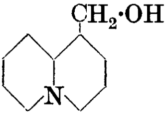
VI.—*New Derivatives of Pyrrole. Part I. The Synthesis of* 3-*Keto*-4 : 5-*dihydrodi*-(1 : 2)-*pyrrole and of* 8-*Keto*-5 : 6 : 7 : 8-*tetrahydropyrrocoline.*

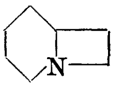
By GEORGE ROGER CLEMO and GEORGE ROWNTREE RAMAGE.

ALTHOUGH it is now known that the nitrogen atom is a common member of two fused ring systems, as in structure (I), in certain alkaloids of the berberine type, and Karrer and co-workers (*Helv. Chim. Acta*, 1928, **11**, 1067) have suggested that lupinine (I) has the same structural feature, the literature records little concerning the synthesis and properties of the simple parent ring systems.

Löffler and Plöcker (*Ber.*, 1907, **40**, 1310) claim to have synthesised substituted conidines, but apparently they failed to synthesise the parent substance (II). Later, Löffler and Kain (*Ber.*, 1909, **42**, 94) stated that δ-coniceine (1-piperolidine) (III) was obtained by the ring closure of β-(α-piperidyl)propionic acid, followed by reduction of the lactam by sodium.



(I.)



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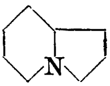
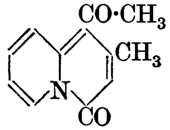


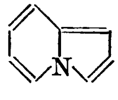
(III.)

Scholtz (*Ber.*, 1912, **45**, 734) obtained α-picolide, to which structure (IV) was assigned, from α-picoline and acetic anhydride, and it is claimed that treatment with hydrochloric acid gives pyrrocoline (V). Recently, Tschitschibabin and Stepanow (*Ber.*, 1927, **60**, 1607;

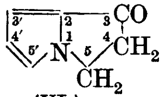
1930, **63**, 470) have obtained substituted pyrrocolines * from α-picoline and various acid anhydrides.



(IV.)



(V.)

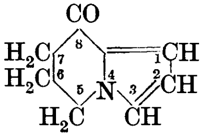


(VI.)

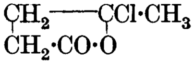
The yields obtained in most if not all of the above reactions are not stated or are poor, *e.g.*, the 5—6% yields in the condensations of α-picoline and acetaldehyde (Meisenheimer and Mahler, *Annalen*, 1928, **462**, 301) and propaldehyde (Löffler and Plöcker, *loc. cit.*) respectively.

The syntheses of 3-*keto*-4 : 5-*dihydrodi*-(1 : 2)-*pyrrole* (VI) and of 8-*keto*-5 : 6 : 7 : 8-*tetrahydropyrrocoline* (VIII) are now described, and it is hoped to record the development of this work, including the reduction of these compounds, in a subsequent communication.

(VII.)



(VIII.)



$$\begin{array}{l} CH_2\text{——}CCl\cdot CH_3 \\ CH_2\cdot CO\cdot O \end{array}$$

(IX.)

Pyrrole has been the starting point : it is surprising that advantage has not hitherto been taken of the combined activity of the α- and the acidic imino-hydrogen atom for synthetic work.

Potassium pyrrole has been prepared by an improved method, and its condensation with halogen-substituted aliphatic compounds and sulphonic esters studied. Ciamician (*Monatsh.*, 1880, **1**, 624) investigated the action of potassium pyrrole on chloroacetic acid in ether, but does not mention the isolation of pure 1-*pyrrylacetic acid*. It has now been found that condensations of the above type can be effected satisfactorily if benzene is used instead of ether. For example, potassium pyrrole and ethyl β-chloropropionate in benzene give a 40% yield of *ethyl* β-1-*pyrrylpropionate*, whereas none is obtained if ether is used. Hydrolysis of this ester with alcoholic potash gives β-1-*pyrrylpropionic acid*, but all attempts to effect ring closure to give (VI) have been unsuccessful.

The fact that E. Fischer's classical uric acid synthesis (*Ber.*, 1895, **28**, 2473) involved a lactam carbonyl group in the ring closure led to attempts to effect similar ring closure of *N*-substituted derivatives of succinimide, *e.g.*, *succino*-n-*butylimide*, but no success has been thus achieved.

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* These workers suggested the name indolizine for the parent structure (V), but we are advised to use the older system of nomenclature.

Attention was then directed to the condensation of potassium pyrrole with β-chloroethyl and β-cyanoethyl toluene-*p*-sulphonates (compare Clemo and Perkin, J., 1922, **121**, 642; Clemo and Walton, J., 1928, 723) and 1-β-*chloroethylpyrrole* and 1-β-*cyanoethylpyrrole* (VII) were thus obtained in yields of 7% and 60% respectively.

These results are linked with the question of the stability of these esters to sodium hydroxide (compare Clemo and Walton, *loc. cit.*) and indicate that potassium pyrrole condenses readily with compounds which are easily hydrolysed by alkalis. 1-γ-*Chloropropylpyrrole* was then prepared from potassium pyrrole and γ-chloropropyl toluene-*p*-sulphonate (*J. Amer. Chem. Soc.*, 1923, **45**, 842), but it was recovered unchanged after prolonged boiling with alcoholic potash, and treatment with aluminium chloride in light petroleum also failed to effect ring closure.

When 1-β-cyanoethylpyrrole was submitted to the Hoesch reaction, ring closure occurred to give (VI), which was most conveniently isolated by forming the *semicarbazone* and hydrolysing this with *N*/2-sulphuric acid in the presence of chloroform (compare Kon, J., 1930, 1616). A *piperonylidene* derivative has also been obtained, but (VI) does not give a hydrochloride or a methiodide.

Concurrently with the above, efforts were made to synthesise the fused six- and five-ring system (VIII). In the first place, β-carbethoxypropionyl chloride (compare Blaise, *Bull. Soc. chim.*, 1899, **21**, 645) was condensed with potassium pyrrole to give *ethyl* β-1-*pyrroylpropionate*, $C_4H_4N{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2Et$, but treatment of this with sodium in xylene and distillation with calcium chloride failed to remove alcohol. Next, the liquid obtained from lævulic acid and thionyl chloride, which has the properties of lævulyl chloride but may have the lactone structure (IX) (compare *Annalen*, 1890, **256**, 334), was condensed with potassium pyrrole, readily giving β-1-*pyrroylethyl methyl ketone*, $C_4H_4N{\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}CH_3$, as shown by the formation of a *phenylhydrazone* and a *semicarbazone*. Treatment of the ketone with acids and alkalis, however, always resulted in amide hydrolysis, as was also the case with ethyl β-1-pyrroylpropionate (above). Finally, γ-1-*pyrrylbutyronitrile* was prepared from potassium pyrrole and γ-bromobutyronitrile, this material being used because γ-cyanopropyl toluene-*p*-sulphonate could not be made from trimethylene cyanohydrin. When the butyronitrile was subjected to the Hoesch reaction, ring closure took place and 8-keto-5 : 6 : 7 : 8-tetrahydropyrrocoline (VIII) was obtained; it was isolated in the first instance as the *semicarbazone*, which gave the free ketone on hydrolysis. The compound readily gives a *piperonylidene* derivative, but not a methiodide.

EXPERIMENTAL.

Potassium Pyrrole.—Potassium (8 g.) was shaken with boiling xylene. To the cooled suspension, absolute alcohol (2 drops) was added, followed by freshly distilled pyrrole (13·4 g.) in small amounts, the reaction being allowed to cease after each addition. More pyrrole (5 g.) was then added to dissolve any remaining potassium, the mixture heated on the water-bath for an hour, and the xylene removed under reduced pressure, leaving potassium pyrrole (21 g.) as a white, highly deliquescent powder (Found : N, 13·0. Calc. : N, 13·3%).

Ethyl 1-*Pyrrylacetate and* 1-*Pyrrylacetic Acid.*—Potassium pyrrole (2·6 g.) was made into a paste with benzene (3 c.c.), and ethyl chloroacetate (3·2 g.) in benzene (3 c.c.) added slowly with constant mixing. When the vigorous reaction ceased, the mixture was heated on the water-bath for ½ hour, treated with water, and extracted with ether. The dried extract on fractionation gave *ethyl* 1-*pyrrylacetate* (1·0 g.), b. p. 112°/20 mm. (Found : C, 62·5; H, 7·35. $C_8H_{11}O_2N$ requires C, 62·7; H, 7·2%).

The ester was heated on a water-bath for 1 hour with excess of methyl-alcoholic potash (10%), water added, the methyl alcohol boiled off, and the solution acidified and extracted with ether. After removal of the ether, 1-*pyrrylacetic acid* remained as a yellow oil which solidified; crystallised from petroleum (b. p. 80—100°), it formed long colourless prisms, m. p. 91° (Found : C, 57·4; H, 5·65. $C_6H_7O_2N$ requires C, 57·6; H, 5·6%). The *amide*, prepared from the ester and concentrated aqueous ammonia, crystallised from xylene in needles, m. p. 169° (Found : C, 58·4; H, 6·5. $C_6H_8ON_2$ requires C, 58·1; H, 6·45%).

Ethyl β-1-*Pyrrylpropionate and* β-1-*Pyrrylpropionic Acid.*—Potassium pyrrole (5·2 g.) in the presence of benzene (6 c.c.) was condensed with ethyl β-chloropropionate (7·5 g.) in the same way as with the chloroacetate, and *ethyl* β-1-*pyrrylpropionate* (3·1 g.), b. p. 122°/23 mm., obtained (Found : C, 64·7; H, 7·8. $C_9H_{13}O_2N$ requires C, 64·7; H, 7·8%). The ester was hydrolysed with methyl-alcoholic potash (10%), and β-1-*pyrrylpropionic acid* obtained as colourless prisms, m. p. 62°, after crystallising from petroleum (b. p. 80—100°) (Found : C, 60·3; H, 6·5; N, 10·2. $C_7H_9O_2N$ requires C, 60·4; H, 6·5; N, 10·1%). The *amide* formed colourless prisms, m. p. 81°, from benzene (Found : C, 60·8; H, 7·4. $C_7H_{10}ON_2$ requires C, 60·9; H, 7·2%). The compound is readily soluble in cold water.

Succino-n-*butylimide.*—Succinimide (10 g.), dissolved in hot absolute alcohol (25 c.c.), was added to a solution of potassium ethoxide (3·9 g. of potassium in 25 c.c. of absolute alcohol), and *n*-butyl bromide (13·7 g.) slowly run in. The mixture was heated on the water-bath for 6 hours, the potassium bromide (12 g.) filtered off, and the filtrate fractionated; *succino*-n-*butylimide* (12·5 g.; 80% of the theoretical yield), b. p. 140°/17 mm., was obtained (Found: C, 61·9; H, 8·1. $C_8H_{13}O_2N$ requires C, 61·9; H, 8·4%).

1-β-*Chloroethylpyrrole.*—Potassium pyrrole (2·6 g.), benzene (3 c.c.), and β-chloroethyl toluene-*p*-sulphonate (5·9 g.) were mixed in one operation and the product was worked up as described for the β-cyano-compound (below); 1-β-*chloroethylpyrrole* (0·25 g.), b. p. 84°/20 mm., was obtained (Found: N, 11·0. C_6H_8NCl requires N, 10·8%).

1-β-*Cyanoethylpyrrole.*—β-Cyanoethyl toluene-*p*-sulphonate (2·8 g.) was well mixed with a suspension of potassium pyrrole (2·6 g.) in benzene (4 c.c.). When the vigorous reaction that took place had abated, a further 2·8 g. of the sulphonic ester were added and the mixture was heated on a water-bath for 1 hour. Water was then added, the mixture extracted with ether, and the extract dried and fractionated, giving 1-β-*cyanoethylpyrrole* (1·8 g.), b. p. 140°/20 mm. (Found: C, 70·2; H, 6·5; N, 23·6. $C_7H_8N_2$ requires C, 70·0; H, 6·7; N, 23·3%). The compound is insoluble in water, and is readily hydrolysed to β-1-pyrrylpropionic acid by boiling alcoholic potash.

1-γ-*Chloropropylpyrrole.*—Potassium pyrrole (2·6 g.), benzene (3 c.c.), and γ-chloropropyl toluene-*p*-sulphonate (6·2 g.) were mixed in one operation and gave 1-γ-*chloropropylpyrrole* (1·4 g.), b. p. 87°/15 mm., as a colourless oil which darkened rapidly on standing (Found: C, 58·6; H, 6·8. $C_7H_{10}NCl$ requires C, 58·5; H, 7·0%).

3-*Keto*-4 : 5-*dihydrodi*-(1 : 2)-*pyrrole* (VI).—A slow stream of dry hydrogen chloride was passed for 45 minutes through β-1-pyrrylpropionitrile (1 g.), dissolved in dry ether (7 c.c.) containing anhydrous zinc chloride (0·25 g.). The mixture was left over-night in a stoppered test-tube, the ether decanted, and the deliquescent pale yellow imino-hydrochloride added in small portions with thorough mixing to sodium acetate (5 g.) and semicarbazide hydrochloride (1 g.). Alcohol (4 c.c.) was added and after being heated for 1 hour on the water-bath the mixture was filtered, diluted with water (3 c.c.), and left over-night. The resulting crystalline *semicarbazone* (0·5 g.) was suspended in chloroform (50 c.c.) and well shaken with *N*/10-sulphuric acid (9 c.c.) for 6 hours, and again for a further hour after being left over-night. The chloroform layer was separated and dried, the solvent removed, and the residue distilled, giving a crystalline solid (0·2 g.), m. p. 54° [Found: C, 69·7, 69·5; H, 6·1, 5·9; N, 11·7; *M* (Rast), 119. C_7H_7ON requires

C, 69·4; H, 5·8; N, 11·6%; *M*, 121]. The *ketone* is fairly easily soluble in cold water (giving a solution neutral to litmus), moderately easily soluble in ether, but readily soluble in alcohol and chloroform. It gives the pine-shaving test for pyrrole and a purple colour reaction with *p*-dimethylaminobenzaldehyde. The compound is unchanged by treatment with nitrous acid.

The semicarbazone obtained from the pure ketone crystallised from alcohol in long, colourless, thin prisms, m. p. 211° (Found: C, 54·1; H, 5·9. $C_8H_{10}ON_4$ requires C, 53·9; H, 5·6%). The *piperonylidene* compound was prepared in alcohol containing a trace of solid sodium hydroxide and crystallised from the same solvent in pale yellow prisms, m. p. 194° (Found: C, 70·9; H, 4·3. $C_{15}H_{11}O_3N$ requires C, 71·15; H, 4·35%).

Ethyl β-1-*Pyrroylpropionate.*—β-Carbethoxypropionyl chloride (4·1 g.) in benzene (2 c.c.) was added slowly with thorough mixing to potassium pyrrole (2·6 g.) in benzene (5 c.c.). The mixture was then heated on the water-bath for 15 minutes, made alkaline with sodium bicarbonate, and extracted with ether. *Ethyl* β-1-*pyrroylpropionate* (1·2 g.) was obtained as a liquid, b. p. 162°/22 mm., which solidified on standing and then crystallised from petroleum (b. p. 40—60°) in stout colourless prisms, m. p. 50° (Found: C, 61·4; H, 6·5; N, 7·2. $C_{10}H_{13}O_3N$ requires C, 61·5; H, 6·7; N, 7·2%).

Lævulyl Chloride.—A mixture of thionyl chloride (10 c.c.) and lævulic acid (10 g.) was warmed gently until the evolution of hydrogen chloride ceased; it was then heated on a water-bath for an hour and fractionated, giving lævulyl chloride (9·6 g.), b. p. 84°/17 mm.

β-1-*Pyrroylethyl Methyl Ketone.*—Lævulyl chloride (3·4 g.) in benzene (3 c.c.) and potassium pyrrole (2·6 g.) in benzene (3 c.c.) were condensed as in the case of ethyl β-1-pyrroylpropionate (above) and gave the *ketone* (1 g.), b. p. 148°/16 mm. (Found: N, 8·7. $C_9H_{11}O_2N$ requires N, 8·5%). The *phenylhydrazone* had m. p. 131° (Found: C, 71·0; H, 6·8. $C_{15}H_{17}ON_3$ requires C, 70·6; H, 6·7%), and the *semicarbazone*, m. p. 190° (Found: C, 54·0; H, 6·4. $C_{10}H_{14}O_2N_4$ requires C, 54·1; H, 6·3%).

γ-1-*Pyrrylbutyronitrile.*—γ-Bromobutyronitrile (3·7 g.) and potassium pyrrole (2·6 g.) in benzene (3 c.c.) were condensed and gave γ-1-*pyrrylbutyronitrile* (0·65 g.), b. p. 152°/23 mm. (Found: N, 20·7. $C_8H_{10}N_2$ requires N, 20·9%).

8-*Keto*-5 : 6 : 7 : 8-*tetrahydropyrrocoline* (VIII).—γ-1-Pyrrylbutyronitrile (1 g.) under the same conditions as for the preparation of (VI) above, gave a *semicarbazone* (0·7 g.), which was hydrolysed by shaking it for 6 hours with *N*/2-sulphuric acid (7 c.c.) in the presence of chloroform (70 c.c.). After removal of the chloroform the residue was distilled in a vacuum; the distillate (0·2 g.)

solidified on cooling, and crystallised from petroleum (b. p. 80—100°) in faintly yellow prisms, m. p. 34° (Found: C, 71·2; H, 6·7. C_8H_9ON requires C, 71·1; H, 6·7%). The *ketone* gives the pine-shaving test for pyrrole and a light purple colour reaction with *p*-dimethylaminobenzaldehyde. The semicarbazone crystallises from alcohol in plates, m. p. 193° (Found: C, 56·1; H, 6·2. $C_9H_{12}ON_4$ requires C, 56·25; H, 6·25%). The *piperonylidene* compound crystallises from alcohol in yellow prisms, m. p. 136° (Found: C, 71·7; H, 5·1. $C_{16}H_{13}O_3N$ requires C, 71·9; H, 4·9%).

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