicating those encountered during the work-up procedure. We therefore consider that a possible mechanism for the formation of (VI) involves conversion of (III) into intermediate (V) followed by a transannular reaction as illustrated.

The formation of compounds (IV) and (VI) represents the first example of a double intermolecular Ritter reaction.

### Experimental

Melting points were determined on a Kofler apparatus and are uncorrected. Infrared spectra were determined as Nujol mulls between sodium chloride plates using a Unicam SP200 instrument. N.m.r. spectra were recorded in deuterochloroform solution at 29° using a Varian HA60-IL spectrometer; all chemical shifts are referred to tetramethylsilane. The u.v. spectrum was determined on a Unicam SP800 spectrometer.

#### Ritter Reaction of 4-Methylpent-3-enonitrile

4-Methylpent-3-enonitrile (20 g) was added dropwise to stirred, ice-cooled sulphuric acid (98%, 20 ml) at such a rate that the temperature did not rise above 20°. When the addition was complete (c. 1 hr) the resulting viscous mixture was left at room temperature for 20 hr, then poured onto ice (400 g) and brought to pH 12 by the addition of concentrated aqueous ammonia.

The precipitate was filtered off and washed with acetone (10 ml) and chloroform (10 ml) to yield analytically pure 5,5,10,10-tetramethyl-1,6-diazacyclodecane-2,7-dione (IV) (900 mg, 4%), as plates, m.p. 227–228°,  $\nu_{\max}$  3250, 1640, and 1560  $\text{cm}^{-1}$  (Found: C, 63.5; H, 9.7; N, 12.5.  $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}_2$  requires C, 63.7; H, 9.8; N, 12.4%).

The aqueous solution was extracted with chloroform (6  $\times$  200 ml) and the combined extracts dried, concentrated to c. 20 ml, and adsorbed on neutral alumina (140 g, Woelm, activity I). Elution with chloroform gave 5,5,10,10-tetramethyl-1,6-diazabicyclo[5,3,0]dec-6-en-2-one (VI) (5 g, 23%), m.p. 44–45° (needles from pentane),  $\nu_{\max}$  1680  $\text{cm}^{-1}$ ,  $\lambda_{\max}$  (EtOH) 228  $\mu$  ( $\log \epsilon$  4.06),  $\lambda_{\max}$  (EtOH+1% HCl) 235  $\mu$  ( $\log \epsilon$  4.19) (Found: C, 69.4; H, 9.6; N, 13.2.  $\text{C}_{12}\text{H}_{20}\text{N}_2\text{O}$  requires C, 69.2; H, 9.7; N, 13.45%).

#### Hydrolysis of (IV)

A suspension of the diamide (80 mg) in sulphuric acid (10%, 3 ml) was heated at 80° for 16 hr. The mixture was cooled, diluted with water (10 ml), and neutralized with solid barium carbonate. The barium sulphate was filtered off and the filtrate evaporated to dryness. Crystallization of the residue from aqueous ethanol gave 4-amino-4-methylpentanoic acid (45 mg, 50%), m.p. 270° (lit.<sup>6</sup> 270°). The i.r. spectrum showed  $\nu_{\max}$  2200, 1640, and 1550  $\text{cm}^{-1}$  and was identical with that of authentic 4-amino-4-methylpentanoic acid prepared by barium hydroxide hydrolysis of 5,5-dimethylpyrrolidone.<sup>6</sup>

#### Hydrogenation of (VI)

A solution of (VI) (500 mg) in ethanol (30 ml) was hydrogenated over platinum oxide (20 mg) at 20° and atmospheric pressure. The uptake of hydrogen was complete after 90 min when 1 mol. propn. of hydrogen had been absorbed. After removal of the catalyst, the ethanol solution was evaporated to dryness and the residue was recrystallized from pentane to give 5,5,10,10-tetramethyl-1,6-diazabicyclo[5,3,0]decan-2-one (330 mg, 65%) as plates, m.p. 85°,  $\nu_{\max}$  3300 and 1680  $\text{cm}^{-1}$  (Found: C, 68.5; H, 10.4; N, 13.4.  $\text{C}_{12}\text{H}_{22}\text{N}_2\text{O}$  requires C, 68.5; H, 10.5; N, 13.3%).

#### Conversion of (VI) into (IV)

A solution of (VI) (180 mg) in water (4 ml) was stirred with silver oxide (500 mg) at room temperature for 10 min. After removal of the silver oxide the filtrate was concentrated to half volume and cooled. The precipitated (IV) (120 mg, 62%), m.p. 226–228°, was filtered off. The i.r. spectrum was identical with that of (IV) obtained from the Ritter reaction.