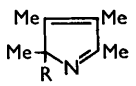
305. *The Alkylation of Tri- and Tetra-alkylpyrroles.*

By H. Booth, A. W. Johnson, E. Markham, and R. Price.

The action of alkyl iodides on the Grignard derivatives of 2 : 3 : 4- and 2 : 3 : 5-trialkylpyrroles and 2 : 3 : 4 : 5-tetra-alkylpyrroles is shown to give tetra- and penta-alkyl-2*H*-pyrroles (pyrrolenines) containing 2 : 2-*gem*-dialkyl groups. The reaction is inhibited by the presence of ester substituents on the pyrrole ring.

Although the structure of the alkylation products of pyrroles caused a lengthy polemic some forty years ago, the subject has scarcely received comment since. In spite of all the early work it is impossible, because of the conflicting claims, to predict the position of alkylation in pyrrole rings containing varying numbers of alkyl groups. Ciamician and Anderlini [1] suggested 1 : 2-dihydropyridine structures for the base $C_9H_{15}N$ obtained by treating sodium pyrrole-2-carboxylate with methyl iodide in methanol and for the base $C_{10}H_{17}N$ from 1-methylpyrrole and methyl iodide in methanol in presence of potassium carbonate. Influenced by Plancher's work on the alkylation of indoles, Ciamician [2] later suggested that the pyrrole alkylation products were more likely to be derivatives of 2*H*-pyrrole (pyrrolenine) and this was eventually substantiated by Plancher himself,[3]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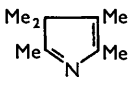
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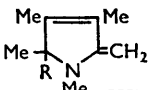
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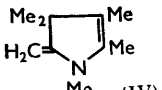

(IV)

although the dihydropyridine structures were still favoured by some authors [4] as late as 1914. The base $C_9H_{15}N$ thus was recognised as a pentamethyl-2*H*-pyrrole or -3*H*-pyrrole although the precise location of the substituents was not established by Ciamician or Plancher, and Beilstein [5] gives the alternative structures, (I; R = Me) and (II), for the methylation product. However, in a related series, an unequivocal proof of structure was apparently obtained by Hess, Wissing, and Suchier [6] who claimed that methylation of 3-ethyl-2 : 5-dimethylpyrrole gave the same product as was formed by ethylation of 2 : 3 : 5-trimethylpyrrole, thus suggesting that in a 2 : 3 : 5-trialkylpyrrole, further alkylation occurs at the 3-(*i.e.* β-)position. It will be shown subsequently that the German experimental work was at fault and the conclusion incorrect.

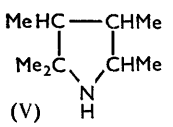
We have prepared the base $C_9H_{15}N$ from methyl iodide and the Grignard derivatives

[1] Ciamician and Anderlini, *Gazzetta*, 1888, **18**, 557; 1889, **19**, 102; *Ber.*, 1888, **21**, 2855; 1889, **22**, 656; Anderlini, *Gazzetta*, 1890, **20**, 61; *Ber.*, 1889, **22**, 2506.
[2] Ciamician, *ibid.*, 1904, **37**, 4200.
[3] Plancher *et al.*, *Atti R. Accad. Lincei*, 1913, **22**, ii, 599, 703, 708; 1914, **23**, ii, 412.
[4] Oddo and Mameli, *Gazzetta*, 1913, **43**, 504; Hess and Wissing, *Ber.*, 1914, **47**, 1416.
[5] *Beilstein's Handbuch*, 1935, **20**, 180.
[6] Hess, Wissing, and Suchier, *Ber.*, 1915, **48**, 1865.

of either 2 : 5-dimethylpyrrole or 2 : 3 : 4 : 5-tetramethylpyrrole [7] and its structure is shown to be 2 : 2 : 3 : 4 : 5-pentamethyl-2*H*-pyrrole (I; R = Me). Thus, ozonolysis of the base gave diacetyl in 23% yield but no 3 : 3-dimethylpentane-2 : 4-dione which would have been formed from structure (II). The nitrogen was obtained from the ozonolysis product as ammonia. Further evidence for structure (I; R = Me) was obtained by treating the corresponding methiodide with alkali; the anhydro-base, identical with Ciamician's base $C_{10}H_{17}N$ referred to above, was then obtained. The ultraviolet spectrum of this compound (max. at 212 and 287 mμ) indicated the presence of a conjugated system as in (III; R = Me) whereas the corresponding structure (IV) derived from (II) would not contain this feature.

Reduction of the 2*H*-pyrrole (I; R = Me) with sodium and alcohol gave 2 : 2 : 3 : 4 : 5-pentamethylpyrrolidine (V), characterised as the picrolonate, m. p. 227—230°, and attempts were made to synthesise this and the isomeric-2 : 3 : 3 : 4 : 5-pentamethylpyrrolidine for comparison. Addition of 2-nitropropane to 3-methylpent-3-en-2-one in the presence of diethylamine [8] gave the γ-nitro-ketone (VI), probably as a mixture of two racemates, which was reductively cyclised in the presence of Raney nickel. Two picrolonates, m. p. 196—198° and 242—244° respectively, neither of which corresponded to that obtained from reduction of the 2*H*-pyrrole, were isolated from the hydrogenation product. γ-Nitro-ketones are said [8] to yield predominantly one form of the pyrrolidine when the hydrogenation is carried out in presence of ammonia, and in the case of the ketone (VI) the pyrrolidine formed in this manner yielded the picrolonate, m. p. 196—198°, identical with that already obtained. As the pyrrolidine (V) can exist in four racemic forms and as attempts to obtain 2 : 3 : 3 : 4 : 5-pentamethylpyrrolidine by addition of nitroethane to 3 : 4-dimethylpent-3-en-2-one and subsequent reduction were uniformly unsuccessful, this approach was abandoned.

The formulation (I; R = Me) of the methylation product of 2 : 3 : 4 : 5-tetramethylpyrrole was confirmed by the discovery that the picrate of 2-ethyl-2 : 3 : 4 : 5-tetramethyl-2*H*-pyrrole (I; R = Et) formed by ethylation of 2 : 3 : 4 : 5-tetramethylpyrrole was identical with that derived from a base obtained by the methylation of 2-ethyl-3 : 4 : 5-trimethylpyrrole.[7] A second base, presumably 5-ethyl-2 : 2 : 3 : 4-tetramethyl-2*H*-pyrrole, was also formed in this alkylation but it was not isolated pure. Each of the alkylation products (I; R = Et) was converted through the methiodide into the anhydro-base (III; R = Et) and once again identical picrates were isolated. The ultraviolet spectra of (III; R = Et) and (III; R = Me) were also identical.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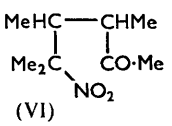
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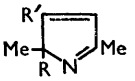
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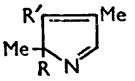
(VIII)

Once the structure of the 2*H*-pyrrole (I; R = Me) had been established it became of interest to consider the claim [6] that further alkylation of 2 : 3 : 5-trialkylpyrroles occurred at the 3-position, and we have therefore repeated the German work. Two products are obtained in each of these alkylations, a 2 : 2 : 3 : 5-tetra-alkyl-2*H*-pyrrole (VII) and a 2 : 2 : 3 : 4 : 5-penta-alkyl-2*H*-pyrrole (I). Thus the methylation of 3-ethyl-2 : 5-dimethylpyrrole [7] gives a mixture of 3-ethyl-2 : 2 : 5-trimethyl-2*H*-pyrrole (VII; R = Me, R′ = Et) and 3-ethyl-2 : 2 : 4 : 5-tetramethyl-2*H*-pyrrole whereas the ethylation of 2 : 3 : 5-trimethylpyrrole [7] gives a mixture of 2-ethyl-2 : 3 : 5-trimethyl-2*H*-pyrrole (VII; R = Et, R′ = Me) and 2 : 4-diethyl-2 : 3 : 5-trimethyl- or 2 : 3-diethyl-2 : 4 : 5-trimethyl-2*H*-pyrrole. It was the two bases (VII; R = Me, R′ = Et and R = Et, R′ = Me) which the German authors claimed to be identical on the basis of the apparent identity (mixed m. p.) of the

[7] Johnson, Markham, Price, and Shaw, *J.*, 1958, 4254.
[8] Kloetzel, *J. Amer. Chem. Soc.*, 1947, **69**, 2271.

respective picrates. It is true that these derivatives melt with decomposition at approximately the same temperature and that there is little depression of this decomposition point when they are mixed, but the crystalline form and the solubilities of the picrates differ markedly and the melting points of the picrolonates differ by about 40°. In addition the picrate of one of the corresponding anhydro-bases (from VII; R = Et, R′ = Me) is crystalline but the other was obtained only as an oil. The structure (VII; R = Et, R′ = Me) was confirmed by its identity (picrate, picrolonate, and picrate of the corresponding anhydro-base) with the tetra-alkyl-2*H*-pyrrole obtained by methylation of 5-ethyl-2 : 4-dimethylpyrrole.[7] The penta-alkyl-2*H*-pyrrole also formed in the last reaction was 2-ethyl-2 : 3 : 4 : 5-tetramethyl-2*H*-pyrrole (I; R = Et) identical with the product of ethylation of 2 : 3 : 4 : 5-tetramethylpyrrole or of methylation of 2-ethyl-3 : 4 : 5-trimethylpyrrole described above.

Thus in the alkylation of 2 : 3 : 5-trialkylpyrroles by the Grignard reaction, the main reaction is α-substitution at the 2-(but not 5-)position of the pyrrole to give a 2 : 2 : 3 : 5-tetra-alkyl-2*H*-pyrrole (max. at *ca.* 237 mμ in neutral and 255 mμ in acid solution); the subsidiary reaction is β-substitution at the 4-position to give the tetra-alkylpyrrole which is then alkylated to the 2 : 2 : 3 : 4 : 5-penta-alkyl-2*H*-pyrrole (max. at *ca.* 242 mμ in neutral and 269 mμ in acid solution).

The alkylation of 2 : 3 : 4-trialkylpyrroles is of interest because of its connection with the biogenesis of porphyrins [9] and it is now shown that the products are 2 : 3 : 4 : 5-tetra-alkylpyrroles and 2 : 2 : 3 : 4-tetra-alkyl-2*H*-pyrroles (VIII) (max. at *ca.* 248 mμ in neutral and 271 mμ in acid solution). Alkylation at the α-position is postulated in this series partly because of the non-identity of the 2 : 2 : 3 : 4-tetra-alkyl-2*H*-pyrroles (VIII; R = Me, R′ = Et and R = Et, R′ = Me respectively) obtained from the methylation of cryptopyrrole and the ethylation of 2 : 3 : 4-trimethylpyrrole, and partly by analogy with the earlier series. The ratio of tetra-alkylpyrroles to tetra-alkyl-2*H*-pyrroles in the alkylation products of the 2 : 3 : 4-trialkylpyrroles varied appreciably according to the nature of the substituent. Thus phyllopyrrole was a minor product from the methylation of cryptopyrrole whereas only the tetra-substituted pyrrole was isolated from the methylation of 3-ethoxycarbonylmethyl-2 : 4-dimethylpyrrole, and 5-ethyl-2 : 3 : 4-trimethylpyrrole was the major product of ethylation of 2 : 3 : 4-trimethylpyrrole.

A complex mixture has been obtained from the methylation of 2 : 5-dimethylpyrrole. Besides 2 : 2 : 3 : 4 : 5-pentamethyl-2*H*-pyrrole already mentioned, 2 : 3 : 4 : 5-tetramethylpyrrole and two isomeric tetramethyl-2*H*-pyrroles, probably 2 : 2 : 3 : 5- and 2 : 2 : 4 : 5-substituted, were obtained. Although alkylation of alkylpyrroles is thus a relatively easy reaction, it is inhibited by electron-attracting substituents attached directly to the ring. Thus the Grignard derivative of 3-ethoxycarbonyl-2 : 4-dimethylpyrrole was not methylated further under the conditions used throughout the present work. Under these conditions, *i.e.* methylation of the Grignard derivative of the pyrrole with methyl iodide, no evidence for substitution at the β-position of the pyrrole ring has been obtained. Other methods of methylation are under examination. If the mode of methylation in Nature is also electrophilic then the methylation step in the biogenesis of vitamin B_{12} from porphobilinogen is unlikely to involve a porphyrinogen.

Experimental

Ultraviolet absorption spectra were determined in 95% ethanol except where otherwise stated.

2 : 2 : 3 : 4 : 5-*Pentamethyl*-2H-*pyrrole* (I; R = Me).—(*a*) 2 : 5-Dimethylpyrrole [10] (62 g.) in dry ether (300 c.c.) was added to a solution of methylmagnesium iodide [from magnesium (15·8 g.) and methyl iodide (93 g.)] in dry ether (300 c.c.), and the mixture was heated under reflux for 1 hr. More methyl iodide (93 g.) was added, and the mixture heated under reflux for

[9] Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.
[10] Young and Allen, *Org. Syntheses*, Coll. Vol. II, 1943, p. 219.

a further 18 hr. The solution was cooled (ice) and treated with saturated ammonium chloride solution (200 c.c.), and the ethereal layer separated. The aqueous solution was washed with ether and the combined ethereal solutions were thoroughly extracted with N-hydrochloric acid. The acid extracts were neutralised with sodium hydroxide solution and again extracted with ether. After removal of solvent from the dried extract, the residual oil was distilled and the following fractions were collected: (i) oil (4·0 g.), b. p. up to 64°/14 mm.; (ii) pale yellow oil (2·4 g.), b. p. 64—80°/14 mm.; (iii) pale yellow oil (2·4 g.), b. p. 80—86°/14 mm.; and (iv) solid (3·0 g.), b. p. 86—88°/14 mm. Fraction (i), consisting largely of tetramethyl-2*H*-pyrroles, was redistilled and three main fractions were collected: (*ia*) oil (1·1 g.), b. p. 30—36°/14 mm.; (*ib*) oil (0·7 g.), b. p. 36—45°/14 mm.; and (*ic*) oil (0·9 g.), b. p. 45—52°/14 mm. Fraction (*ia*) showed $\lambda_{max.}$ 233 mμ, log ε 3·38, and in dilute ethanolic hydrochloric acid, $\lambda_{max.}$ 250 mμ, log ε 3·47. [*Picrate*, yellow needles (ethanol), m. p. 169—170° (Found: C, 48·0; H, 4·85; N, 16·2. $C_{14}H_{16}O_7N_4$ requires C, 47·7; H, 4·6; N, 15·9%). *Picrolonate*, yellow needles (ethanol), m. p. 197—198° (Found: C, 55·9; H, 5·4; N, 18·5. $C_{18}H_{21}O_5N_5$ requires C, 55·8; H, 5·45; N, 18·1%).] Fraction (*ib*) showed $\lambda_{max.}$ 236 mμ, log ε 3·42, and in dilute ethanolic hydrochloric acid, $\lambda_{max.}$ 255 mμ, log ε 3·48. [*Picrate*, yellow plates (ethanol), m. p. 195—196° (Found: C, 47·9; H, 4·65; N, 15·7. $C_{14}H_{16}O_7N_4$ requires C, 47·7; H, 4·6; N, 15·9%). *Picrolonate*, yellow plates (ethanol), m. p. 202—203° (Found: C, 55·8; H, 5·6; N, 17·8. $C_{18}H_{21}O_5N_5$ requires C, 55·8; H, 5·45; N, 18·1%).] Fraction (*ic*) yielded the same derivatives as those obtained from fraction (*ib*).

Fraction (ii), consisting largely of 2 : 2 : 3 : 4 : 5-pentamethyl-2*H*-pyrrole, was converted into the picrate, which formed yellow plates (ethanol), m. p. 167—168° (lit.,[11] 168—169°) (Found: C, 49·0; H, 5·0; N, 15·7. Calc. for $C_{15}H_{18}O_7N_4$: C, 49·2; H, 5·0; N, 15·3%). A sample of the base regenerated (lithium hydroxide) from the picrate had b. p. 51—53°/12 mm., n_D^{25} 1·4573; (i) $\lambda_{max.}$ 243 mμ, log ε 3·40, (ii) in dilute ethanolic hydrochloric acid, $\lambda_{max.}$ 266 mμ, log ε 3·45. [*Picrolonate*, yellow plates (ethanol), m. p. 219—221° (Found: C, 56·5; H, 5·8. $C_{19}H_{23}O_5N_5$ requires C, 56·85; H, 5·8%). *Methiodide*, prisms (acetone–ethyl acetate), m. p. 173—174° (Found: C, 42·9; H, 6·5. $C_{10}H_{18}NI$ requires C, 43·0; H, 6·5%); $\lambda_{max.}$ in ethanol at 218 (iodide) and 270 mμ (log ε 4·18 and 3·75). Methopicrate, orange needles (water), m. p. 144—146° (lit.,[11] 148°) (Found: C, 50·3; H, 5·1; N, 14·7. Calc. for $C_{16}H_{20}O_7N_4$: C, 50·5; H, 5·3; N, 14·7%).] Treatment of the methiodide with aqueous sodium hydroxide followed by ether extraction gave 1 : 3 : 4 : 5 : 5-pentamethyl-2-methylene-Δ^3-pyrroline, b. p. 126—128° (bath temp.)/68 mm., n_D^{19} 1·5070, $\lambda_{max.}$ 212 and 287 mμ (log ε 4·06 and 3·83 respectively) (in hexane). The derived picrate crystallised from water in orange needles, m. p. 144—145° undepressed when mixed with the methopicrate of 2 : 2 : 3 : 4 : 5-pentamethyl-2*H*-pyrrole.

Fraction (iv) of the original distillation was a solid which crystallised from light petroleum as plates, m. p. 110° (lit.,[7] 110°). The picrate formed yellow-brown prisms (ethanol), m. p. 127° not depressed on admixture with an authentic specimen of 2 : 3 : 4 : 5-tetramethylpyrrole picrate.

(*b*) 2 : 3 : 4 : 5-Tetramethylpyrrole [7] (8 g.) in ether (30 c.c.) was added slowly to a solution of methylmagnesium iodide, prepared from magnesium (1·44 g.) and methyl iodide (8·45 g.) in dry ether (20 c.c.), and the mixture kept overnight. Methyl iodide (8·45 g.) was added next day, and the solution heated under reflux for 20 hr. and then cooled to 0°. A saturated solution of ammonium chloride (50 c.c.) was added and the ethereal layer separated. The aqueous solution was extracted several times with ether and the combined ethereal extracts were shaken repeatedly with N-hydrochloric acid. The acid extracts were made alkaline with sodium hydroxide solution and again extracted with ether. After removal of the solvent from the dried extract, the residue was distilled, and 2 : 2 : 3 : 4 : 5-pentamethyl-2*H*-pyrrole collected, b. p. 80°/40 mm. (3·15 g.; 35·5%). The picrate, m. p. 167—168°, was identical with that obtained in the previous experiment.

2 : 2 : 3 : 4 : 5-*Pentamethylpyrrolidine* (V).—(*a*) Sodium (3·3 g.) was added gradually to a solution of 2 : 2 : 3 : 4 : 5-pentamethyl-2*H*-pyrrole (0·82 g.) in dry ethanol (25 c.c.). The mixture was heated under reflux for 1 hr., cooled, diluted with aqueous ethanol (75%; 20 c.c.) and then acidified with hydrochloric acid. The alcohol was removed by distillation, and the residue dissolved in water (20 c.c.) and made alkaline with aqueous sodium hydroxide. The solution was then extracted several times with ether, the ethereal extracts were dried, and the solvent was removed. Distillation of the residue gave an oil (0·5 g.; 60%), b. p. 122—124° (bath

[11] Plancher and Zambonini, *Atti R. Accad. Lincei*, 1913, **22**, ii, 708.

temp.)/200 mm. The *picrolonate* formed yellow prisms (acetone), m. p. 227—230° (decomp.) (Found: C, 56·6; H, 6·7; N, 17·7. $C_{19}H_{27}O_5N_5$ requires C, 56·3; H, 6·7; N, 17·3%).

(*b*) Raney nickel (4·0 g.; washed with methanol) was added to a solution of 3 : 4 : 5-trimethyl-5-nitrohexan-2-one (8·0 g.; see below) in methanol (50 c.c.), and the mixture hydrogenated at 50 atm. and 105° for 90 min. After removal of the catalyst, the solution was acidified with hydrochloric acid, and the methanol removed by distillation. The solution of the residue in water (20 c.c.) was made alkaline (aqueous sodium hydroxide) and repeatedly extracted with ether. After removal of the solvent from the dried ethereal extract and distillation the product was obtained as an oil (1·2 g.; 20%), b. p. (bath temp.) 125—130°/190 mm. The product gave two picrolonates which were separated by fractional crystallisation from acetone: (i) m. p. 196—198° (decomp.), yellow cubes (Found: C, 56·0; H, 6·4; N, 16·9%); (ii) m. p. 242—244° (decomp.), yellow cubes, but the amount obtained was not sufficient for analysis.

(*c*) The nitro-hexanone (2·0 g.) was dissolved in a mixture of methanol (30 c.c.) and aqueous ammonia (1 c.c.; *d* 0·88). Raney nickel (1 g.; washed with methanol) was added, and the mixture hydrogenated at 50 atm. at 100° for 90 min. The product (0·17 g., 11·5%), b. p. 115—120°/156 mm., was isolated as in the foregoing experiment. The picrolonate which formed yellow cubes (acetone) had m. p. 195—197°, not depressed on admixture with that obtained above.

3 : 4 : 5-*Trimethyl*-5-*nitrohexan*-2-*one* (VI).—3-Methylpent-3-en-2-one (46·7 g.), 2-nitropropane (425 g.), and diethylamine (34·8 g.) were heated under reflux for 20 hr. The unchanged reagents were removed by distillation (up to 55°/20 mm.), and the residue was distilled, the fraction boiling at 125—128°/10—12 mm. being collected as a pale yellow oil (19·1 g.; 21%). The *semicarbazone* formed prisms (ethanol), m. p. 186—187° (Found: N, 23·0. $C_{10}H_{20}O_3N_4$ requires N, 22·95%).

Ozonolysis of 2 : 2 : 3 : 4 : 5-*Pentamethyl*-2H-*pyrrole*.—A solution of the pentamethyl-2*H*-pyrrole (1·0 g.) in dry chloroform (15 c.c.) was cooled (ice), and a slow stream of ozonised oxygen passed through it for 5 hr. Acetic acid (10 c.c.) and zinc dust (1·0 g.) were added and the mixture was heated under reflux for 15 min. The excess of zinc was removed, and the filtrate distilled in steam, the first fraction (50 c.c.) of the distillate being collected (distillate *A*). The residue in the distillation flask was made alkaline with sodium hydroxide and again distilled in steam, the first fraction (20 c.c.) again being collected (distillate *B*). Phenylhydrazine (0·5 g.) was added to distillate *A*, and the mixture heated on the steam-bath for 30 min. The yellow precipitate, which was obtained when the solution was cooled, was separated, washed with a little ethanol, and crystallised from nitrobenzene; it formed fawn-coloured crystals (0·25 g; 23·5%), m. p. 239—242° not depressed when mixed with an authentic specimen of diacetyl osazone (Found: N, 21·5. Calc. for $C_{16}H_{18}N_4$: N, 21·05%). Addition of picric acid (0·5 g.) to distillate *B* gave ammonium picrate (0·36 g., 20·1%) which formed yellow needles, m. p. (sealed tube) 270—272° (decomp.) (Found: N, 22·4. Calc. for $C_6H_6O_7N_4$: N, 22·75%).

2-*Ethyl*-2 : 3 : 4 : 5-*tetramethyl*-2H-*pyrrole* (I; R = Et).—(*a*) The Grignard derivative of 2 : 3 : 4 : 5-tetramethylpyrrole (10·2 g.) was ethylated with ethyl iodide (17 g.) in the manner already described for methylation. The product was treated similarly and distilled under reduced pressure to give the base as a pale yellow oil (5·9 g., 47%), b. p. 98—100°/72 mm. The *picrate* formed golden yellow needles (ethanol), m. p. 177—178° (Found: C, 50·6; H, 5·5; N, 14·9. $C_{16}H_{20}O_7N_4$ requires C, 50·5; H, 5·3; N, 14·7%). Light absorption of the base regenerated from the picrate: (i) $\lambda_{max.}$ 241 mμ, log ε 3·50, (ii) in ethanolic hydrochloric acid $\lambda_{max.}$ 268 mμ, log ε 3·62.

(*b*) The Grignard derivative of 2-ethyl-3 : 4 : 5-trimethylpyrrole [7] (4·4 g.) was methylated in the usual manner. The product, a mixture of 2-ethyl-2 : 3 : 4 : 5-tetramethyl- and (presumably) 5-ethyl-2 : 2 : 3 : 4-tetramethyl-2*H*-pyrrole, formed a pale yellow oil (1·6 g., 33%), b. p. 106—112°/78 mm. The picrate formed yellow needles, m. p. 176—177° after repeated crystallisation from ethanol. The m. p. of a mixture with the product from the previous experiment was 176—177° (Found: C, 50·6; H, 5·4; N, 14·8%).

(*c*) 2-Ethyl-3 : 5-dimethylpyrrole [7] (18·7 g.) was methylated with methyl iodide in the usual manner. The basic oil so obtained was fractionated and three main fractions were collected: (i) oil (2·05 g.), b. p. 58—66°/13 mm.; (ii) oil (1·8 g.), b. p. 68—78°/13 mm.; and (iii) pale yellow oil (2·2 g.), b. p. 80—88°/13 mm. Fractions (i) and (ii) gave identical picrates and were combined and treated separately (see below; 2-ethyl-2 : 3 : 5-trimethyl-2*H*-pyrrole). Fraction

(iii) was converted into the picrate which formed yellow needles (ethanol), m. p. 174—176°, not depressed on admixture with the picrates from the previous two experiments (Found: C, 50·2; H, 5·5; N, 14·8%).

5-Ethyl-1 : 3 : 4 : 5-tetramethyl-2-methylene-Δ³-pyrroline (III; R = Et).—(i) 2-Ethyl-2 : 3 : 4 : 5-tetramethyl-2*H*-pyrrole from the ethylation of 2 : 3 : 4 : 5-tetramethylpyrrole (above) was converted into its methiodide, m. p. 162—163°. The methiodide (2·0 g.) was added to a solution of potassium hydroxide (1·5 g.) in water (10 c.c.), and the resulting oil extracted with ether (3 × 10 c.c.). The solvent was removed from the dried ether extract, and the residue distilled to give a pale yellow oil (0·7 g., 62%), b. p. (bath temp.) 115—120°/35 mm., $\lambda_{max.}$ (ethanol), 209 and 272 mμ, log ε 3·80 and 3·62, respectively. The *picrate* formed yellow prisms (ethanol), m. p. 134—135° (Found: C, 52·1; H, 5·6; N, 14·3. $C_{17}H_{22}O_7N_4$ requires C, 51·8; H, 5·6; N, 14·2%).

(ii) The mixed bases obtained from the methylation of 2-ethyl-3 : 4 : 5-trimethylpyrrole (above) were converted into the methiodides, which had m. p. 138—146° and were treated directly (1·7 g.) with alkali as above to give the mixed anhydro-bases (0·5 g.), b. p. (bath temp.) 115—124°/35 mm.; $\lambda_{max.}$ 210 and 270 mμ, log ε 3·68 and 3·70. The corresponding picrate formed yellow prisms (ethanol), m. p. 133—134° after repeated crystallisation, not depressed on admixture with the picrate obtained in the previous experiment (Found: C, 51·5; H, 5·4; N, 14·6%).

2-Ethyl-2 : 3 : 5-trimethyl-2H-pyrrole (VII; R = Et, R′ = Me).—(i) Fractions (i) and (ii) from the methylation product of 2-ethyl-3 : 5-dimethylpyrrole (above) were combined (3·85 g.) and redistilled, the main fraction (2·4 g.), b. p. 52—56°/11 mm., being obtained as an oil with strong camphoraceous odour; $\lambda_{max.}$ (ethanol) 237 mμ, log ε 3·50, $\lambda_{max.}$ (ethanolic hydrochloric acid) 255 mμ, log ε 3·54. The *picrate* formed yellow plates (ethanol), m. p. 193—195° after sintering and darkening about 175° (Found: C, 49·2; H, 5·1; N, 15·4. $C_{15}H_{18}O_7N_4$ requires C, 49·2; H, 4·95; N, 15·3%). The *picrolonate* formed yellow needles (ethanol), m. p. 165—166° (Found: C, 56·9; H, 5·9; N, 17·4. $C_{19}H_{23}O_5N_5$ requires C, 56·85; H, 5·8; N, 17·45%).

(ii) 2 : 3 : 5-Trimethylpyrrole [7] (47·2 g.) was ethylated with ethyl iodide. The basic oil so obtained was distilled and the following fractions were collected: (i) oil (7·8 g.), b. p. 58—68°/18 mm.; (ii) oil (12·7 g.), b. p. 76—90°/18 mm.; (iii) pale yellow oil (3·9 g.), b. p. 92—98°/18 mm., which was treated separately (see below; 2 : 4-diethyl-2 : 3 : 5-trimethyl-2*H*-pyrrole). Fractions (i) and (ii), which gave identical picrates, were combined and re-distilled, the fraction, b. p. 54—56°/12 mm., being collected as an oil (6·1 g.) with camphoraceous odour; $\lambda_{max.}$ (in ethanol) 235 mμ, log ε 3·49, $\lambda_{max.}$ (in ethanolic hydrochloric acid) 254 mμ, log ε 3·60. Picrate, yellow plates (ethanol), m. p. 194—195° (with previous darkening) not depressed on admixture with the picrate of the base prepared in the foregoing experiment (Found: C, 49·2; H, 4·95; N, 15·0%). Picrolonate, golden-yellow needles (ethanol), m. p. 166—167° again undepressed by admixture with the foregoing picrolonate (Found: C, 56·6; H, 5·9; N, 17·1%).

5-Ethyl-1 : 4 : 5-trimethyl-2-methylene-Δ³-pyrroline.—(i) 2-Ethyl-2 : 3 : 5-trimethyl-2*H*-pyrrole, obtained from the ethylation of 2 : 3 : 5-trimethylpyrrole (above), was converted into the methiodide, m. p. 204—208°, which (1·9 g.) was converted into the anhydro-base by the action of alkali. The base (0·65 g.; 63%) was obtained as a pale yellow oil, b. p. (bath temp.) 110—115°/50 mm.; $\lambda_{max.}$ 210 mμ (log ε 3·94), 288 mμ (log ε 3·66). The *picrate* formed small yellow needles (ethanol), m. p. 160—164° (with previous darkening) (Found: C, 50·4; H, 5·65; N, 14·7. $C_{16}H_{20}O_7N_4$ requires C, 50·5; H, 5·3; N, 14·7%).

(ii) The same 2*H*-pyrrole, obtained from the methylation of 3 : 5-dimethyl-2-ethylpyrrole (above), was similarly converted through the methiodide into the anhydro-base; $\lambda_{max.}$ 211 mμ (log ε 3·94), 290 mμ (log ε 3·63). The corresponding picrate (Found: C, 50·2; H, 5·35; N, 14·8%) had m. p. 160—162°, not depressed on admixture with the picrate obtained from the previous experiment.

2 : 4-Diethyl-2 : 3 : 5-trimethyl- or 2 : 3-Diethyl-2 : 4 : 5-trimethyl-2H-pyrrole.—The high-boiling fraction from the ethylation of 2 : 3 : 5-trimethylpyrrole was converted into the *picrate*, which formed yellow needles (ethanol), m. p. 140—141° (Found: C, 51·8; H, 5·45; N, 14·2. $C_{17}H_{22}O_7N_4$ requires C, 51·8; H, 5·6; N, 14·2%). The free base (0·6 g.), b. p. (bath temp.) 95—100°/32 mm., was regenerated from the picrate by aqueous lithium hydroxide. It had light absorption: (i) in ethanol, $\lambda_{max.}$ 242 mμ, log ε 3·55; (ii) in ethanolic hydrochloric acid, $\lambda_{max.}$ 267 mμ, log ε 3·66. *Picrolonate*, yellowish-brown needles (ethanol), m. p. 144—146° (Found: C, 58·9; H, 6·25; N, 15·9. $C_{21}H_{27}O_5N_5$ requires C, 58·75; H, 6·35; N, 16·3%).

3-Ethyl-2 : 2 : 5-trimethyl-2H-pyrrole (VII; R = Me, R′ = Et).—3-Ethyl-2 : 5-dimethylpyrrole [7] was methylated with methyl iodide. The basic oil so obtained was distilled and the following fractions were collected: (i) oil (3·4 g.), b. p. 68—78°/11 mm.; (ii) pale yellow oil (5·1 g.), b. p. 82—88°/11 mm.; (iii) pale yellow oil (3·5 g.), b. p. 88—92°/11 mm. Fraction (i) was redistilled, and the fraction (2·6 g.), 70—72°/11 mm., collected. This oil, of the usual camphoraceous odour, had light absorption: (i) in ethanol, $\lambda_{max.}$ 235 mμ, log ε 3·48; (ii) in ethanolic hydrochloric acid, $\lambda_{max.}$ 257 mμ, log ε 3·56. The *picrate* (Found: C, 49·2; H, 4·75; N, 15·4. $C_{15}H_{18}O_7N_4$ requires C, 49·2; H, 4·95; N, 15·3%) formed yellow needles (ethanol), m. p. 189—190°, mixed m. p. 190—192° (darkening *ca.* 170°) with the picrate (m. p. 194—195°) of 2-ethyl-2 : 3 : 5-trimethyl-2*H*-pyrrole (above). The *picrolonate* formed pale yellow prisms (ethanol), m. p. 200—203° (Found: C, 57·1; H, 5·5; N, 17·8. $C_{19}H_{23}O_5N_5$ requires C, 56·85; H, 5·8; N, 17·45%).

4-Ethyl-1 : 5 : 5-trimethyl-2-methylene-Δ³-pyrroline.—The methiodide (1·6 g.), m. p. 195—197°, of 3-ethyl-2 : 2 : 5-trimethyl-2*H*-pyrrole was converted into the anhydro-base by the action of alkali. The pale yellow product (0·5 g.; 57%) had b. p. (bath temp.) 110—115°/45 mm.; $\lambda_{max.}$ (ethanol) 210 and 290 mμ, log ε 3·85 and 3·58. Neither the picrate nor the picrolonate could be obtained solid.

4-Ethyl-2 : 2 : 3 : 5-tetramethyl- or 3-Ethyl-2 : 2 : 4 : 5-tetramethyl-2H-pyrrole.—Fraction (ii) from the methylation of 3-ethyl-2 : 5-dimethylpyrrole was converted into the *picrate*, yellow needles, m. p. 161—162° after crystallisation from ethanol (Found: C, 50·3; H, 5·3; N, 14·8. $C_{16}H_{20}O_7N_4$ requires C, 50·5; H, 5·3; N, 14·7%). The free base was regenerated from the picrate (3·2 g.) by the action of aqueous lithium hydroxide and distilled. It was a pale yellow oil (0·45 g.) with the usual camphor-like odour, b. p. (bath temp.) 85—90°/40 mm.; $\lambda_{max.}$ in ethanol 244 mμ, log ε 3·34, $\lambda_{max.}$ in ethanolic hydrochloric acid 269 mμ, log ε 3·42. The *picrolonate* formed yellow prisms (ethanol), m. p. 203° (Found: C, 57·8; H, 6·05; N, 16·8. $C_{20}H_{25}O_5N_5$ requires C, 57·8; H, 6·05; N, 16·85%).

2-Ethyl-2 : 3 : 4-trimethyl-2H-pyrrole (VIII; R = Et, R′ = Me).—2 : 3 : 4-Trimethylpyrrole [7] (33·4 g.) was converted into the Grignard derivative and ethylated with ethyl iodide. The product was treated with saturated ammonium chloride solution (100 c.c.), and the basic fraction separated by extraction into N-hydrochloric acid and then back again into ether after neutralisation of the acid extract. The solvent was removed, and the residue fractionated under reduced pressure, the following fractions being collected: (i) oil (3·3 g.), b. p. 70—88°/14 mm.; (ii) pale yellow oil (11·8 g.), b. p. 88—96°/14 mm.; (iii) pale yellow oil (6·7 g.), b. p. 96—98°/14 mm. Fraction (i) was redistilled, and the product collected of b. p. 74—78°/14 mm. (1·2 g.); $\lambda_{max.}$ 248 mμ, log ε 3·49, $\lambda_{max.}$ in dilute ethanolic hydrochloric acid 271 mμ, log ε 3·58. The *picrate* formed yellow needles (ethanol), m. p. 156—157° which was not depressed on admixture with the picrate of the base obtained by methylation of 3-ethyl-2 : 4-dimethylpyrrole although it is a different compound (Found: C, 49·3; H, 5·2; N, 15·2. $C_{15}H_{18}O_7N_4$ requires C, 49·2; H, 4·95; N, 15·3%). The *picrolonate* formed yellow prisms (ethanol), m. p. 166—168° depressed to 136—146° on admixture with the picrolonate of the base obtained by methylation of 3-ethyl-2 : 4-dimethylpyrrole (Found: C, 56·9; H, 6·0; N, 17·4. $C_{19}H_{23}O_5N_5$ requires C, 56·85; H, 5·8; N, 17·45%).

Fractions (ii) and (iii) were combined and redistilled to give 5-ethyl-2 : 3 : 4-trimethylpyrrole [7] (15·7 g.; 42·5%), b. p. 94—96°/15 mm. (Found: C, 78·6; H, 10·8. Calc. for $C_9H_{15}N$: C, 78·8; H, 11·0%).

3-Ethyl-2 : 2 : 4-trimethyl-2H-pyrrole (VIII; R = Me, R′ = Et).—Freshly distilled cryptopyrrole (25 g.) was converted into the Grignard derivative which was treated with methyl iodide. The product was decomposed by addition of saturated ammonium chloride solution, and the ethereal layer extracted with N-hydrochloric acid. The solvent was removed from the neutral fraction, and the residue distilled at 97—110°/15 mm. to give a pale yellow solid which was purified by sublimation at 80°/14 mm. Phyllopyrrole was then obtained as plates (2·3 g.), m. p. 68—69° (lit.[12] m. p. 67°) after crystallisation from light petroleum. The picrate formed yellow prisms (ethanol), m. p. 104—105° (lit.[13] m. p. 104—105°) (Found: N, 15·3. Calc. for $C_{15}H_{18}O_7N_4$: N, 15·3%).

The acidic extracts were neutralised with aqueous ammonia (*d* 0·88) and extracted with ether (3 × 20 c.c.). The combined ethereal extracts were dried, the solvent was removed, and the

[12] Fischer, Baumann, and Riedl, *Annalen*, 1929, **475**, 205.
[13] Fischer and Klarer, *ibid.*, 1926, **450**, 181.

residue fractionated. Fraction (i) had b. p. 75—95°/22 mm. (5·3 g.); $\lambda_{max.}$ 251 mμ, log ε 3·42, $\lambda_{max.}$ in dilute hydrochloric acid 273 mμ, log ε 3·47. Fraction (ii), b. p. 95—100°/22 mm. (1·0 g.). The *picrate*, m. p. 158—160°, from fraction (i) formed yellow needles (ethanol) (Found: C, 49·3; H, 5·0; N, 15·4. $C_{15}H_{18}O_7N_4$ requires C, 49·2; H, 4·95; N, 15·3%). The *picrolonate*, m. p. 170°, from fraction (i) formed yellow prisms (ethanol) (Found: C, 57·0; H, 5·8; N, 17·45. $C_{19}H_{23}O_5N_5$ requires C, 56·85; H, 5·8; N, 17·45%). Fraction (ii) appeared to be the 3-ethyl-2 : 2 : 4-trimethyl-2*H*-pyrrole of fraction (i) contaminated with phyllopyrrole.

3-*Ethoxycarbonylmethyl*-2 : 4 : 5-*trimethylpyrrole*.—The Grignard derivative of 3-ethoxycarbonylmethyl-2 : 4-dimethylpyrrole [7] (1·0 g.) was treated with methyl iodide (0·73 g.) in dry ether (10 c.c.), and the suspension heated under reflux for 1 hr. More methyl iodide (3·65 g.) was added, and the suspension heated for 4 hr., cooled to 0°, and decomposed by the addition of saturated ammonium chloride solution (30 c.c.). The ethereal layer was separated, the aqueous layer washed with ether, and the combined ethereal extracts were washed and dried, and the solvent was removed. The residual oil was distilled, and the fraction, b. p. 165—168° (bath temp.)/10 mm. (0·05 g.; 5%), collected as an oil (Found: C, 67·4; H, 8·8; N, 7·4. $C_{11}H_{17}O_2N$ requires C, 67·7; H, 8·8; N, 7·2%).

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