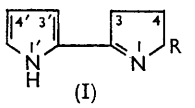
173. 2-*Pyrrolylpyrrolines: Some Further Reactions.*

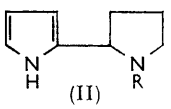
By J. H. Atkinson, R. Grigg, and A. W. Johnson.

Various 2-2′-pyrrolyl-1-pyrrolines have been synthesised and their reactions studied. Attempts to effect additions, other than hydrogenation, to the pyrroline ring have been unsuccessful. The acid-catalysed dimerisation of pyrroles yields 5-2′-pyrrolyl-1-pyrrolines which are readily cyclised to derivatives of indole, isoindole, or indolizine, depending on the alkyl substitution pattern of the original pyrrole.

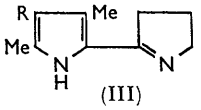
In an earlier paper,[1] we assessed the methods available for the preparation of 2-2′-pyrrolylpyrrolines, which are intermediates of possible value for the synthesis of the corrin macrocycle. More recently, Rapoport and Castagnoli [2] described an improved method, consisting of the reaction of a pyrrole with a 2-pyrrolidone in the presence of phosphorus oxychloride, for the synthesis of 2-2′-pyrrolyl-1-pyrrolines. The parent compound (I; R = H) is obtainable in good yield from the reaction of pyrrole with 2-pyrrolidone [2] and has served as a model for a study of some further reactions of 2-2′-pyrrolylpyrrolines. Thus, reduction with lithium aluminium hydride gave an almost quantitative yield of 2-2′-pyrrolylpyrrolidine (II; R = H) which had been synthesised previously [3] by the addition of pyrrole to 1-pyrroline. Furthermore, the compound prepared by Nenitzescu and Ioan,[4] by hydrogenation of pyrrole in glacial acetic acid, is almost certainly 2-2′-pyrrolylpyrrolidine rather than the tricyclic structure proposed by these authors. 2-2′-Pyrrolylpyrrolidine can be dehydrogenated back to 2-2′-pyrrolyl-1-pyrroline by mercuric acetate in acetic acid, manganese dioxide in chloroform, or diphenylpicrylhydrazyl in chloroform.



(I)



(II)



(III)

Attempts to effect additions to the pyrroline ring of (I) by reactions with methylmagnesium iodide or methyl-lithium (heating an ethereal solution of the reactants under reflux for 6 hours), or hydrogen cyanide (heating with aqueous potassium cyanide and 2N-hydrochloric acid under reflux for 6 hours), gave only starting material and suggest that the azamethine linkage is appreciably sterically hindered. Reaction of (I) with methyl iodide gave the corresponding pyrroline methiodide which did not yield identifiable products with either methylmagnesium iodide or methyl-lithium under the conditions outlined above for the free base. Reduction of the *N*-methylpyrrolinium salt with sodium borohydride in aqueous methanol gave a high yield of 1-methyl-2-2′-pyrrolylpyrrolidine (II; R = Me) and this base was used for attempted condensation with 2-formylpyrroles, *e.g.*, 4-ethyl-2-formyl-3,5-dimethylpyrrole, in an attempt to prepare reduced tripyrrolic systems. However, no reaction (development of colour) between (II; R = Me) and the formylpyrrole was observed with hydrogen bromide in acetic acid as the condensing agent (methanolic solution at room temperature for 3 days), presumably because the formation of the pyrrolidinium salt deactivated the pyrrole ring towards electrophilic attack (cf. ref. 5).

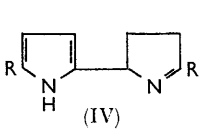
Certain analogues of (I) and (II) have been obtained from alkylpyrroles by similar methods. Thus 2-(4-ethyl-3,5-dimethyl-2-pyrrolyl)-1-pyrroline (III; R = Et) was

[1] Booth, Johnson, and Johnson, *J.*, 1962, 98.
[2] Rapoport and Castagnoli, *J. Amer. Chem. Soc.*, 1962, **84**, 2178.
[3] Fuhlhage and VanderWerf, *J. Amer. Chem. Soc.*, 1958, **80**, 6249.
[4] Nenitzescu and Ioan, *Rev. Chim.* (*Acad. R.P.R.*), 1956, **1**, 55.
[5] Bullock, Grigg, Johnson, and Wasley, *J.*, 1963, 2326.

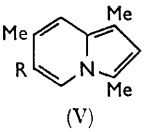
obtained in 74% yield by the phosphorus oxychloride route from cryptopyrrole and 2-pyrrolidone, but only in 3—5% yield from cryptopyrrolylmagnesium iodide and 4-chlorobutyronitrile (cf. ref. 1). Neither methylmagnesium iodide nor methyl-lithium (heating an ethereal solution of the reactants under reflux for 6 hours) could be added to the azamethine grouping of the base (III; R = Et) or the corresponding pyrroline methiodide. Reaction of 2-pyrrolidone with 2,4-dimethylpyrrole in the presence of phosphorus oxychloride gave 2-(3,5-dimethyl-2-pyrrolyl)-1-pyrroline (III; R = H) which was hydrogenated to the corresponding 2-2′-pyrrolylpyrrolidine.

2-2′-Pyrrolyl-1-pyrroline-5-carboxylic acid (I; R = CO_2H) has also been prepared with a view to using the carboxyl group for further condensations with suitable pyrrolic compounds. DL-2-Oxopyrrolidine-5-carboxylic acid [6] was prepared from L-glutamic acid, and the ethyl ester condensed with pyrrole by the usual method to give the pyrrolylpyrroline-5-carboxylic acid. Addition of hydrogen cyanide (potassium cyanide and 2N-hydrochloric acid at room temperature overnight) to the azamethine linkage of the ester (I; R = CO_2Et) could not be effected although hydrogenation gave ethyl 2-2′-pyrrolylpyrrolidine-5-carboxylate. No condensation product could be isolated from an attempted reaction of the pyrrolylpyrrolidine ester and 4-ethyl-2-formyl-3,5-dimethylpyrrole in presence of hydrogen bromide (methanolic solution at room temperature for 3 days). Reduction of ethyl 2-2′-pyrrolyl-1-pyrroline-5-carboxylate with lithium aluminium hydride gave 5-hydroxymethyl-2-2′-pyrrolylpyrrolidine.

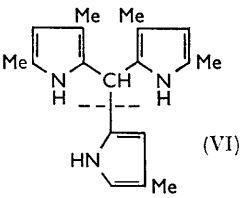
Certain members of the isomeric 5-2′-pyrrolyl-1-pyrroline series can be obtained by the dimerisation of 2-substituted pyrroles. Thus 2-phenylpyrrole [7] and 2-methylpyrrole [1,8] have been converted into the 5-2′-pyrrolyl-1-pyrrolines (IV; R = Ph or Me), the dimethyl-substituted compound being then easily cyclised by acid to the corresponding 2,4-disubstituted indole; the diphenyl compound could not be cyclised.



(IV)



(V)



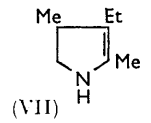
(VI)

2,4-Dimethylpyrrole has been stated to yield a non-crystalline hydrochloride with anhydrous hydrogen chloride,[9] and the base can be converted into 1,3,5,7-tetramethylindolizine (V; R = H) by the action of zinc acetate in acetic acid.[10] It has now been found that the indolizine (V; R = H) can be produced by heating a suspension of dry 2,4-dimethylpyrrole hydrochloride in benzene with 2,4-dimethylpyrrole, although none of the pyrrolylpyrroline precursor could be isolated in this case. However, the major product of the reaction has been identified as 3,3′,5,5′-tetramethyldipyrromethene,[11] which presumably is formed through the tripyrromethane (VI) (cf. ref. 12), with fission as indicated.

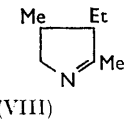
We have not been able to repeat the preparation of the dimer of cryptopyrrole by heating the monomer with picric acid in ethyl acetate.[1,13] Hydrogenation of an acidified solution of cryptopyrrole has been stated [9] to yield 3-ethyl-2,4-dimethyl-2-pyrroline (VII)

[6] Lichtenstein and Grossowicz, *J. Biol. Chem.*, 1947, **171**, 387; see also Hubert, Buyle, and Hargitay, *Helv. Chim. Acta*, 1963, **46**, 1429.
[7] Allen, Gilbert, and Young, *J. Org. Chem.*, 1938, **2**, 227, 235.
[8] Dennstedt, *et al.*, *Ber.*, 1888, **21**, 1478, 3429.
[9] Bullock, *Canad. J. Chem.*, 1958, **36**, 1686.
[10] Saxton, *J.*, 1951, 3239.
[11] Fischer and Zerweck, *Ber.*, 1923, **56**, 519.
[12] Corwin and Andrews, *J. Amer. Chem. Soc.*, 1937, **59**, 1973.
[13] Fischer, *Ber.*, 1915, **48**, 401.

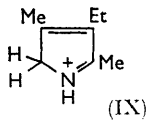
but a repetition of this experiment has shown that the product is the isomeric 1-pyrroline (VIII) formed by hydrogenation of the protonated species (IX).[14] However, the action of hydrogen chloride on 2,3,4-trimethylpyrrole has now been shown to yield 2,3,4-trimethyl-5-(3,4,5-trimethyl-2-pyrrolyl)-1-pyrroline (cf. IV), 1,2,3,5,6,7-hexamethylindolizine (cf. V), and 3,3′,4,4′,5,5′-hexamethyldipyrromethene. The hexamethyl-pyrrolylpyrroline was hydrogenated to the corresponding hexamethyl-pyrrolylpyrrolidine (X). Only 2,6-diethyl-1,3,5,7-tetramethylindolizine was isolated from the action of hydrogen chloride on cryptopyrrole, and 1,3,5,6,7-pentamethylindolizine (V; R = Me) and 3,3′,4,4′,5,5′-hexamethyldipyrromethene were isolated from a similar reaction on a mixture of 2,4-dimethylpyrrole and 2,3,4-trimethylpyrrole hydrochloride. In this case the hexamethyldipyrromethene was obtained by self-condensation of the 2,3,4-trimethylpyrrole as before. The indolizine (V; R = Me) was formulated as shown, partly because of the method of formation (*i.e.*, use of 2,3,4-trimethylpyrrole hydrochloride as the electrophilic component), and partly because of the lack of evidence for *meta*-coupling in the nuclear magnetic resonance spectrum, as might have been expected from the isomeric 1,2,3,5,7-pentamethylindolizine.



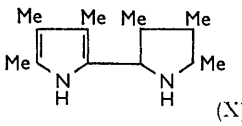
(VII)



(VIII)



(IX)



(X)

Attempts to use 2,3,4,5-tetramethylpyrrole[15] for the formation of derivatives of 2-2′-pyrrolyl-1-pyrroline containing an angular methyl group on the 2,2′-linkage as in the corrin ring system have so far been unsuccessful. Reaction of 2,3,4,5-tetramethylpyrrole hydrochloride with 2,4-dimethylpyrrole gave only 1,3,5,7-tetramethylindolizine (from the self-condensation of 2,4-dimethylpyrrole), and reaction of 2,3,4,5-tetramethylpyrrole with 2,3,4-trimethylpyrrole hydrochloride gave only 3,3′,4,4′,5,5′-hexamethyldipyrromethene hydrochloride (from the self-condensation of 2,3,4-trimethylpyrrole). There are therefore three modes of cyclisation of 5-2′-pyrrolyl-1-pyrrolines. Those derived from 2-monoalkyl- or 2,3-dialkyl-pyrroles yield indoles whilst those derived from 2,4-dialkyl- or 2,3,4-trialkyl-pyrroles yield indolizines. A third pathway is represented by the formation of 1,3,4,7-tetramethylisoindoline by the reductive self-condensation of 2,5-dimethylpyrrole.[16]

Experimental

Ultraviolet and visible absorption spectra were determined for ethanol solutions except where otherwise stated. Nuclear magnetic resonance (n.m.r.) spectra were determined on an A.E.I. RS2 instrument operating at 60 Mc./sec.

2-2′-*Pyrrolyl*-1-*pyrroline*.—(*a*) Prepared by the method of Rapoport and Castagnoli,[2] this had m. p. 162—164° (lit.,[2] 162—163°). The n.m.r. spectrum showed bands at (τ values): 7·04 (3-H; triplet, J = 8·4 c./sec.); 7·98 (4-H; multiplet); 5·93 (5-H; triplet, J = 7·3 c./sec.); −1·0 (1′-H; singlet); 3·43 (3′-H; multiplet); 3·73 (4′-H; multiplet); 3·03 (5′-H; multiplet).

(*b*) 2-2′-Pyrrolylpyrrolidine (1 g.; see below) was dissolved in acetic acid (100 c.c.; 10%) together with mercuric acetate (9·4 g., 4 mol.) and the solution heated under reflux for 12 hr. The precipitated mercurous acetate was separated and the remainder of the mercury in the filtrate precipitated as the sulphide. After filtration, the filtrate was basified with potassium carbonate and the base extracted with ether (3 × 50 c.c.). Removal of the solvent from the combined dried extract gave a pale yellow solid from which a colourless crystalline solid (88 mg., 9%), m. p. 162—164°, was obtained after repeated sublimation at 110°/0·2 mm. (Found: C, 71·8; H, 7·25; N, 21·2. Calc. for $C_8H_{10}N_2$: C, 71·6; H, 7·5; N, 20·9%); $\lambda_{max.}$

[14] Abraham, Bullock, and Mitra, *Canad. J. Chem.*, 1959, **37**, 1859.
[15] Johnson and Price, *Org. Synth.*, 1962, **42**, 92.
[16] Bonnett and White, *J.*, 1963, 1648.

280 mμ (ε 15,800), inflection at 241 mμ (ε 4070); $\lambda_{max.}$ (in ethanolic hydrogen chloride) 318 mμ (ε 27,500), inflection at 268 mμ (ε 3020). The infrared spectrum (KBr disc) contained a prominent band at 1623 cm.$^{-1}$ (C=N). The *picrate* formed needles (from chloroform), m. p. 233—235° (Found: C, 46·1; H, 3·8; N, 19·0. $C_{14}H_{13}N_5O_7$ requires C, 46·3; H, 3·6; N, 19·3%).

(*c*) Manganese dioxide (1 g.) was added to a solution of 2-2′-pyrrolylpyrrolidine (250 mg.) in chloroform (25 c.c.) and the suspension heated under reflux for 12 hr. The manganese dioxide was separated and washed well with chloroform. The solvent was removed from the combined filtrate and washings, leaving a colourless solid (23·5 mg.) which, after vacuum sublimation, was identical with the product from (*b*).

(*d*) 2-2′-Pyrrolylpyrrolidine (2 g.) was dissolved in chloroform (5 c.c.), and diphenylpicrylhydrazyl (0·5 g.) was added slowly during 15 min. The solution was heated under reflux for 6 hr. in an atmosphere of nitrogen, cooled, and diluted with light petroleum (b. p. 40—60°; 50 c.c.). The precipitated phenylhydrazine was separated, the solvent removed, and the residue dissolved in light petroleum (b. p. 40—60°) and chromatographed on a short column of alumina (Spence type H). Elution with light petroleum–chloroform (5 : 1) gave two fractions: (i) diphenylamine, m. p. 52—54°, and (ii) a compound, m. p. 162—163° after vacuum sublimation, identical with the product from (*b*) and (*c*).

2-2′-*Pyrrolylpyrrolidine*.—(*a*) Prepared according to Fuhlhage and VanderWerf,[3] this had m. p. 85·5—86·5° (lit.,[3] 86·3—87·8°). The picrate formed orange-yellow cubes (from methanol), m. p. 163—165°.

(*b*) 2-2′-Pyrrolyl-1-pyrroline (1 g.) was extracted (Soxhlet) into a solution of lithium aluminium hydride (1 g.) in dry ether (50 c.c.) and the mixture heated under reflux for 3 hr. The complex was decomposed with saturated aqueous sodium potassium tartrate solution and the ethereal layer separated. The aqueous layer was further extracted with ether (2 × 50 c.c.), and removal of solvent from the combined extract and washings gave a pale brown solid (0·98 g.) from which a colourless crystalline solid (0·9 g.; 89%) was obtained by sublimation at 80°/0·2 mm. This was identical with the product from (*a*). The thiocarbanilide formed hexagonal plates, m. p. 127—128·5° (from ether) (Found: C, 66·7; H, 6·35; N, 15·7. $C_{15}H_{17}N_3S$ requires C, 66·4; H, 6·3; N, 15·5%), $\lambda_{max.}$ 204 and 249 mμ (ε 23,750 and 16,250).

1-*Methyl*-2′-*pyrrolylpyrrolidine*.—The *methiodide* of 2-2′-pyrrolylpyrroline formed needles, m. p. 189—190° (from dry methanol–ether) (Found: C, 39·3; H, 4·85; N, 9·7. $C_9H_{13}IN_2$ requires C, 39·2; H, 4·7; N, 10·1%), $\lambda_{max.}$ 267·5 and 316 mμ (ε 2750 and 3160). The methiodide (8 g.) was dissolved in a mixture of methanol (120 c.c.) and water (60 c.c.) and to the solution potassium borohydride (7 g.) was added during 1 hr. at room temperature. After 2 days, the methanol was removed under reduced pressure, more water was added, and the solution saturated with sodium chloride. Extraction with ether (3 × 50 c.c.) followed by removal of the solvent gave a residue which, on distillation, gave a main fraction, b. p. 102—104°/16 mm., n_D^{20} 1·5362 (3·31 g., 75%). This solidified to give needles, m. p. 36—38° (Found: N, 18·7. $C_9H_{14}N_2$ requires N, 18·65%), $\lambda_{max.}$ 215 mμ (ε 10,000). The *picrate* formed needles (from ethanol), m. p. 154—156° (Found: C, 47·1; H, 4·35; N, 18·6. $C_{15}H_{17}N_5O_7$ requires C, 47·5; H, 4·5; N, 18·45%).

2-(4-*Ethyl*-3,5-*dimethyl*-2-*pyrrolyl*)-1-*pyrroline*.—(*a*) A solution of cryptopyrrole (15 g.) in dry ether (50 c.c.) was added during 10 min. to a solution of methylmagnesium iodide (from 17·2 g. of methyl iodide) in ether (150 c.c.). A solution of 4-chlorobutyronitrile (12·6 g.) in ether (20 c.c.) was then added and the mixture heated under reflux overnight. The mixture was treated with water, basified, and the ethereal layer separated. The aqueous layer was extracted with ether and the combined ethereal solutions extracted with saturated aqueous potassium dihydrogen phosphate (3 × 100 c.c.) and then re-extracted with ether (3 × 100 c.c.) after the addition of a slight excess of 40% aqueous potassium hydroxide. Evaporation of the solvent from the dried ethereal extract gave a dark brown syrup (6·5 g.) from which a colourless crystalline solid (0·52 g.), m. p. 119—121° was obtained by sublimation at 100°/0·25 mm. [Found: C, 75·7; H, 9·4%; *M* (Rast), 217. $C_{12}H_{18}N_2$ requires C, 75·75; H, 9·55%; *M*, 190]; $\lambda_{max.}$ 304 mμ (ε 17,000), inflection at 260·5 mμ (ε 4570); $\lambda_{max.}$ (in ethanolic hydrogen chloride) 344 mμ (ε 27,500), inflection at 291·5 mμ (ε 5900). The *picrate* formed needles, m. p. 183—185° (from methanol) (Found: C,51·5; H, 5·0; N, 16·9. $C_{18}H_{21}N_5O_7$ requires C, 51·55; H, 5·05; N, 16·7%).

(*b*) 2-Pyrrolidone (3·1 g.) in dry ether (10 c.c.) was added, with stirring, to a mixture of cryptopyrrole (5·4 g.) and redistilled phosphorus oxychloride (4·65 g.) in dry ether (20 c.c.)

at 0°. After stirring for 30 min. at room temperature, the ether was decanted and the residual imine hydrochloride dissolved in water (100 c.c.). A slight excess of aqueous sodium hydroxide solution was added and the precipitated base separated, washed with water, and dried. After sublimation at 110°/0·3 mm. it gave a product (6·2 g., 74%) identical with that from (*a*). The *methiodide* formed thick needles, m. p. 141° (from ether–ethanol) (Found: C, 47·3; H, 6·7; N, 8·5. $C_{13}H_{21}IN_2$ requires C, 47·0; H, 6·35; N, 8·45%), $\lambda_{max.}$ 295 and 344 mμ (ε 5900 and 27,000).

2-(3,5-*Dimethyl*-2-*pyrrolyl*)-1-*pyrroline*.—Prepared from 2-pyrrolidone (15·1 g.), 2,4-dimethylpyrrole (17·0 g.), and phosphorus oxychloride (27·1 g.) by the method described in the previous experiment, and after sublimation at 120°/0·5 mm., the base (19·1 g., 66%) was obtained as pale yellow needles, but further crystallisation from ethanol gave colourless cubes, m. p. 128—130° (Found: C, 73·5; H, 8·35; N, 17·3. $C_{10}H_{14}N_2$ requires C, 74·0; H, 8·7; N, 17·25%); $\lambda_{max.}$ 293 mμ (ε 17,800), inflection at 250 mμ (ε 3400); $\lambda_{max.}$ (in ethanolic hydrogen chloride) 329 mμ (ε 20,000), inflection at 280 mμ (ε 4900). The *picrate* formed needles, m. p. 204—205° (from chloroform–methanol) (Found: C, 48·7; H, 4·4; N, 18·0. $C_{16}H_{17}N_5O_7$ requires C, 49·1; H, 4·4; N, 17·9%).

2-(3,5-*Dimethyl*-2-*pyrrolyl*)*pyrrolidine*.—2-(3,5-Dimethyl-2-pyrrolyl)-1-pyrroline (3·0 g.) was dissolved in methanol (50 c.c.) and hydrogenated at atmospheric pressure and room temperature using Adams catalyst. After the absorption of 1 mole of hydrogen, the catalyst and solvent were removed, to give a pale yellow oil (2·9 g., 95%) which slowly crystallised at 0°. The *thiocarbanilide*, prepared from the base and phenyl isothiocyanate in light petroleum (b. p. 60—80°), formed colourless needles, m. p. 168—171° (from ether) (Found: C, 68·0; H, 7·15; N, 14·2. $C_{17}H_{21}N_3S$ requires C, 68·2; H, 7·05; N, 14·05%), $\lambda_{max.}$ 207, 248, and 265 mμ (ε 25,100, 17,850, and 13,680).

Ethyl 2-*Oxopyrrolidine*-5-*carboxylate*.—DL-2-Oxopyrrolidine-5-carboxylic acid,[6] m. p. 184—186° (lit.,[17] 188°), was prepared by cyclisation of L-glutamic acid. The acid (50 g.) was suspended in dry ethanol (500 c.c.) containing dry hydrogen chloride (30 g.) and dissolved by shaking. After keeping for 1 hr. the ethanol was removed under reduced pressure, ether was added to the cooled residue, and the mixture set aside overnight. The precipitated ester hydrochloride was separated, dried, and dissolved in dry methanol (200 c.c.). The solution was neutralised with ammonia, the ammonium chloride separated, and the methanol removed under reduced pressure. The product formed needles (46·0 g., 76%), m. p. 54—56° (from dry ether) (lit.,[18] 60—61·5°).

Ethyl 2-2′-*Pyrrolyl*-1-*pyrroline*-5-*carboxylate*.—Ethyl 2-oxopyrrolidine-5-carboxylate (11·75 g.) was added during 1 hr. to a vigorously stirred solution of freshly distilled pyrrole (5·0 g.) and freshly distilled phosphorus oxychloride (21·4 g.) in dry ether (100 c.c.) at 0°. After stirring for a further 2 hr. at room temperature the ether was decanted and the residue dissolved in water (100 c.c.). After the addition of a slight excess of aqueous sodium hydroxide the precipitated base was separated, washed with water, and dried. Sublimation at 80°/0·05 mm. gave rhombs (6·75 g., 46·5%), m. p. 91—92° (Found: C, 64·2; H, 6·75; N, 13·8. $C_{11}H_{14}N_2O_2$ requires C, 64·05; H, 6·85; N, 13·6%); $\lambda_{max.}$ 284·5 mμ (ε 19,000), inflection at 245 mμ (ε 4170); $\lambda_{max.}$ (in ethanolic hydrogen chloride) 324 mμ (ε 29,500), inflection at 272 mμ (ε 3800). The *picrate* formed plates (from chloroform–methanol), m. p. 168—170° (Found: C, 46·8; H, 3·9; N, 15·9. $C_{17}H_{17}N_5O_9$ requires C, 46·9; H, 3·9; N, 16·1%).

Ethyl 2-2′-*Pyrrolylpyrrolidine*-5-*carboxylate*.—The foregoing pyrrolylpyrroline ester (2 g.) in methanol (50 c.c.) was hydrogenated at room temperature and atmospheric pressure in presence of Adams catalyst, until no more hydrogen was absorbed. After removal of the catalyst and solvent the residue was distilled, to give a rather unstable oil (1·44 g., 71·5%), b. p. 128—132°/0·5 mm. (Found: N, 13·8. $C_{11}H_{16}N_2O_2$ requires N, 13·45%), $\lambda_{max.}$ 215·5 mμ (ε 8700). The *thiocarbanilide* formed plates (from ether), m. p. 148—150° (Found: C, 62·6; H, 6·15; N, 12·1. $C_{18}H_{21}N_3O_2S$ requires C, 62·95; H, 6·15; N, 12·25%), $\lambda_{max.}$ 206, 220, and 251·5 mμ (ε 21,900, 18,600, and 13,800).

5-*Hydroxymethyl*-2-2′-*pyrrolylpyrrolidine*.—Ethyl 2-2′-pyrrolyl-1-pyrroline-5-carboxylate (4·0 g.) was extracted continuously from a thimble with dry ether (150 c.c.) in presence of lithium aluminium hydride (5·0 g.). After heating the mixture under reflux for 4 hr. it was

[17] Gray, *J.*, 1928, 1264.
[18] Abderhalden and Kautzsch, *Z. physiol. Chem.*, 1912, **78**, 115.

cooled and the complex decomposed with saturated aqueous sodium potassium tartrate solution. The ether layer was separated and the aqueous solution washed with ether (2 × 50 c.c.). The combined ethereal extract and washings were dried and evaporated to give a pale yellow oil (2·11 g., 67%) which eventually solidified. After crystallisation from ether it formed colourless needles, m. p. 96—98° (Found: C, 64·8; H, 8·1; N, 16·9. $C_9H_{14}N_2O_2$ requires C, 65·05; H, 8·5; N, 16·85%), $\lambda_{max.}$ 216 mμ (ε 9940).

Dimerisation of 2,3,4-*Trimethylpyrrole*.—2,3,4-Trimethylpyrrole (10 g., 1 mol.) was added to a suspension of 2,3,4-trimethylpyrrole hydrochloride [1] (13·3 g., 1 mol.) in sodium-dried benzene (240 c.c.). Dry oxygen-free nitrogen was bubbled through the solution for 10 min. and the mixture was then heated under reflux for 2 hr. in an atmosphere of nitrogen. The flask was cooled, stoppered, and kept at room temperature for 14 hr. The precipitated hydrochloride was separated, and washed with dry benzene (2 × 10 c.c.) and ether (10 c.c.); it was obtained as a pink solid (11·6 g.). It was dissolved in water (200 c.c.), and the insoluble methene hydrochloride (460 mg.) was separated, to give 3,3′,4,4′,5,5′-hexamethyldipyrromethene hydrochloride as red prisms with a blue reflex, m. p. 286—287° (decomp.) (from chloroform–methanol) (lit.,[19] 287—288°) (Found: C, 67·7; H, 7·7; N, 11·0; Cl, 13·7. Calc. for $C_{15}H_{21}ClN_2$: C, 68·05; H, 8·0; N, 10·6; Cl, 13·4%), $\lambda_{max.}$ ($CHCl_3$) 289, 365, and 489 mμ (ε 1170, 5900, and 105,400).

The aqueous filtrate was treated with sodium acetate and the free bases extracted into ether. The ethereal extract was dried and the solvent removed under reduced pressure to yield a brown solid (8 g.). This was triturated with light petroleum (b. p. 60—80°; 15 c.c.), filtered off, and washed with light petroleum (3 × 5 c.c.), to give a pink crystalline solid, m. p. 126—130°. Crystallisation from light petroleum (b. p. 60—80°), followed by sublimation at 110°/0·1 mm., gave 2,3,4-*trimethyl*-5-(3,4,5-*trimethyl*-2-*pyrrolyl*)-1-*pyrroline* as colourless plates, m. p. 135—138° [Found: C, 76·8; H, 10·4; N, 13·1%; *M* (Rast), 209. $C_{14}H_{22}N_2$ requires C, 77·0; H, 10·2; N, 12·8%; *M*, 218]; $\lambda_{max.}$ 221 mμ (ε 9000) $\lambda_{max.}$ (in ethanolic hydrochloric acid) 218 and 317 mμ (ε 9130 and 655); $\nu_{max.}$ 1641 (C=N) and 3470 cm.$^{-1}$ (NH). The *picrate* formed red prisms, m. p. 173° (decomp.) (from ethanol) (Found: C, 53·9; H, 5·35; N, 15·3. $C_{20}H_{25}N_5O_7$ requires C, 53·7; H, 5·6; N, 15·65%).

The red benzene mother-liquors from the original condensation were washed with 10% sodium hydroxide solution and then with water. The benzene layer was dried and the solvent removed to leave a brown oil (11 g.) which was dissolved in light petroleum (b. p. 60—80°; 30 c.c.) and chromatographed on alumina (Spence type H) using light petroleum for elution. The pale yellow band which was eluted first yielded a gummy solid (1·4 g.). Crystallisation from methanol and sublimation at 100°/0·1 mm. gave 1,2,3,5,6,7-hexamethylindolizine as yellow plates, m. p. 125—127° [Found: C, 83·2; H, 9·55; N, 7·4%; *M* (Rast), 201. $C_{14}H_{19}N$ requires C, 83·55; H, 9·5; N, 7·0%; *M*, 201], $\lambda_{max.}$ 246, 294, 301, 309, and 357 mμ (ε 20,900, 2900, 7000, 7250, and 3700), $\lambda_{max.}$ (in ethanol–0·01N-hydrochloric acid) 228, 252, and 331 mμ (ε 19,250, 5600, and 4550).

2,3,4-*Trimethyl*-5-(3,4,5-*trimethyl*-2-*pyrrolyl*)*pyrrolidine*.—2,3,4-Trimethyl-5-(3,4,5-trimethyl-2-pyrrolyl)-1-pyrroline (2·0 g.) in methanol (30 c.c.) was hydrogenated in the presence of Adams catalyst (20 mg.). The reaction was complete in 3 hr. (absorption of 1 mole of hydrogen). The product (2·1 g.) was a colourless oil which solidified at 0°, $\lambda_{max.}$ 225 mμ (ε 6100), $\lambda_{max.}$ (in ethanol–0·01N-hydrochloric acid) 221 and 236 mμ (ε 6000 and 6410), $\nu_{max.}$ 1611 (C=C), 3352 (bonded NH), and 3467 cm.$^{-1}$ (NH). The *thiocarbanilide* formed needles, m. p. 195° (from ether) (Found: C, 71·1; H, 8·25; N, 11·7. $C_{21}H_{29}N_3S$ requires C, 70·95; H, 8·2; N, 11·8%).

Dimerisation of 2,4-*Dimethylpyrrole*.—The reaction was carried out as in the previous experiment but using 2,4-dimethylpyrrole (13·5 g.), the corresponding hydrochloride [9] (18·6 g.; this salt can be obtained as a solid, rather than a semi-solid as described in ref. 8, by avoiding a large excess of hydrogen chloride), and dry benzene (270 c.c.). The mixture was heated under reflux for 4 hr. and the insoluble fraction (4·85 g.) shown to consist of methene contaminated with a little gum. Crystallisation from chloroform–methanol gave 3,3′,5,5′-tetramethyldipyrromethene hydrochloride [11] as red needles with a blue reflex (Found: C, 65·9; H, 7·05; N, 12·0; Cl, 15·0. Calc. for $C_{13}H_{17}ClN_2$: C, 65·95; H, 7·25; N, 11·85; Cl, 15·0%), $\lambda_{max.}$ 286, 303, 346, and 469 mμ (ε 1420, 1780, 4360, and 101,800).

The benzene filtrate was worked up as described in the previous experiment to yield, after

[19] Fischer and Walach, *Annalen*, 1926, **450**, 109.

chromatography, a gummy solid (4·8 g.) which was triturated with methanol (7 c.c.) and cooled to 0°. The resulting yellow solid (1·65 g.), m. p. 69—72°, was crystallised from methanol to give 1,3,5,7-tetramethylindolizine as yellow needles, m. p. 74—76° (lit.,[10] 74—75°) [Found: C, 83·4; H, 8·7; N, 8·25; *M* (Rast), 172. Calc. for $C_{12}H_{15}N$: C, 83·2; H, 8·75; N, 8·1; *M*, 173], $\lambda_{max.}$ 242, 285, 294, 307, and 370 mμ (ε 28,600, 3800, 5500, 6000, and 2300), $\lambda_{max.}$ (in ethanol–0·01N-hydrochloric acid) 217, 240, and 310 mμ (ε 24,100, 6000, and 6500).

Acid Reduction of Cryptopyrrole.—This was carried out as described by Bullock,[9] to yield the pyrroline (VIII), b. p. 154—159° (lit.,[9] 152—155°); picrate, yellow needles (from ethanol), m. p. 162·5—164° (lit.,[9] 157—159°) (Found: C, 47·5; H, 5·2; N, 15·9. Calc. for $C_{14}H_{18}N_4O_7$: C, 47·45; H, 5·1; N, 15·8%). The free base showed strong infrared absorption at 1648 cm.$^{-1}$ (C=N), and no absorption corresponding to an NH grouping.

Dimerisation of Cryptopyrrole.—Cryptopyrrole (10 g.) was added to cryptopyrrole hydrochloride [9] (13 g.) in dry benzene (240 c.c.) for 2 hr. as for the other dimerisations. The insoluble pink hydrochloride (2·0 g.) was dissolved in aqueous sodium acetate solution but neither the corresponding base nor its picrate could be obtained pure. The benzene filtrate was treated as described previously. Removal of the solvent gave a dark brown oil which was fractionally distilled and the fraction (4·3 g.) of b. p. 80—90°/7 mm. shown to be unchanged cryptopyrrole (picrate, m. p. 138°; lit.,[20] 138°). The residue was chromatographed as described previously and 2,6-*diethyl*-1,3,5,7-*tetramethylindolizine* (2·1 g.) was obtained from the first fraction. After crystallisation from methanol and sublimation at 82°/0·1 mm. it formed yellow plates, m. p. 85—87° [Found: C, 84·1; H, 10·05; N, 6·65; *M* (Rast), 210. $C_{16}H_{23}N$ requires C, 83·8; H, 10·1; N, 6·1; *M*, 229], $\lambda_{max.}$ 248, 286, 297, 310, and 353 mμ (ε 26,000, 3900, 4300, 4200, and 2300), $\lambda_{max.}$ (in ethanol–0·01N-hydrochloric acid) 229, 256, and 333 mμ (ε 19,200, 5900, and 5000).

Condensation of 2,4-*Dimethylpyrrole and* 2,3,4-*Trimethylpyrrole Hydrochloride.*—2,4-Dimethylpyrrole (10 g.) and 2,3,4-trimethylpyrrole hydrochloride (15·4 g.) in dry benzene (240 c.c.) were heated under reflux for 2 hr. in an atmosphere of nitrogen, as in the previous experiments. The insoluble fraction (4·8 g.) was separated, washed with water (50 c.c.), and then crystallised from chloroform–methanol, to yield 3,3′,4,4′,5,5′-hexamethyldipyrromethene (as from the dimerisation of 2,3,4-trimethylpyrrole, and with identical light absorption).

The benzene layer was treated as described previously and gave a brown oil (18·0 g.) which on distillation gave impure 2,3,4-trimethylpyrrole (4·0 g.), b. p. 68—100°/10 mm. (picrate, m. p. 138°; lit.,[20] 139—141°). The distillation residue was chromatographed on alumina and yielded a brown oil which solidified on keeping. Crystallisation from methanol afforded, 1,3,5,6,7-pentamethylindolizine as yellow plates, m. p. 92—93° [Found: C, 83·2; H, 8·9; N, 7·55; *M* (thermistor drop), 186·7. $C_{13}H_{17}N$ requires C, 83·4; H, 9·15; N, 7·5; *M*, 187·3] $\lambda_{max.}$ 251, 285, 298, 310, and 345 mμ (ε 22,900, 2600, 3450, 3900, and 1700), (in ethanol–0·01N-hydrochloric acid) 221, 249, and 322 mμ (ε 21,700, 7150, and 6000), n.m.r. spectrum (CCl_4 solution using tetramethylsilane as internal reference) showed peaks at τ 7·91 (3 protons), 7·8 (6), 7·35 (6), 4·21 (1), and 3·24 (1).

We are grateful to Dr. H. Booth for helpful discussions, to the D.S.I.R. for a maintenance grant to one of us (J. H. A.), and to the Glaxo Triangle Trust for financial support (to R. G.).

THE UNIVERSITY, NOTTINGHAM. [*Received, August 14th,* 1963.]

[20] Johnson, Markham, Price, and Shaw, *J.*, 1958, 4254.