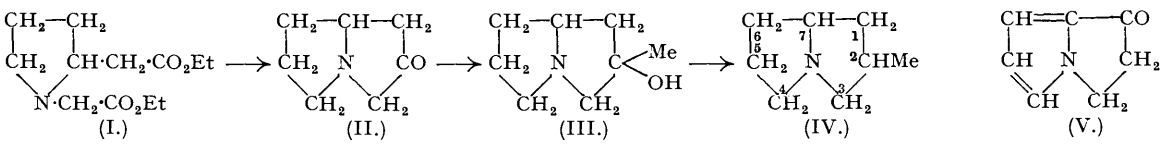
78. *The Synthesis of 2-Methylpyrrolizidine.*

By G. R. Clemo and T. A. Melrose.

2-Methylpyrrolizidine (IV) has been synthesised as follows :



(I.) (II.) (III.) (IV.) (V.)

It does not correspond with the product prepared by Menschikoff from 2-*iso*butylpyrrolidine. Attempts to prepare 1-methylpyrrolizidine have been unsuccessful. A new derivative of 3-methylpyrrole is described.

The work of Menschikoff and others has shown heliotridane to be a methylpyrrolizidine. Adams and Rogers (*J. Amer. Chem. Soc.*, 1941, **63**, 228) have demonstrated conclusively that it is 1-methylpyrrolizidine, although they have not effected a direct synthesis of the base. A synthesis is claimed by Menschikoff (*Bull. Acad. Sci. U.R.S.S.*, 1937, 1035), by the drastic cyclisation of 1-bromo-2-*sec.*-butylpyrrolidine with concentrated sulphuric acid, but the amount of base obtained was insufficient for its complete characterisation. He has also described a synthesis of 2-methylpyrrolizidine (*Ber.*, 1936, **69**, 1802) in much better yield by a similar cyclisation of 1-bromo-2-*iso*butylpyrrolidine.

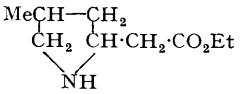
A 2-methylpyrrolizidine structure has been suggested for solanidine (Clemo, Morgan, and Raper, J., 1931, 1299). The synthesis of the 1- and the 2-methyl base by unambiguous methods is thus of considerable interest and this has now been accomplished in the case of the 2-methyl compound.

A likely route to the 1-methyl compound, from 3-keto-4 : 5-dihydrodi(1 : 2)pyrrole (V) and methylmagnesium iodide, failed, since the Grignard reaction gave only a clear resin-like gum. With methyl iodide and zinc wool or sodamide, however, the ketone (V) yielded a crystalline condensation *product* formed by elimination of a molecule of water from two molecules of the ketone.

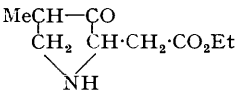
Hydrogen and platinum oxide or palladised charcoal were without effect on the ketone (V), and stronger reducing agents, *e.g.*, sodium and alcohol, were too drastic. Reduction with sodium amalgam gave a *pinacol*.

3-Keto-4 : 5-dihydrodi(1 : 2)pyrrole was first prepared by Clemo and Ramage (J., 1931, 53) by a Hoesch reaction on 1-β-cyanoethylpyrrole. It has now been found possible to hydrolyse the intermediate imino-compound directly with dilute alkali, giving double the yield.

The preparation of 2-methylpyrrolizidine from ethyl 4-methylpyrrolidine-2-acetate (VI) and ethyl bromoacetate could not be tested because of the inaccessibility of 3-methylpyrrole and its derivatives.



(VI.)



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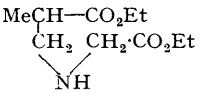
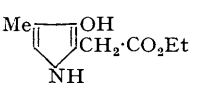


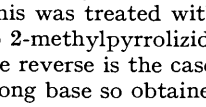
(VIII.)



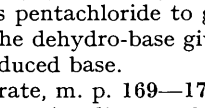
(IX.)

An alternative route, *viz.*, reduction of ethyl 3-keto-4-methylpyrrolidine-2-acetate (VII), prepared by cyclisation of carbethoxymethyl-β-carbethoxy-*n*-propylamine (VIII), failed because, although ring-closure took place readily enough, enolisation and oxidation followed, yielding *ethyl 3-hydroxy-4-methylpyrrole-2-acetate* (IX).

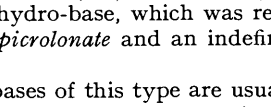
Condensation of urea with methyl methacrylate (cf. Fischer, *Ber.*, 1901, **34**, 3751) led to 5-methyl-4 : 5-dihydrouracil (X)—the conditions now described give a greatly improved yield—which on hydrolysis to β-*carbethoxy*-n-*propylamine* (XI) and subsequent condensation with ethyl bromoacetate gave (VIII). Attempts to prepare carbethoxymethyl-β-carbomethoxypropylamine (XII) by condensing *methyl* β-*bromo*isobutyrate and glycine ester gave only sufficient product to make a picrate.



(X.)



(XI.)



(XII.)

2-Methylpyrrolizidine was finally prepared by the route indicated in the summary. Ethyl pyrrole-2-acetate was reduced to the corresponding *pyrrolidine*, and this condensed with ethyl bromoacetate to give *ethyl pyrrolidine*-1 : 2-*diacetate* (I). The Dieckmann condensation of the latter, followed by hydrolysis and decarboxylation, gave 2-ketopyrrolizidine (II), which yielded the carbinol (III) with methylmagnesium iodide. This was treated with phosphorus pentachloride to give the dehydro-base, which was reduced catalytically to 2-methylpyrrolizidine (IV). The dehydro-base gives a good *picrolonate* and an indefinite picrate, whereas the reverse is the case with the reduced base.

The strong base so obtained gave a picrate, m. p. 169—170°. Free bases of this type are usually difficult to analyse correctly and this base is exceptionally so, the carbon values invariably coming low. The 2-methylpyrrolizidine described by Menschikoff (*loc. cit.*) gave a picrate, m. p. 182—184°. It may be that these two bases are stereoisomers, as two racemic forms are possible.

Experimental.

3-*Keto*-4 : 5-*dihydrodi*(1 : 2)*pyrrole*.—Dry hydrogen chloride was passed for 45 minutes through β-1-pyrrylpropionitrile (1 g.) in dry ether (10 c.c.) and anhydrous zinc chloride (0·25 g.). After 12 hours, the ether was decanted and a solution of the iminohydrochloride in water made just alkaline (potassium carbonate), warmed for ¾ hour on the water-bath, and cooled. The product extracted by chloroform crystallised from light petroleum (b. p. 40—60°) in very pale yellow needles (0·5 g.), m. p. 54°.

Reaction of Zinc and Methyl Iodide with the Ketone (V).—The ketone (0·2 g.), zinc wool (0·03 g.), and excess of methyl iodide were heated in a sealed tube in the water-bath until the mixture began to darken (1 hour). Ice was added, and the solution acidified with hydrochloric acid and basified (potassium carbonate). The *product* extracted by chloroform was extracted once with light petroleum (b. p. 40—60°) to remove unchanged ketone and crystallised from acetone or methyl alcohol, giving fine yellow needles (0·1 g.), m. p. 209° [Found: C, 75·2; H, 5·1; N, 12·8; *M* (Rast), 199. $C_{14}H_{12}ON_2$ requires C, 75·0; H, 5·3; N, 12·5%; *M*, 224].

Reduction of the Ketone (V).—The ketone (0·2 g.) in water was warmed on the water-bath, and sodium amalgam (10 g., 4%) added during 3 hours, acetic acid being added from time to time to prevent the mixture from becoming alkaline. The colourless solution was decanted and extracted with chloroform, which removed the *pinacol*; this separated from alcohol in almost colourless crystals, m. p. 183—184° (Found: C, 68·9; H, 6·5. $C_{14}H_{16}O_2N_2$ requires C, 68·8; H, 6·6%).

*Methyl β-Bromo*isobutyrate.—Dry hydrogen bromide was passed through a solution of methyl methacrylate (10 g.) in glacial acetic acid (10 c.c.) and a trace of iodine, cooled in ice, until the weight had increased by 8 g. The solution was kept overnight, shaken with water, and extracted with ether, which removed the *ester*, a pleasant smelling colourless liquid (16·3 g.), b. p. 63—65°/15 mm., or 75°/22 mm. (Found: Br, 44·8. $C_5H_9O_2Br$ requires Br, 44·2%).

5-*Methyl*-4 : 5-*dihydrouracil* (cf. Fischer, *loc. cit.*).—Methyl methacrylate (10 g.), methyl alcohol (12 c.c.), and urea (9 g.) were heated in a sealed tube at 130—135° for 24 hours. The solvent was removed, and the residue extracted and crystallised from ethyl alcohol. Yield 7·5 g., m. p. 260°.

β-*Carbethoxy*-n-*propylamine*.—5-Methyl-4 : 5-dihydrouracil (1 g.) was heated with concentrated hydrochloric acid (8 c.c.) in a sealed tube for 12 hours at 120°, and the liquid then evaporated. The residue was repeatedly evaporated with absolute alcohol to remove all water. It was then kept overnight with excess of alcoholic hydrogen chloride and refluxed for 2 hours, the alcohol removed, and the residue made into a paste with ice-cold saturated potassium carbonate solution and extracted with ether, which removed a colourless, strongly basic liquid (0·35 g.), b. p. 35—36°/1 mm., or 71°/13 mm. (Found: C, 54·2; H, 9·5. $C_6H_{13}O_2N$ requires C, 54·9; H, 9·9%). The *picrate* had m. p. 108—109° (Found: C, 39·9; H, 4·6. $C_6H_{13}O_2N$,$C_6H_3O_7N_3$ requires C, 40·0; H, 4·4%).

Carbethoxymethyl-β-carbethoxy-n-*propylamine*.—β-Carbethoxy-*n*-propylamine (1·5 g.), ethyl chloroacetate (1·4 g.), alcohol (10 c.c.), and excess of sodium acetate were heated on the water-bath for 1 hour, the sodium acetate removed,

and the filtrate acidified (hydrochloric acid) and taken rapidly to dryness. The residue was dissolved in a little water, basified (potassium carbonate), and extracted with ether, which removed a colourless liquid (1·1 g.), b. p. 110°/1 mm. (Found: C, 55·3; H, 8·1. $C_{10}H_{19}O_4N$ requires C, 55·3; H, 8·7%). The *picrolonate* had m. p. 137—138° (Found: C, 49·8; H, 5·8. $C_{10}H_{19}O_4N,C_{10}H_8O_5N_4$ requires C, 49·9; H, 5·6%).

Ethyl 3-*Hydroxy*-4-*methylpyrrole*-2-*acetate*.—The above diester (1 g.) was heated with potassium (0·3 g.) in toluene (5 c.c.) on the water-bath for 3 hours, alcohol added to destroy the excess of potassium, the solvents removed under reduced pressure, and the residue made very faintly acid (hydrochloric acid, 1 : 1), then alkaline with solid potassium carbonate, and extracted with ether. The ether was removed at room temperature in a vacuum; the residue solidified and crystallised from light petroleum (b. p. 40—60°) in pale yellow needles (0·2 g.), m. p. 85° (Found: C, 56·7; H, 6·6; N, 8·5. $C_8H_{11}O_3N$ requires C, 56·8; H, 6·5; N, 8·3%). The compound (IX) is very sensitive to acids and heat, soluble in sodium hydroxide solution, and gives a purple colour with *p*-dimethylaminobenzaldehyde and hydrochloric acid on warming.

The p-*nitrobenzoyl* derivative was prepared from the above pyrrole (0·1 g.) and *p*-nitrobenzoyl chloride (0·1 g.) in ether over anhydrous potassium carbonate; after 12 hours the solid was removed, the ether evaporated, and a solution of the residue in warm alcohol treated with water until precipitation began. The derivative, recrystallised from light petroleum (b. p. 40—80°), had m. p. 152° (Found: C, 56·5; H, 4·6; N, 8·9. $C_{15}H_{14}O_6N_2$ requires C, 56·6; H, 4·4; N, 8·8%).

Ethyl Pyrrolidine-2-*acetate*.—A solution of ethyl pyrrole-2-acetate (5·3 g.) in alcohol (5 c.c.) and glacial acetic acid (10 c.c.) was shaken for 24 hours with platinum oxide (0·1 g.) and charcoal (0·1 g.) in presence of hydrogen at 100 lb./sq. in. A further 0·1 g. of platinum oxide was then added, and shaking continued for another 24 hours. The liquid was filtered, and the solvents removed on the water-bath under reduced pressure. The residue was shaken with a few c.c. of dilute hydrochloric acid, and extracted with ether to remove unchanged pyrrole ester. The aqueous solution was evaporated, and the residue basified (saturated potassium carbonate solution) and extracted with ether, which removed a colourless liquid (2·8 g.), b. p. 110°/27 mm. (Found: C, 60·7; H, 9·1. $C_8H_{15}O_2N$ requires C, 61·1; H, 9·55%). The *picronolate* had m. p. 146° (Found: C, 51·0; H, 5·8. $C_8H_{15}O_2N,C_{10}H_8O_5N_4$ requires C, 51·3; H, 5·5%).

Ethyl Pyrrolidine-1 : 2-*diacetate*.—Ethyl pyrrolidine-2-acetate (1·4 g.), ethyl bromoacetate (2 g.), and anhydrous potassium carbonate (2·5 g.) were heated on the water-bath for 4 hours, water added, and the *ester* (1·7 g.) extracted with ether; b. p. 125°/1 mm. (Found: C, 59·5; H, 8·5. $C_{12}H_{21}O_4N$ requires C, 59·3; H, 8·5%).

2-*Ketopyrrolizidine*.—The ester (1·3 g.) was added to potassium (0·6 g.) under xylene (5 c.c.), with initial cooling and with final heating on the water-bath for 3 hours. After destruction of the excess of potassium with alcohol, water (1 c.c.) was added, followed by concentrated hydrochloric acid (10 c.c.). The solution was heated for 18 hours on the water-bath and evaporated to dryness, and the residue basified (saturated potassium carbonate solution), extracted, dried, and distilled, giving a colourless liquid (0·35 g.), which rapidly darkened in the air, b. p. 78°/1 mm. The *picrolonate* had m. p. 212—213° (Found: C, 52·4; H, 5·0. $C_7H_{11}ON,C_{10}H_8O_5N_4$ requires C, 52·4; H, 4·9%).

2-*Hydroxy*-2-*methylpyrrolizidine*.—The Grignard reagent prepared from magnesium (0·3 g.) and excess of methyl iodide was redissolved in ether (5 c.c.), cooled in ice, and the above ketone (0·3 g.) in ether (1·5 c.c.) added slowly with shaking. A white solid formed and redissolved. After remaining at room temperature for 12 hours, the solution was decomposed with ice, acidified with dilute hydrochloric acid, and basified with sodium hydroxide solution, and the base distilled in steam. The distillate was acidified (hydrochloric acid) and evaporated to dryness, and the residue basified (saturated potassium carbonate solution) and extracted with ether, which removed 0·2 g. of a colourless liquid, b. p. 95°/1 mm. The *picrolonate* had m. p. 198° (Found: C, 53·4; H, 5·7. $C_8H_{15}ON,C_{10}H_8O_5N_4$ requires C, 53·5; H, 5·5%).

Dehydro-2-*hydroxy*-2-*methylpyrrolizidine*.—An ice-cold solution of the carbinol (0·15 g.) in chloroform (2 c.c.) was treated with phosphorus pentachloride (0·5 g.) in five separate lots and then refluxed for 15 minutes on the water-bath. A fragment of ice was added, the chloroform removed in steam, 10N-sodium hydroxide added, and the mixture distilled in steam until the distillate was no longer alkaline to litmus. The distillate was acidified with hydrochloric acid and evaporated, and the residue basified (50% potassium hydroxide solution) and extracted with ether, which removed a colourless, mobile, strongly basic oil (0·05 g.). The *picrolonate* crystallised from alcohol in deep yellow prisms, m. p. 169—170° (Found: C, 55·8; H, 5·4. $C_8H_{13}N,C_{10}H_8O_5N_4$ requires C, 55·5; H, 5·9%).

2-*Methylpyrrolizidine*.—A solution of dehydro-base (0·05 g.) in glacial acetic acid (5 c.c.) was shaken with platinum oxide (0·05 g.) in hydrogen at 100 lb./sq. in. for 24 hours; more catalyst (0·025 g.) was then added, and shaking continued for 3 hours. The solution was filtered, and evaporated to dryness after addition of concentrated hydrochloric acid (3 drops). The residue was basified (50% potassium hydroxide solution), and the base extracted with ether, dried (potassium carbonate and potassium hydroxide), and distilled, giving a colourless, mobile, very strongly basic liquid (0·05 g.), b. p. 62°/25 mm. (Found: C, 74·7; H, 11·7. Calc. for $C_8H_{15}N$: C, 76·8; H, 12·0%). The *picrate* separated from alcohol in elongated, bright yellow prisms, m. p. 169—170° (Found: C, 47·6; H, 5·1. $C_8H_{15}N,C_6H_3O_7N_3$ requires C, 47·5; H, 5·1%).

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