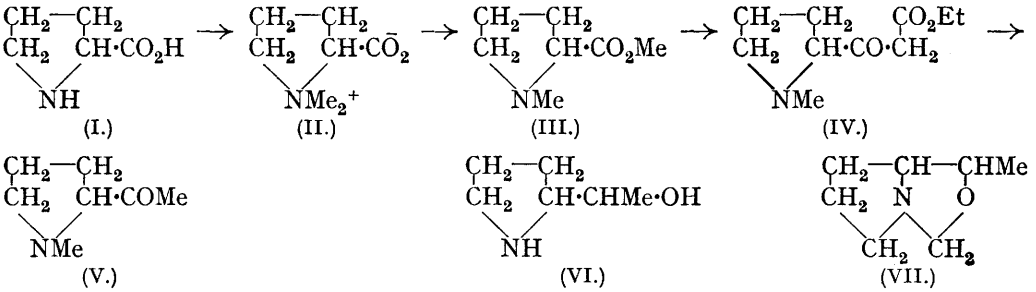
64. 2-*Acetyl*-1-*methylpyrrolidine*.

By Harold King.

2-Acetyl-1-methylpyrrolidine has been synthesised from proline. It is different from bellaradine.

The alkaloidal base, bellaradine, $C_7H_{13}ON$, was obtained from Bulgarian belladonna root, only in sufficient quantity to establish its composition with certainty and to show the presence of a pyrrolidine ring with a tertiary nitrogen atom (King and Ware, preceding paper). The most likely structure for such a base seemed to be that of 2-acetyl-1-methylpyrrolidine. The latter base has now been synthesised from proline (I) by conversion into the betaine stachydrine (II) and dry distillation of the latter with the formation of methyl hygrate (III). This ester was condensed with ethyl acetate in the presence of sodamide to yield ethyl 1-methylpyrrolidoyl-2-acetate (IV), which was not isolated but was hydrolysed with loss of carbon dioxide to form 2-acetyl-1-methylpyrrolidine (V).



This substituted amino-ketone is an unstable substance which on keeping deposits a viscous oil having possibly a tricyclic structure. It can, however, be stabilised in the form of salts, the *aurichloride*, picrate and methopicrate being obtained crystalline. The properties of the base, its salts and derivatives are completely different from those of bellaradine.

Hess, Merck, and Uibrig (*Ber.*, 1915, **48**, 1900), by the action of formaldehyde at 120° in the presence of mineral acid on methyl-2-pyrrolidylcarbinol (VI), obtained a substance which they described as 2-acetyl-1-methylpyrrolidine (V). Hess, however, in a private communication to the editors of Beilstein's "Handbuch" (4th Edition, Supplementary

Vol., XXI, p. 263) considers this structure as doubtful and prefers to regard it as 5-methyl-3 : 4-trimethyleneoxalidine (VII). The latter structure is probably correct, since the properties of 2-acetyl-1-methylpyrrolidine now synthesised from proline are different from those of the base described by Hess and his collaborators. The following table gives a comparison of the properties of bellaradine, 5-methyl-3 : 4-trimethyleneoxalidine, and 2-acetyl-1-methylpyrrolidine :

	B. p.	Picrate, m. p.	Aurichloride, m. p.	Methopicrate, m. p.
Bellaradine	—	225°	189°?, unstable	228°
Methyltrimethyleneoxalidine	56—57°/26 mm.	175	—	—
2-Acetyl-1-methylpyrrolidine	75—80/30 mm.	118	108—109	202

Experimental.

Preparation of Proline.—For the preparation of this amino-acid Town's copper salt method (*Biochem. J.*, 1928, **22**, 1083; 1936, **30**, 1837) was applied with modification to gelatin, the purification of the proline and separation from hydroxyproline (compare Klabunde, *J. Biol. Chem.*, 1931, **90**, 293) being assisted by cadmium chloride precipitation as described by Kapfhammer and Eck (*Z. physiol. Chem.*, 1927, **170**, 299).

Gelatin (100 g. of Coignet's gold label) was dissolved in water (400 c.c.), sulphuric acid (200 g.) added, and the solution boiled for 6 hours. When cold, baryta (640 g. of octahydrate in 3 l. of water) was added until the reaction was neutral or faintly alkaline. The filtered solution was concentrated to a small bulk at 50° and digested on the water-bath with copper carbonate in excess. The filtrate was evaporated to a syrup, which was stirred with acetone, and the granular copper salts kneaded several times with fresh portions of dry acetone until they were obtained as a fine powder. This was quickly transferred to a dish and dried in a high vacuum over sulphuric acid. It was repowdered and redried in a vacuum and then finally in an oven at 110° for 2 hours. It was quickly transferred to a wide-mouthed stoppered bottle, allowed to cool, and treated, once only, with dry methyl alcohol (500 c.c.). The contents were kept for 24 hours with occasional shaking. The solution was then filtered, the methyl alcohol distilled off, the residue dissolved in water, and the copper removed as sulphide. The filtrate was evaporated to a syrup, and excess of ethyl alcohol added gradually to precipitate crude hydroxyproline, which often separated in the crystalline state. After removal of this crude hydroxyproline the filtrate was again evaporated to dryness and again treated with excess of ethyl alcohol to precipitate a further quantity of hydroxyproline. The alcoholic filtrate was then treated with a saturated solution of cadmium chloride in spirit so long as a precipitate formed. After a few hours the cadmium chloride–proline precipitate was collected and dissolved in water, saturated silver sulphate solution added in slight excess, and the filtrate from the silver chloride saturated with hydrogen sulphide to remove silver and cadmium ions. The filtrate from the sulphides was aerated and then treated with baryta to remove sulphate ions exactly. The filtrate from the barium sulphate was evaporated to a thick syrup under reduced pressure in a tared flask, and the syrup weighed. Double its weight of picric acid was added, suspended in its own weight of water. On warming, all passed into solution; proline picrate (about 18 g.) separated on standing. Further small quantities may be obtained by reworking the copper salts after redrying and by working up the cadmium chloride precipitation mother-liquor, since precipitation of the proline by cadmium chloride is not quantitative.

Recrystallised proline picrate (86 g.) was treated with sulphuric acid (20 g.) and water (200 c.c.), the picric acid being removed first by filtration, then by ether extraction, and finally by charcoal. Sulphuric acid was then removed exactly by baryta, the proline solution evaporated to dryness, and the proline crystallised from absolute ethyl alcohol or ethyl alcohol and dry ether.

Preparation of Stachydrine.—Proline (26 g.), methyl alcohol (270 c.c.), methyl iodide (43·5 c.c.), and sodium hydroxide (27 g.) were boiled under reflux for 6 hours. As the solution was still alkaline, a further quantity of methyl iodide (10 c.c.) was added and boiling was continued for a further 6 hours. The methyl alcohol was distilled off, and the residue dissolved in water and heated with excess of freshly precipitated silver chloride. The filtrate was evaporated to dryness, and the stachydrine hydrochloride extracted by absolute ethyl alcohol. It was obtained completely free from sodium chloride by a repetition of the process and crystallised readily in needles. It was dissolved in water and treated with freshly precipitated silver oxide to remove chloride ion, and the filtrate evaporated to dryness at room temperature over sulphuric acid in a vacuum. Hydrated stachydrine separated at first, but eventually

this was dehydrated to the anhydrous solid. Yield, quantitative. The gold salt melted at 231° in agreement with the highest m. p. recorded in the literature by Yoshimura (*Z. physiol. Chem.*, 1913, **88**, 338).

Methyl Hygrate.—The following process is an improvement on that given by Trier (*ibid.*, 1910, **67**, 328). 5 G. quantities of the perfectly anhydrous stachydrine, in a roomy flask with a low wide side-arm bent to serve as a receiver, were heated in a metal-bath to about 230°; effervescence then took place. When the temperature was then allowed to rise to 260°, methyl hygrate passed over as an almost colourless liquid (yield, 78%). The combined distillate from several experiments was redistilled and had b. p. 90°/18 mm., the first few drops being discarded, as they had a blackening effect on gold chloride solution. The main distillate gave methyl hygrate aurichloride, m. p. 85°; Trier (*loc. cit.*) gives m. p. 84—86°. The ester seemed to be the racemic form, since in a 1 dcm. tube the observed rotation for the mercury green line was + 0·04°.

Condensation of Methyl Hygrate with Ethyl Acetate. Preparation of 2-Acetyl-1-methylpyrrolidine.—Methyl hygrate (7·15 g.), dry ethyl acetate (4·4 g.), dry benzene (15 c.c.), and sodamide (2·0 g.) were boiled for 5½ hours, a clear solution being obtained. Hydrochloric acid (16%) was added in excess and after the benzene had been distilled off the contents of the flask were boiled until carbon dioxide was no longer evolved (about 2·5 hours). The solution was neutralised with 50% sodium hydroxide solution, made strongly alkaline by addition of a further 25 c.c., and repeatedly extracted with chloroform; on removal of this solvent by distillation a pale yellow oil (2·5 g.) was obtained. On keeping, it deposited a brown viscous oil which increased in quantity with time. Its formation was accelerated during the distillation of the base, which boiled at 75—80°/30 mm.

2-Acetyl-1-methylpyrrolidine, when dissolved in 3N-hydrochloric acid and treated with gold chloride solution, gave an oily gold salt which soon crystallised. The *aurichloride*, recrystallised from N-hydrochloric acid, formed small tablets, m. p. 108—109°. The solutions, unlike bellaradine gold chloride solution, showed no tendency to precipitate metallic gold [Found (micro-analyses): C, 17·5; H, 3·0; N, 3·7, 3·2, 3·5; Au, 42·5, 42·4, 41·8. $C_7H_{13}ON,HAuCl_4$ requires C, 18·0; H, 3·0; N, 3·0; Au, 42·2%]. The picrate separated as an oil from an alcoholic solution of the components, but crystallised on keeping and could then be recrystallised from water, from which it separated in plates, m. p. 118°. A portion of the base formed an oily methiodide on dissolving in methyl iodide, and on double decomposition with aqueous sodium picrate gave a crystalline methopicrate, m. p. about 202° (without decomp.).

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