334.—*Some Derivatives of 3-Ethylpyridine and 2 : 3-Furano(2′ : 3′)pyridine.*

By Robert Robinson and J. S. Watt.

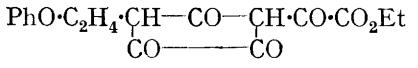
The substances herein described have all been obtained in the course of various attempts to synthesise meroquinenine or an equivalent substance which could be utilised as a starting point for synthetical work. Some promising routes have been developed, but the poor overall yields have usually set a limit to their useful exploitation and an entirely satisfactory method is still to be found.

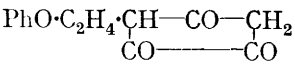
The account must necessarily cover a somewhat diverse range of topics and the following are the chief points.

(1) ββ′-*Dicyanodiethylaniline* has been prepared from the related glycol and dichloro-derivative. It is very stable towards basic catalysts and exhibits no tendency towards ring closure (Thorpe reaction).

(2) An attempt to prepare β-phenoxyethylchelidonic acid failed because the condens-

ation of γ-phenoxypropyl methyl ketone and ethyl oxalate did not yield a derivative of ethyl acetonedioxalate but a cyclic *ketone* (I).

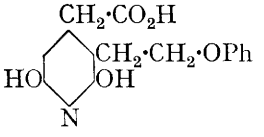
(I.) 

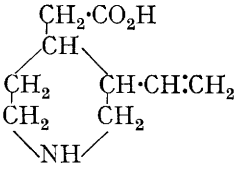
 (II.)

Diels, Sielisch, and Müller (*Ber.*, 1906, **39**, 1328) have observed analogous reactions. On hydrolysis by means of aqueous alcoholic hydrochloric acid, the *triketone* (II) was obtained. The acidic properties of the latter substance make it evident that an enolic modification is the stable form; this is not represented in the formulæ on account of the difficulty of deciding the position of the hydroxyl group. Further, the properties of (II) exclude the unsaturated lactone alternative formula.

(3) It seemed feasible to apply the 2 : 6-dihydroxypyridine synthesis of Rogerson and Thorpe (J., 1905, **87**, 1685) to ethyl acetonedicarboxylate and ethyl cyanoacetate, but this project could not be realised, according to either the original conditions, or those of Rogerson and Thorpe (J., 1908, **89**, 658), or of Kon and Nanji (J., 1931, 566).

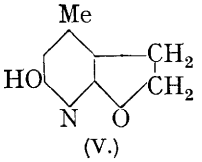
We therefore turned to condensations of ethyl α-cyano-γ-phenoxybutyrate with ethyl muconate (compare Farmer, J., 1927, 1065; 1930, 1614; 1931, 1762), with ethyl β-chloroglutarate and with ethyl β-chloroglutaconate. The last reaction gave the best result and we obtained the pyridine acid (III) as a hydrochloride by hydrolysis of the product.

(III.) 

 (IV.)

Unfortunately, this acid proved to be very intractable and a method for the reduction of the pyridine nucleus was sought in vain. The relation of the substance to meroquinenine (IV) is, however, so close that further work in this direction has been planned.

(4) A method of protection of the oxygen in the side chain that seemed worth prosecuting was that suggested by the isolation of a dihydrofuranopyridine (V) as a by-product of the hydrolysis of the condensation product of ethyl potassio-α-cyano-β-methylglutaconate and β-phenoxyethyl iodide (Matejka, Robinson, and Watt, J., 1932, 2020). This method of preparation, however, could not be developed to a practicable extent. Accordingly we have devised other methods for the synthesis of simple representatives of the furanopyridine group.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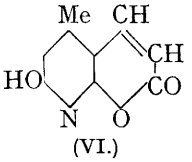
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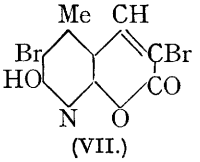
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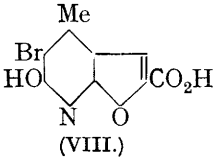
2 : 6-Dihydroxy-4-methylpyridine (Rogerson and Thorpe, J., 1905, **87**, 1685) condenses with malic acid in the presence of sulphuric acid at 100° with formation of the *hydroxymethylpyridino-α-pyrone* (VI) in approximately 50% yield (v. Pechmann's coumarin synthesis). Bromination of this substance or its *O*-benzoyl derivative in neutral solvents was not a convenient operation, but in acetic acid solution a *dibromo*-derivative (VII) was produced. The coumarilic acid-type rearrangement (compare W. H. Perkin, sen., *Z. Chem.*,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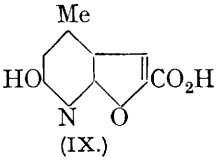
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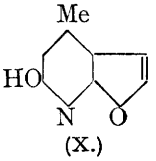
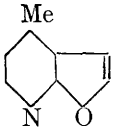

(X.)

1871, **7**, 178; Fittig and Ebert, *Annalen*, 1883, **216**, 163) was brought about by the action of alcoholic potassium hydroxide and the *product* (VIII) was reduced by means of zinc dust and sodium hydroxide to the *hydroxymethylfuranopyridinecarboxylic acid* (IX), which was decarboxylated by heating with a mixture of hydrochloric and acetic acids after other methods had been found to fail. The *hydroxyfuranopyridine* (X) could not be directly reduced, but the hydroxyl group was replaced successively by a chlorine atom, the hydrazino-group, and a hydrogen atom, with eventual formation of 4-methyl-2 : 3-furano-(2′ : 3′)pyridine (XI).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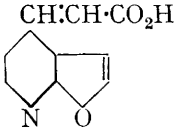
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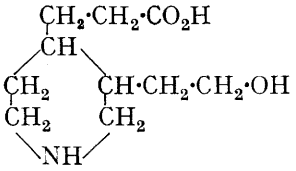
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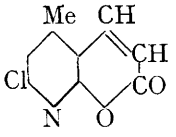
We confidently anticipated that, by known methods, this base could be converted into (XII) and (XIII), but under all conditions tried the initial condensation with chloral could not be effected; the methyl group appears to be inactive. It is therefore proposed to continue the investigation starting with a carboxyl group already *in situ* in the 4-positioned side chain.

The action of phosphoryl chloride on the hydroxymethylpyridinopyrone (VI) furnishes the *chloro*-compound (XIV) and on reduction with hydriodic acid and phosphorus, β-(*2-hydroxy-4-methyl-3-pyridyl*)*propionic acid* (XV) is obtained. Zinc and hydrochloric acid, however, reduce the double bond only and again the lactone ring is opened; the *product* has the formula (XVI). Chlorination of (XV) by means of phosphoryl chloride furnishes the acid (XVII), which appears to possess a considerable degree of stability towards hydriodic acid and phosphorus, as it was only obtained pure after vigorous treatment with these reagents.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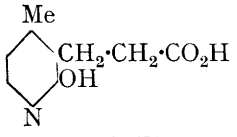
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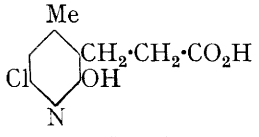
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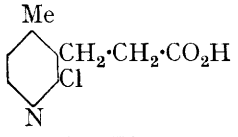
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Experimental.

ββ′-*Dichlorodiethylaniline*.—Phosphorus pentachloride (60 g.) was added in small portions with cooling to a solution of ββ′-dihydroxydiethylaniline (50 g., redistilled in a vacuum; m. p. 54°) in chloroform (100 c.c.). A very vigorous reaction occurred, the chloroform boiled, and the flask was immersed in cold water. When the reaction had subsided, the mixture was heated on the steam-bath until no more hydrogen chloride was evolved (2—3 hours). The chloroformic solution was then mixed with ice-water, and the chloroform layer separated, washed with water, dried, and distilled, a fraction, b. p. 164°/14 mm., being collected. After 2 days, the distillate solidified and on recrystallisation from methyl alcohol was obtained as colourless stout prisms, m. p. 45° (yield, 45 g. or 75%) (Found: C, 55·3; H, 5·7; Cl, 33·8. $C_{10}H_{13}NCl_2$ requires C, 55·1; H, 5·9; Cl, 32·6%).

ββ′-*Dicyanodiethylaniline*.—Potassium cyanide (40 g. in 70 c.c. of water) was gradually added to a boiling solution of ββ′-dichlorodiethylaniline (40 g.) in methyl alcohol (200 c.c.). The solution was refluxed for 6 hours; the chloride gradually passed into solution and potassium chloride was precipitated. Most of the solvent was distilled and the oil which separated on addition of water to the residue solidified almost immediately to a brownish-white mass. Recrystallised many times from alcohol or alcohol–ether, the colourless plates had m. p. 81°, not raised by further crystallisation from benzene–light petroleum. The substance is sparingly soluble in ether and light petroleum, but readily soluble in most other solvents and in acids of moderate concentration (Found: C, 72·2; H, 6·9; N, 20·8. $C_{12}H_{13}N_3$ requires C, 72·4; H, 6·5; N, 21·1%).

The *dinitrile* is a very stable substance. It was recovered unchanged after refluxing for several hours with absolute alcoholic sodium ethoxide (0·1 mol.), and after several hours' boiling with 20% hydrochloric acid. On heating with caustic soda solution, the oily layer of dinitrile gradually dissolved and ammonia was evolved. Attempts to induce ring closure by means of sodium in toluene suspension in hot diethylaniline were not successful. Dry hydrogen chloride was passed through an absolute alcoholic solution of the dinitrile for some time, but there was no apparent change. On heating, however, a rapid separation of ammonium chloride occurred and after 2 hours the contents of the flask were poured into water and the oil which separated was collected by means of ether and distilled, giving (1) b. p. 55—60°/15 mm., (2) b. p. 140—160°/15 mm., and a gummy residue. On redistillation at the ordinary pressures, (1) had b. p. 162—163° and was identified as ethyl β-chloropropionate, b. p. 162—163°/760 mm. Fraction (2) was redistilled in a vacuum, but it again boiled over a wide range and no pure sample could be secured. No picrate or picrolonate could be obtained, but it probably consisted essentially of ethyl β-anilinopropionate.

5-β-*Phenoxyethyl*cyclo*pentane*-1 : 3 : 4-*trione*-2-*oxalate* (I).—γ-Phenoxypropyl methyl ketone was obtained by the method of Boyd-Barrett and Robinson (J., 1932, 318); the intermediate *ethyl γ-phenoxy-α-acetylbutyrate* was isolated, b. p. 195°/30 mm. (Found: C, 67·0; H, 7·3. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). The ketone obtained on hydrolysis was condensed with ethyl oxalate according to the prescription of Willstätter and Pummerer (*Ber.*, 1904, **37**, 3734) for the preparation of ethyl acetonedioxalate. Sodium (2·3 g.) was dissolved in absolute alcohol (33 c.c.), and the solution divided into two equal parts. To one, a mixture of γ-phenoxypropyl methyl ketone (7·9 g.) and ethyl oxalate (8 g.) was added with shaking and cooling. A further amount of ethyl oxalate (8 g.) and the second half of the alcoholic sodium ethoxide were then added and the flask was heated without a condenser in an oil-bath at 110°. As the alcohol distilled, the contents of the flask gradually solidified and were occasionally stirred. After 30 minutes the cooled melt was decomposed by means of dilute hydrochloric acid and an abundant crop of crystals (11 g.) was obtained; recrystallised from alcohol, clusters of very small plates, m. p. 145°, were formed (Found: C, 61·3; H, 4·9. $C_{17}H_{16}O_7$ requires C, 61·4; H, 4·8%). The substance is acid to litmus and methyl-orange, and gives a dark green ferric reaction in alcoholic solution.

5-β-*Phenoxyethyl*cyclo*pentane*-1 : 3 : 4-*trione* (II).—The ester was hydrolysed by refluxing for 2—3 hours with concentrated hydrochloric acid containing sufficient alcohol to dissolve the oil at the boiling point. A small amount of tar separated, the liquid was filtered hot and the filtrate, on cooling, deposited needles. Recrystallisation from aqueous alcohol afforded colourless needles, m. p. 119·5° (Found: C, 67·1; H, 5·3. $C_{13}H_{12}O_4$ requires C, 67·2; H, 5·2%). The substance is acidic to litmus and methyl-orange, gives a light reddish-brown ferric reaction, and is readily soluble in alcohol.

Attempts to prepare Derivatives of Succinacetic Ester.—These can be briefly mentioned. The condensation product of ethyl sodio-γ-phenoxy-α-acetylbutyrate and β-carbomethoxypropionyl chloride furnished, on carefully graduated hydrolysis with aqueous sodium hydroxide, only γ-phenoxybutyric acid, m. p. 62° (Found: C, 66·7; H, 6·8. Calc. for $C_{10}H_{12}O_3$: C, 66·7; H, 6·7%). The product of condensation of ethyl sodioacetoacetate and carbomethoxypropionyl chloride (30 g.) in dry ether had b. p. 148—150°/20 mm. (yield, 18·2 g.) and on hydrolysis with cold 2% aqueous sodium hydroxide it furnished the acid, $Me{\cdot}CO{\cdot}CH(CO_2Et){\cdot}CO{\cdot}CH_2{\cdot}CH_2{\cdot}CO_2H$, which crystallised from light petroleum in colourless prisms, m. p. 82·5° (Found: C, 52·5; H, 6·2. Calc. for $C_{10}H_{14}O_6$: C, 52·2; H, 6·1%). This acid has been previously obtained by Scheiber (*Ber.*, 1911, **44**, 2423) as a reaction product from ethyl sodioacetoacetate and succinyl chloride. More vigorous hydrolysis broke up the molecule too completely and we were unable to obtain the desired succinacetic ester by splitting off the acetyl group alone.

The methods of hydrolysis tried were the action of ammonium chloride with or without ammonia on the sodio-derivative (cf. Claisen, *Annalen*, 1906, **291**, 70) and shaking the ethereal solution of the ester with concentrated ammonia for an hour (cf. Borsche and Blount, *Ber.*, 1930, **63**, 2419).

Finally, the attempted condensation of ethyl fumarate and ethyl acetate by means of sodium gave ethyl acetoacetate and a black viscous residue which set to a glassy resin.

Ethyl α-Cyano-γ-phenoxybutyrate.—After numerous experiments the following conditions, based on the method of G. M. Robinson (J., 1924, **125**, 226), were adopted. A mixture of β-phenoxyethyl bromide (40 g.), cyanoacetic ester (113 g.), and anhydrous potassium carbonate (28 g.) was refluxed under 40—60 mm. pressure (oil-bath at 130—140°) for 4 hours. The temperature was then raised to 140—150° for 30 minutes and the oil which separated on the addition

of water was collected by means of ether and distilled, b. p. 190—195°/14—15 mm. (yield, 41·5 g. or 90%) (Found: C, 67·0; H, 6·4. $C_{13}H_{15}O_3N$ requires C, 66·9; H, 6·4%). The sodio-derivative of this ester was condensed in alcoholic solution with ethyl β-chloroglutarate (obtained by the method of Dreifuss and Ingold, J., 1923, **123**, 2964, from dichlorohydrin, but only in 10% yield instead of the 75% reported; some important detail must have been omitted from the description), but the expected condensation product, b. p. *ca.* 200°/0·2 mm., gave no crystalline products on hydrolysis.

Condensation of Ethyl α-Cyano-γ-phenoxybutyrate and Ethyl Muconate.—Ethyl cyanophenoxybutyrate (24 g.) was added to alcoholic sodium ethoxide (0·375 g. of sodium in 15 c.c.), and dry ether introduced until a faint turbidity appeared; ethyl muconate (20 g.) was then added, and the mixture refluxed for 6—8 hours. Acetic acid (1 g.) and water (10 c.c.) were then added with vigorous shaking and the ethereal solution was washed, dried, and distilled, giving unchanged materials (22 g.) and a very viscous yellow oil (18·5 g.), b. p. 212°/0·2 mm. (Found: C, 64·1; H, 6·6; N, 3·5. $C_{23}H_{29}O_7N$ requires C, 64·0; H, 6·7; N, 3·3%). The pale yellow oil is doubtless *ethyl α-cyano-α-β-phenoxyethyl-β-carbethoxymethyladip-γδ-enate.*

Hydrolysis. The use of sulphuric acid as recommended in similar cases was not successful and a better method was the following. The crude product of the reaction after the removal of unchanged initial material was used for the hydrolysis. The addition product (10·8 g.) and potassium hydroxide (12·5 g.) were dissolved in methyl alcohol (130 c.c.) and heated on the steam-bath until a sample was completely soluble in water (*ca.* 2 hours). The solvent was then removed, water and hydrochloric acid added to the residue, and the separated oil was collected by ether and solidified after trituration with light petroleum. It is freely soluble in most organic solvents with the exception of benzene and light petroleum, but cannot be crystallised from these media. Finally, and after great difficulty, the acid was purified by many recrystallisations from water containing a little acetic acid (charcoal). The white crystals, m. p. 137—138°, are acid to litmus and exhibit no iron reaction (Found: N, 4·0. $C_{17}H_{17}O_7N$ requires N, 4·0%). The estimation of carbon was unsatisfactory and the amount of pure acid obtained was very small. In the hope of improving the method by altering the order of the stages, the addition of cyanoacetic ester to muconic ester was studied, but without useful outcome.

Condensation of Ethyl Sodiocyanophenoxybutyrate with Ethyl β-Chloroglutaconate.—Ethyl β-chloroglutaconate was prepared from citric acid by the method of Ingold and Nickolls (J., 1922, **121**, 1642. See also Pechmann, *Ber.*, 1887, **20**, 147). Ethyl cyanophenoxybutyrate (31 g. and 100 c.c. of alcohol) was added to a solution of sodium ethoxide (sodium, 3·1 g., and alcohol, 40 c.c.), and ethyl β-chloroglutaconate (29·7 g. and 10 c.c. of alcohol) was then introduced with cooling in ice-water. A vigorous reaction set in and the alcohol finally boiled; the mixture was heated on the steam-bath for 30 minutes, then poured into water, and the oil which separated was collected by means of ether (yield, almost quantitative). The viscous oil was usually hydrolysed immediately as described below; a sample was obtained as a light yellow oil, b. p. *ca.* 210°/0·2 mm. (Found: C, 65·2; H, 7·1. $C_{22}H_{27}O_7N$ requires C, 63·3; H, 6·5%. $C_{19}H_{23}O_5N$ requires C, 66·1; H, 6·7%). Hence the main constituent of the product has the formula $PhO{\cdot}C_2H_4{\cdot}CH(CN){\cdot}C(CH_2{\cdot}CO_2Et){:}CH{\cdot}CO_2Et$.

Hydrolysis of the above Condensation Product. Formation of the Hydrochloride of 2 : 6-Dihydroxy-3-(β-phenoxyethyl)pyridyl-4-acetic Acid (III).—The crude oil from the above condensation was boiled with a large excess of concentrated hydrochloric acid for 10—12 hours. The solution was concentrated and, on cooling, the hydrochloride of the dihydroxypyridine acid separated together with tar. The solid was collected and extracted with moderately concentrated hydrochloric acid as often as required, and, on cooling these extracts, the hydrochloride separated as white crystals (yield, 13 g. from 30 g. of chloroglutaconic ester). The substance recrystallised from acetic acid in colourless prisms, m. p. 146° (decomp.) (Found: C, 55·1; H, 4·9; N, 4·4. $C_{15}H_{16}O_5NCl$ requires C, 55·3; H, 4·9; N, 4·3%) with the properties of a 2 : 6-dihydroxypyridine. It gives a reddish-brown coloration with ferric chloride, and in alkaline media it turns green on exposure to air; it also stains the skin purple. The free base was obtained as a viscous oil that could not be crystallised.

The action of phosphoryl chloride and of thionyl chloride on this salt gave only amorphous products and no homogeneous methyl ether was obtained by treating it with diazomethane.

Bromination afforded colourless elongated prisms, m. p. 187—188° (decomp.) (Found: C, 31·3; H, 2·5; Br, 48·8%), which seem to be a mixture of tribromo- and tetrabromo-compounds. This substance could not be chlorinated (replacement of OH). Attempted reductions of the dihydroxypyridine acid were also made in several promising directions, but without useful result.

Lactone of β-(2 : 6-*Dihydroxy*-4-*methyl*-3-*pyridyl*)*acrylic Acid* (VI).—Malic acid (22 g.) was added to a mixture of 2 : 6-dihydroxy-4-methylpyridine (20 g.) and concentrated sulphuric acid (60 c.c.), and the whole heated on a steam-bath for 5—6 hours, precautions being taken against frothing. The deep brown solution was then cooled and poured into water; almost immediately a light brown solid began to separate. After cooling and keeping for some hours, the substance was collected and dried at 100° (yield, about 50%). It crystallised from 96% alcohol, in which it was sparingly soluble, or from acetic acid, in colourless needles, m. p. 295—296° (Found: C, 61·1; H, 3·9; N, 8·1. $C_9H_7O_3N$ requires C, 61·0; H, 4·0; N, 7·9%). The substance develops a reddish-brown coloration with alcoholic ferric chloride; it is soluble in moderately concentrated acids, and readily soluble in alkalis.

The *benzoyl* derivative could not be prepared by the Schotten–Baumann method, and benzoylation was therefore carried out in pyridine solution by means of an excess of benzoyl chloride. The crude product was collected, washed free from pyridine, and crystallised from alcohol, forming long colourless needles, m. p. 209° (yield, 70—75%) (Found: N, 5·1. $C_{16}H_{11}O_4N$ requires N, 5·0%). The substance gives no coloration with alcoholic ferric chloride.

Lactone of α-*Bromo*-(5-*bromo*-2 : 6-*dihydroxy*-4-*methyl*-3-*pyridyl*)*acrylic Acid* (VII).—(A) As the above benzoyl derivative is very sparingly soluble in the usual neutral solvents, bromination was effected without solvent or in acetic acid solution. In the former case an excess of bromine was added cautiously and with cooling; heat was evolved and hydrogen bromide was produced, giving evidence of substitution. After a short time the clear liquid solidified; alcohol was then added and the product separated as a yellow sandy powder, which was washed with alcohol and recrystallised from much glacial acetic acid, forming minute, light yellow cubes, decomposing at *ca.* 297° (Found: Br, 46·8. $C_9H_5O_3NBr_2$ requires Br, 47·7%).

(B) The product obtained by brominating the pyridinopyrone itself was the same as that obtained from the benzoyl derivative, proving that the latter had been hydrolysed during the process. Various conditions were tried in the hope of confining the halogenation to the pyrone nucleus, but in all cases a bromine atom was introduced into the pyridine nucleus as well. Thus bromination in hot or cold acetic acid and in pyridine produced the same substance. Finally the following method was adopted for the preparation of the derivative.

The lactone (17·7 g.) was dissolved in the minimum quantity of hot acetic acid, and bromine (12·8 c.c.) in acetic acid (25 c.c.) was added in small portions with constant stirring. Hydrogen bromide was copiously evolved and very soon a voluminous, sandy, reddish-yellow deposit was formed and after keeping for a few hours this was collected and well washed with alcohol. The solution deposited a little more of the product on long keeping (yield, 30·4 g. or 91%). Recrystallised from acetic acid, it had m. p. 298° (decomp.) and was identical in all respects with the product from the benzoyl derivative (A) (Found: C, 32·7; H, 1·9; Br, 46·8. $C_9H_5O_3NBr_2$ requires C, 32·2; H, 1·5; Br, 47·7%).

5-*Bromo*-6-*hydroxy*-4-*methyl*-2 : 3-*furano*(2′ : 3′)*pyridine*-5′-*carboxylic Acid* (VIII).—The bromo-derivative was boiled for 2 hours with an excess of ethyl-alcoholic potash, much flocculent material separating. Water was added to dissolve the solid; when the solution was acidified with hydrochloric acid, voluminous crystals separated. The substance crystallised from acetic acid, in which it was sparingly soluble, in colourless pointed prisms which decomposed without melting at 245° (Found: C, 39·6; H, 2·7; Br, 28·6. $C_9H_6O_4NBr$ requires C, 39·7; H, 2·2; Br, 29·0%) and gave a positive ferric reaction.

6-*Hydroxy*-4-*methyl*-2 : 3-*furano*(2′ : 3′)*pyridine*-5-*carboxylic Acid* (IX).—(A) The bromo-acid (3 g.) was dissolved in 10% aqueous sodium hydroxide (70 c.c.), zinc dust (10 g.) added, and the whole refluxed for 4 hours. The filtered solution was acidified, giving a very fine, white precipitate, which was recrystallised from acetic acid, forming clusters of needles, m. p. 278° (decomp.) (Found: C, 55·9; H, 3·8; N, 7·5. $C_9H_7O_4N$ requires C, 56·0; H, 3·6; N, 7·3%). The following details refer to the combination of two stages.

(B) The dibromo-pyridinopyrone (12·5 g.) was heated with 10% aqueous sodium hydroxide (250 c.c.) for 30 minutes, zinc dust (10 g.) was then introduced, and the heating continued for a further 3—4 hours. The filtered solution was cooled, and the acid isolated (6·7 g. or 93%), m. p. 278° (decomp.).

6-*Hydroxy*-4-*methyl*-2 : 3-*furano*(2′ : 3′)*pyridine* (X).—Ordinary methods of decarboxylation were tried but did not succeed and it was then found that loss of carbon dioxide occurred in concentrated sulphuric acid solution. The yield was bettered by the use of concentrated hydrochloric acid and the following method gave still improved results.

A mixture of the furanopyridinecarboxylic acid (14 g.), acetic acid (120 c.c.), and concentrated hydrochloric acid (40 c.c.) was refluxed; the solid gradually disappeared with frothing and

solution was complete in 30 minutes. The cooled liquid was diluted with water, and sufficient ammonia added to neutralise only the hydrochloric acid present. The solid was collected, dried, and extracted with hot ethyl acetate, which dissolved the desired product and left an amorphous residue. The recovered material crystallised from alcohol in plates, m. p. 203° (Found : C, 64·4; H, 4·8; N, 9·5. $C_8H_7O_2N$ requires C, 64·4; H, 4·7; N, 9·4%).

This *hydroxymethylfuranopyridine* is a moderately strong acid and even decomposes sodium carbonate in aqueous solution. It develops a reddish-brown coloration with alcoholic ferric chloride and is very readily converted into amorphous material when subjected to the action of reagents.

6-*Chloro*-4-*methyl*-2 : 3-*furano*(2′ : 3′)*pyridine*.—The reduction of the substance last described was attempted by means of heating with zinc dust in a stream of hydrogen. On the cooler parts of the tube a crystalline product separated in very small amount, recognised as unchanged hydroxy-compound. In addition, there was a substance of pyridine-like odour, which was later obtained by other methods of reduction and recognised as the hydroxyl-free base.

Attempts were made to replace the hydroxyl group by chlorine with the help of phosphorus pentachloride and a little phosphoryl chloride at 120—130°, but only amorphous material was obtained. Refluxing with phosphoryl chloride alone gave mainly unchanged initial material together with a little decomposition product.

Finally chlorination by means of phosphoryl chloride in a sealed tube was successful. The hydroxyfuranopyridine was heated with twice its weight of phosphoryl chloride for 4 hours at 170—180°. The contents of the tube were poured carefully into ice-water; a dark oil separated, and solidified on cooling. The crude material was extracted with light petroleum (b. p. 40—60°) and the chloro-derivative was obtained on concentration in a pure condition as beautiful clusters of long thin plates, m. p. 45°, not changed by recrystallisation (yield, 40% but variable) (Found : C, 57·3; H, 3·7; Cl, 21·3. C_8H_6ONCl requires C, 57·3; H, 3·6; Cl, 21·2%). The substance is readily soluble in the cold in ether, alcohol, benzene and to a lesser extent in light petroleum; it is soluble in moderately concentrated hydrochloric acid but is insoluble in alkalis; it gives no ferric reaction.

6-*Hydrazino*-4-*methyl*-2 : 3-*furano*(2′ : 3′)*pyridine*.—Chloromethylfuranopyridine (4·3 g.) was refluxed with hydrazine hydrate (30 c.c. of 95%) for 4 hours. The oil gradually entered into reaction; an appreciable amount undissolved was found to be the hydrazino-derivative and not unchanged initial material. On cooling and keeping, almost all of the *hydrazine* separated in clusters of needles, which were recrystallised from benzene–light petroleum, forming very pale yellow, fine needles, m. p. 88·5° (yield, 88%) (Found : C, 59·1; H, 5·4; N, 25·6. $C_8H_9ON_3$ requires C, 58·9; H, 5·4; N, 25·8%). The substance reduces Fehling's solution readily.

4-*Methyl*-2 : 3-*furano*(2′ : 3′)*pyridine* (XI).—A solution of copper sulphate (16 g.) in water (50 c.c.) was added to one of the hydrazine (2 g.) in a little acetic acid. Nitrogen was evolved slowly in the cold, but rapidly, with the production of troublesome emulsions, on gentle heating; when no more gas was evolved, the solution was basified with ammonia, filtered, and the filtrate extracted 3 or 4 times with ether. On removal of the ether there remained an oil (1 g.) with an odour resembling that of pyridine, b. p. 118°/20 mm. The *picrate*, prepared in alcoholic solution, crystallised from alcohol as yellow rhombic plates, m. p. 151° (Found : C, 46·5; H, 2·8; N, 15·4. $C_8H_7ON,C_6H_3O_7N_3$ requires C, 46·4; H, 2·8; N, 15·5%). Copper acetate was also used for the oxidation, with inferior results.

Attempts to condense 4-methyl-2 : 3-furano(2′ : 3′)pyridine with chloral were made without solvent, by heating the oily base with a large excess of chloral together with a trace of zinc chloride for 18 hours at 80°. The brown oily product yielded the picrate, m. p. 151°, described above.

The condensation was also attempted in *iso*amyl acetate solution, but again without success.

Lactone of β-(2 : 6-*Dihydroxy*-4-*methyl*-3-*pyridyl*)*acrylic Acid* (XIV).—The hydroxy-lactone (4·3 g.) and phosphoryl chloride (15 c.c.) were heated at 150—160° for 4 hours in a sealed tube, and the reddish-purple liquid decomposed by ice-water. A copious precipitate of a reddish-coloured crystalline solid separated and on crystallisation from alcohol (norite) it separated as long, pale yellow needles, m. p. 175° (Found : C, 55·2; H, 3·0; N, 6·8; Cl, 18·1. $C_9H_6O_2NCl$ requires C, 55·3; H, 3·1; N, 7·2; Cl, 18·2%). The substance gives no coloration with alcoholic ferric chloride; it is soluble in moderately concentrated acids and readily soluble in cold dilute alkalis.

β-(2-*Hydroxy*-4-*methyl*-3-*pyridyl*)*propionic Acid* (XV).—The chloro-compound (1 g.) along with hydriodic acid (10 c.c., *d* 1·7) and a little red phosphorus was refluxed for 18 hours. Water was added to the clear solution, which was filtered and evaporated on the steam-bath, almost to

dryness. Water was then added, and the solution basified with ammonia and made acid with acetic acid. The brownish-yellow precipitate crystallised from alcohol (norite) as irregular plates, m. p. 214° (Found : C, 59·2; H, 6·0; N, 7·7. $C_9H_{11}O_3N$ requires C, 59·7; H, 6·1; N, 7·7%). The substance is acid to litmus, soluble in both aqueous acids and alkalis, and gives a ferric reaction. It does not yield a picrate in alcoholic solution. The yield in the reduction is good.

6-*Chloro*-β-(2-*hydroxy*-4-*methyl*-3-*pyridyl*)*propionic Acid* (XVI).—The chloro-compound (1 g.) and zinc dust (3 g.) were added to dilute hydrochloric acid and when all the zinc had dissolved the solution was made alkaline with ammonia, acid with acetic acid, and extracted several times with ether. After removal of the solvent the small residual solid crystallised from alcohol in irregular plates, m. p. 204—206° (Found : C, 50·3; H, 4·9; N, 6·3. $C_9H_{10}O_3NCl$ requires C, 50·1; H, 4·7; N, 6·5%). The substance gives a ferric reaction and possesses acidic properties.

β-(2-*Chloro*-4-*methyl*-3-*pyridyl*)*propionic Acid* (XVII).—Hydroxymethylpyridylpropionic acid (1 g.) was heated with phosphoryl chloride (5 c.c.) in a sealed tube at 210° for 4 hours. The product was decomposed with ice-water, and the solution was basified with ammonia, filtered from amorphous dark brown material, acidified with acetic acid, and extracted several times with ether. After evaporation of the solvent, the residual oil solidified (0·5 g.) on trituration with light petroleum. Alcohol dissolved most of the solid and the residue after recrystallisation from alcohol gave a very small amount of a substance, m. p. 142—143°, not further investigated owing to the small yield. The more soluble constituent crystallised from benzene–light petroleum (b. p. 60—80°) in long prisms, m. p. 101° (Found : C, 59·3; H, 4·7; Cl, 11·6%). It is probable that this specimen was a mixture of $C_9H_{10}O_2NCl$ (see below) and $C_9H_9O_2N$ (C, 66·3; H, 5·5%), the latter being the composition of the lactone of hydroxymethylpyridylpropionic acid. When the substance, m. p. 101°, was submitted to the action of boiling hydriodic acid and phosphorus, and the product isolated by means of ether and crystallised from benzene–light petroleum, an acid, m. p. 128°, was obtained (Found : C, 54·1; H, 5·1; N, 7·0; Cl, 18·2. $C_9H_{10}O_2NCl$ requires C, 54·1; H, 5·0; N, 7·0; Cl, 17·8%). The hydriodic acid and phosphorus had brought about no essential change, but the process merely acted as a method of purification.

THE DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, August 9th*, 1934.]