

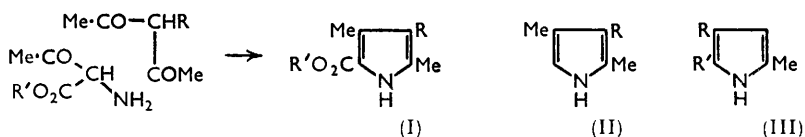
### 864. *The Synthesis of Tri- and Tetra-alkylpyrroles.*

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Some tri- and tetra-alkylpyrroles have been prepared by modifications of the Knorr synthesis. Benzyl esters in the pyrrole series have been subjected to a one-stage hydrogenolysis and decarboxylation in order to remove the ester group.

TRI- and TETRA-ALKYLPYRROLES are useful synthetic intermediates but their preparation frequently is tedious and involves several stages. Application of direct Knorr syntheses gives only low yields of trialkylpyrroles, *e.g.*, 2 : 3 : 5-trimethylpyrrole from the condensation of 3-aminobutan-2-one and acetone<sup>1</sup> and the product is contaminated with the symmetrical pyrazine. On the other hand better yields of pyrroles are obtained from Knorr condensations of  $\alpha$ -amino-ketones with  $\beta$ -keto-esters, but the products contain ester and acyl substituents and additional stages are necessary to prepare the alkylpyrroles. Such an approach is exemplified in a detailed preparation of crytopyrrole<sup>2</sup> although the use of lithium aluminium hydride for reduction of ester and acyl groups in the pyrrole series is a further improvement on existing methods.<sup>3</sup> Another variant is the introduction of methyl groups into dialkylpyrroles by formylation and subsequent reduction.<sup>4</sup> The synthesis of pyrroles containing propionic acid or ester groupings has been achieved by an acid-catalysed addition of acrylic ester to the preformed pyrrole ring in certain favourable cases<sup>5</sup> but more frequently by a several-stage process involving formylation and subsequent condensation with malonic acid.<sup>6</sup> Likewise the preparation of pyrroles containing acetic ester groups is usually a multi-stage process.

In a recent paper,<sup>7</sup> we described the use of 3-alkylpentane-2 : 4-diones in pyrrole syntheses where reactions with  $\alpha$ -aminoacetoacetic esters (*e.g.*, to form I; R = Me) were not of the usual Knorr type:



This reaction has now been utilised to provide a convenient route to trisubstituted pyrroles. Condensation of *tert.*-butyl<sup>8</sup> or, better, benzyl  $\alpha$ -aminoacetoacetate<sup>9</sup> gave the pyrroles

<sup>1</sup> Piloty and Hirsch, *Annalen*, 1913, **395**, 68.

<sup>2</sup> Fischer, *Org. Synth.*, 1955, Coll. Vol. III, p. 513.

<sup>3</sup> Treibs *et al.*, *Annalen*, 1952, **577**, 139; 1954, **589**, 188.

<sup>4</sup> Fischer and Treibs, *Ber.*, 1927, **60**, 380.

<sup>5</sup> Treibs and Michl, *Annalen*, 1954, **589**, 163.

<sup>6</sup> Fischer *et al.*, *Ber.*, 1924, **57**, 602; *Annalen*, 1924, **439**, 180.

<sup>7</sup> Bullock, Johnson, Markham, and Shaw, *J.*, 1958, 1430.

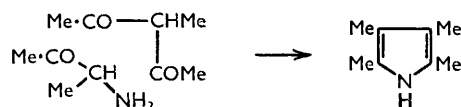
<sup>8</sup> Treibs and Hintermeier, *Chem. Ber.*, 1954, **87**, 1167.

<sup>9</sup> MacDonald, *J.*, 1952, 4176.

(I; R' = Bu<sup>t</sup> or CH<sub>2</sub>Ph) from which the *tert.*-butyl ester group could be removed in one stage by pyrolysis<sup>8</sup> and the benzyl ester group in one stage by hydrogenolysis and decarboxylation in the presence of Raney nickel usually at <120° under pressure (above this temperature, reduction of the trialkylpyrroles was liable to occur although the presence of an ester group in the side-chain appeared to have a stabilising effect). In this manner a variety of trisubstituted pyrroles (II; R = Me, Et, CO<sub>2</sub>Et, Ac, CH<sub>2</sub>·CO<sub>2</sub>Et, and CH<sub>2</sub>·CH<sub>2</sub>·CO<sub>2</sub>Me) has been prepared in overall yields of the order of 40—60%.

A variation of the reaction, *viz.*, condensation of benzyl acetoacetate with alkyl 1-aminoalkyl ketones gave the benzyl 2:4-dialkyl-5-methylpyrrole-3-carboxylates from which 2:3:5-trisubstituted pyrroles (III; R = Me, Et, R' = Me; R = Me, R' = Et) were obtained by removal of the ester group as before.

Finally, by condensation of the 3-alkylpentane-2:4-diones with 1-aminoalkyl methyl ketones, the tetrasubstituted pyrroles (2:3:4:5-tetramethyl- and 2-ethyl-3:4:5-trimethyl-pyrrole) have been obtained in one stage. Tetra-alkylpyrroles have usually been prepared hitherto by insertion of an additional alkyl group into trisubstituted pyrroles, *e.g.*, by direct methylation<sup>10</sup> by formylation and reduction,<sup>11,12</sup> or by aminomethylation and subsequent reduction.<sup>13</sup>



#### EXPERIMENTAL

*Preparation of Benzyl 3:4:5-Trisubstituted Pyrrole-2-carboxylates.*—Benzyl 3:4:5-trimethylpyrrole-2-carboxylate. A solution of sodium nitrite (29 g.) in water (60 c.c.) was added with stirring during 30 min. to benzyl acetoacetate (67.5 g.) in glacial acetic acid (140 c.c.) at <10°. The cooled mixture was stirred for a further 4 hr., then kept overnight at room temperature. This solution was added to 3-methylpentane-2:4-dione (40 g.) in acetic acid (140 c.c.) in the presence of zinc dust (46 g.) with stirring, while the temperature was kept at about 70°. After the addition, the product was heated under reflux for 15 min., then poured on crushed ice (*ca.* 1 kg.). The crude *ester* was separated, washed with water, and crystallised from ethanol as needles (41.0 g., 45.5%), m. p. 119—120° (Found: C, 73.9; H, 6.85; N, 5.7. C<sub>15</sub>H<sub>17</sub>O<sub>2</sub>N requires C, 74.05; H, 7.05; N, 5.8%).

By similar condensations the following pyrrole esters have also been prepared. Benzyl 4-ethyl-3:5-dimethylpyrrole-2-carboxylate [from 3-ethylpentane-2:4-dione (see below)], needles, m. p. 103° (34%) (Found: C, 74.6; H, 7.65; N, 5.3. C<sub>18</sub>H<sub>19</sub>O<sub>2</sub>N requires C, 74.7; H, 7.45; N, 5.45%). Benzyl 4-ethoxycarbonylmethyl-3:5-dimethylpyrrole-2-carboxylate [from ethyl 3-acetyl-4-oxopentanoate (see below)], fine needles (38%), m. p. 76—78° (Found: C, 68.8; H, 6.9; N, 4.65. C<sub>18</sub>H<sub>21</sub>O<sub>4</sub>N requires C, 68.6; H, 6.7; N, 4.45%). Benzyl 4:2'-methoxycarbonylethyl-3:5-dimethylpyrrole-2-carboxylate [from methyl 4-acetyl-5-oxohexanoate (see below)], needles (42%), m. p. 99—101° (Found: C, 68.7; H, 6.65; N, 4.05. C<sub>18</sub>H<sub>21</sub>O<sub>4</sub>N requires C, 68.6; H, 6.7; N, 4.45%). Benzyl 4-acetyl-3:5-dimethylpyrrole-2-carboxylate (by a normal Knorr condensation from acetylacetone and benzyl α-aminoacetoacetate), needles (52%), m. p. 135° (Found: C, 70.9; H, 6.0; N, 5.15. C<sub>16</sub>H<sub>17</sub>O<sub>3</sub>N requires C, 70.8; H, 6.3; N, 5.2%). Benzyl 4-ethoxycarbonyl-3:5-dimethylpyrrole-2-carboxylate (similarly from ethyl acetoacetate and benzyl α-aminoacetoacetate), needles (61%), m. p. 120—121° (Found: C, 67.4; H, 6.0; N, 4.75. C<sub>17</sub>H<sub>19</sub>O<sub>4</sub>N requires C, 67.75; N, 6.3; N, 4.65%).

*Preparation of Benzyl 2:4:5-Trisubstituted Pyrrole-3-carboxylates.*—Benzyl 2:4:5-trimethylpyrrole-3-carboxylate. A solution of 1-hydroxyiminoethyl methyl ketone<sup>14</sup> (185 g.) in glacial acetic acid (750 c.c.) was added to benzyl acetoacetate (350 g.) in acetic acid (800 c.c.) in the presence of zinc dust (234 g.) during 90 min. with stirring, the temperature being kept as close to 70° as possible. The mixture was then heated under reflux for 1 hr. and poured on

<sup>10</sup> Fischer and Bartholomäus, *Z. physiol. Chem.*, 1912, **80**, 10.

<sup>11</sup> Fischer and Walach, *Annalen*, 1926, **450**, 109.

<sup>12</sup> Treibs and Scherer, *ibid.*, 1954, **589**, 196; MacDonald and Michl, *Canad. J. Chem.*, 1956, **34**, 1671.

<sup>13</sup> Treibs and Zinmeister, *Chem. Ber.*, 1957, **90**, 87.

<sup>14</sup> Semon and Damerell, *Org. Synth.*, Coll. Vol. II, 1943, p. 204.

crushed ice (5 kg.). The crude ester was separated, washed, and crystallised from aqueous ethanol; it formed needles (228 g., 51%), m. p. 85—86° (Found: C, 74.4; H, 7.0; N, 6.15.  $C_{15}H_{17}O_2N$  requires C, 74.05; H, 7.05; N, 5.76%). Benzyl 4-ethyl-2:5-dimethylpyrrole-3-carboxylate, prepared (40.5%) by a similar method from diethyl ketone, had m. p. 88—89° (Found: C, 74.4; H, 7.4; N, 5.4.  $C_{16}H_{19}O_2N$  requires C, 74.7; H, 7.45; N, 5.45%). Benzyl 5-ethyl-2:4-dimethylpyrrole-3-carboxylate (37%), needles (from ethanol), m. p. 126—127°, was obtained similarly from methyl *n*-propyl ketone (Found: C, 74.3; H, 7.4; N, 5.5%).

*Preparation of Trisubstituted Pyrroles.—Hydrogenolysis and decarboxylation of benzyl esters.* 2:3:4-Trimethylpyrrole. Benzyl 3:4:5-trimethylpyrrole-2-carboxylate (20 g.) was dissolved in methanol (100 c.c.), and methanol-washed Raney nickel (5 g.) was added. The mixture was hydrogenated at 150—160°/140 atm. for 2 hr., after which the catalyst and solvent were removed. The residue was distilled under reduced pressure, and the fraction of b. p. 78—85°/12 mm. collected as a colourless oil (lit.,<sup>15</sup> b. p. 71—72°/11 mm. for 2:3:4-trimethylpyrrole) which solidified (m. p. 36—38°) (4.1 g., 46%). The picrate formed yellow prisms, m. p. 139—141° (lit.,<sup>16</sup> m. p. 140°), from ethanol (Found: C, 46.5; H, 4.4; N, 16.2. Calc. for  $C_{13}H_{14}O_7N_4$ : C, 46.2; H, 4.2; N, 16.5%).

By similar reactions at 110—120°/100 atm. for 2 hr. the following trisubstituted pyrroles have also been prepared from the appropriate benzyl esters. Cryptopyrrole (80%), b. p. 84—87°/12 mm. (lit.,<sup>2</sup> b. p. 85.5—87°/12.5 mm.) (Found: C, 77.9; H, 10.7. Calc. for  $C_8H_{13}N$ : C, 78.0; H, 10.65%),  $\lambda_{max.}$  (in EtOH) 213  $\mu$  ( $\log \epsilon$  3.85) [picrate, yellow needles, m. p. 138° from ethanol (lit.,<sup>17</sup> 137.5°)]. 2:3:5-Trimethylpyrrole (58%), b. p. 72—74°/10—11 mm. (lit.,<sup>16</sup> b. p. 75.5—76.5°/16 mm.) (Found: C, 76.8; H, 9.9. Calc. for  $C_7H_{11}N$ : C, 77.0; H, 10.15%). 3-Ethyl-2:5-dimethylpyrrole (66.5%), b. p. 115—117°/60 mm. (lit.,<sup>18</sup> b. p. 121°/63 mm.) (Found: C, 78.0; H, 10.4; N, 11.2. Calc. for  $C_8H_{13}N$ : C, 78.0; H, 10.65; N, 11.35%). 2-Ethyl-3:5-dimethylpyrrole (63%), b. p. 112—114°/63 mm. (lit.,<sup>19</sup> b. p. 93—94°/21 mm.) (Found: C, 77.8; H, 10.6%). 3-Acetyl-2:4-dimethylpyrrole (55%), plates (from ethanol), m. p. 135—137° (lit.,<sup>20</sup> 137°), b. p. 170—173°/12 mm. (Found: C, 70.4; H, 7.9; N, 10.3. Calc. for  $C_8H_{11}ON$ : C, 70.05; H, 8.1; N, 10.2%). 3-Ethoxycarbonyl-2:4-dimethylpyrrole (66%), plates (from ethanol), m. p. 76° (lit.,<sup>8</sup> m. p. 75—76°), sublimes at 150°/9 mm. 3-Ethoxycarbonylmethyl-2:4-dimethylpyrrole (19%), b. p. 140—146°/9 mm. (Found: C, 66.0; H, 8.15.  $C_{10}H_{15}O_2N$  requires C, 66.25; H, 8.35%). 3-2'-Methoxycarbonylethyl-2:4-dimethylpyrrole (62%) was obtained as an oil, b. p. 144—146°/9 mm. (lit.,<sup>21</sup> b. p. 151°/12 mm.), m. p. 47°. The picrate formed yellow prisms (from ethanol), m. p. 106—108° (lit.,<sup>21</sup> m. p. 107—108°) (Found: C, 46.8; H, 4.5; N, 13.3. Calc. for  $C_{16}H_{18}O_9N_4$ : C, 46.8; H, 4.4; N, 13.65%).

*Thermal Decomposition of tert.-Butyl Esters.—2:3:4-Trimethylpyrrole.* A mixture of *tert.*-butyl 3:4:5-trimethylpyrrole-2-carboxylate<sup>7</sup> (30.9 g.) and toluene-*p*-sulphonic acid (0.1 g.) was heated at 210° until decomposition ceased. The residue was distilled under reduced pressure and the fraction of b. p. 76—80°/12 mm. collected (7.6 g., 46%); it solidified. The picrate, m. p. 138—140° (from ethanol), was identical with the product described above.

*Cryptopyrrole.* *tert.*-Butyl 3-acetyl-2:4-dimethylpyrrole-2-carboxylate<sup>8</sup> (23.7 g.), 90% hydrazine hydrate (10 c.c.), potassium hydroxide (25 g.), and ethylene glycol (150 c.c.) were heated under gentle reflux for 1 hr. Excess of water was then distilled off until the temperature of the mixture rose to 175—180°, then the mixture was heated under reflux for a further 3 hr. The solution was cooled, diluted with water (100 c.c.), and steam-distilled in an atmosphere of nitrogen until the distillate gave only a faint Ehrlich reaction. The distillate was extracted with ether (3 × 50 c.c.), the ethereal layer dried, and the solvent removed. Distillation of the residue gave cryptopyrrole (1.0 g., 8%), b. p. 93—98°/17 mm. (picrate, m. p. 136°, identical with the product obtained as above).

*Preparation of Tetrasubstituted Pyrroles.—2:3:4:5-Tetramethylpyrrole.* 1-Hydroxyiminoethyl methyl ketone (42 g.) in glacial acetic acid (150 c.c.) was added to 3-methylpentane-2:4-dione (52.5 g.) in acetic acid (250 c.c.) in the presence of zinc dust (54.5 g.) during 45 min. with

<sup>15</sup> Fischer and Walach, *Annalen*, 1926, **447**, 38.

<sup>16</sup> Piloty and Hirsch, *ibid.*, 1913, **395**, 63.

<sup>17</sup> Fischer and Bartholomäus, *Ber.*, 1912, **45**, 1979.

<sup>18</sup> Hess, Wissing, and Suchier, *Ber.*, 1915, **48**, 1865.

<sup>19</sup> Knorr and Hess, *Ber.*, 1911, **44**, 2758; 1912, **45**, 2626.

<sup>20</sup> Fischer and Ernst, *Ber.*, 1926, **59**, 140.

<sup>21</sup> Fischer and Röse, *Ber.*, 1912, **45**, 3274.

stirring while the temperature was kept at 65–70°. The mixture was then heated under reflux for 2 hr., after which water (500 c.c.) was added and the product distilled in steam until the distillate no longer gave a positive Ehrlich test (hot). The product was separated from the distillate (ca. 1 l.), washed, and dried *in vacuo*, being obtained as colourless plates (22.5 g., 44%), m. p. 109–110° (lit.,<sup>11</sup> m. p. 112°) (Found: C, 78.0; H, 10.6. Calc. for C<sub>8</sub>H<sub>13</sub>N: C, 78.0; H, 10.65%),  $\lambda_{\max}$ . 219 m $\mu$  (log  $\epsilon$  3.74).

By a similar method from 1-hydroxyimino-*n*-propyl methyl ketone there was produced 2-ethyl-3:4:5-trimethylpyrrole (17%) as a pale yellow oil, b. p. 110–114°/25 mm. (lit.,<sup>11</sup> b. p. 114–115°/27 mm.), which solidified. The picrate formed yellow plates (from ethanol), m. p. 102–104° (lit.,<sup>11</sup> m. p. 104°) (Found: C, 49.2; H, 4.9; N, 15.2. Calc. for C<sub>13</sub>H<sub>18</sub>O<sub>7</sub>N<sub>4</sub>: C, 49.2; H, 4.95; N, 15.3%).

*3-Ethylpentane-2:4-dione*.—Acetylacetone (66.8 c.c.), ethyl iodide (60 c.c.), anhydrous potassium carbonate (84 g.), and dry acetone (74 c.c.) were heated under reflux on the water-bath for 24 hr. The product was cooled, the solid separated, and the residue distilled. The fraction of b. p. 178–182°/760 mm. (lit.,<sup>22</sup> b. p. 178–179°) (48 g.) was collected. By a similar process using methyl iodide (50 c.c.), 3-methylpentane-2:4-dione was prepared, having b. p. 170–172°/760 mm. (56 g.).

*Ethyl 3-Acetyl-lævulale*.—The sodio-derivative of acetylacetone was treated with ethyl bromoacetate following Garner, Reddick, and Fink's directions.<sup>23</sup> The product was obtained as a colourless oil (48%), b. p. 165°/55 mm.

*Methyl 4-Acetyl-5-oxohexanoate*.—Acetylacetone was treated with methyl acrylate as described<sup>7</sup> for the ethyl ester. The product was a pale yellow oil (48%), b. p. 142–148°/14 mm. (lit.,<sup>24</sup> b. p. 153–155°/19 mm.).

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<sup>22</sup> von Auwers and Jacobsen, *Annalen*, 1921, **426**, 227.

<sup>23</sup> Garner, Reddick, and Fink, *J. Amer. Chem. Soc.*, 1909, **31**, 668.

<sup>24</sup> March, *Ann. Chim. (France)*, 1902, **26**, 333.