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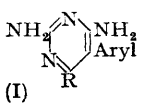
713. *Synthesis of* 2 : 6-*Diamino*-3-*arylpyridines.*

By B. H. Chase and James Walker.

2 : 6-Diamino-3-phenylpyridine and 2 : 6-diamino-3-*p*-chlorophenylpyridine were required for examination for antimalarial activity in view of their relation to other highly active compounds. Methods for their synthesis *via* 3-aryl-2 : 6-dihydroxypyridines are described.

The outstanding antimalarial activity of 2 : 4-diamino-5-arylpyrimidines (I; R = H or alkyl) (Falco, Goodwin, Hitchings, Rollo, and Russell, *Brit. J. Pharmacol.*, 1951, **6**, 185; Chase, Thurston, and Walker, *J.*, 1951, 3439) and of 4 : 6-diamino-1-*p*-chlorophenyl-1 : 2-dihydro-2 : 2-dimethyl-1 : 3 : 5-triazine (II), the biologically active metabolite of proguanil (III) (Carrington, Crowther, Davey, Levi, and Rose, *Nature*, 1951, **168**, 1080), made desirable a further study of the relationship between structure and biological activity amongst appropriately substituted diamino-heterocyclic compounds. Antimalarial activity, for example, is retained in the *as*-triazine series (IV) (Hitchings, Maggiolo, Russell, VanderWerff, and Rollo, *J. Amer. Chem. Soc.*, 1952, **74**, 3201), but it is lost when the six-membered hetero-ring is replaced by a five-membered ring as in 3 : 5-diamino-1-aryl-1 : 2 : 4-triazoles (1-arylguanazoles) (V) (Thurston and Walker, *J.*, 1952, 4542). The work described in the present communication was carried out to see whether the antimalarial activity of (I) would be retained in 2 : 6-diamino-3-arylpyridines (VI), in which one of the ring-nitrogen atoms (N_1) of (I) is replaced by a =CH– group.

An attractive direct route to diaminopyridines of type (VI) would appear to be by Tschitschibabin amination (Tschitschibabin and Seide, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216) of the appropriate 3-arylpyridines but the latter are unfortunately not readily accessible. We therefore turned to the synthesis, as intermediates, of 3-aryl-2 : 6-



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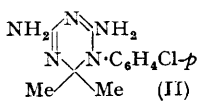

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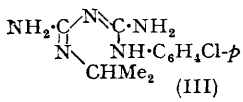

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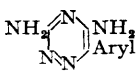

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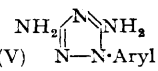

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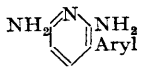

(VI)

dihydroxypyridines, which are, of course, tautomeric forms of the imides of α-arylglutaconic acids, and it was expected that these would be convertible into 3-aryl-2 : 6-dichloropyrid-

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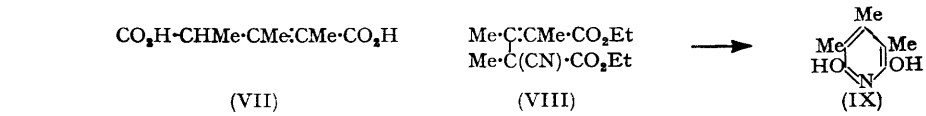
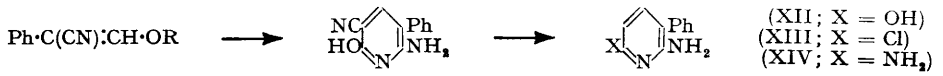
ines and thence into the required 2 : 6-diamino-3-arylpyridines (VI). Several alkyl-substituted 2 : 6-dihydroxypyridines have been prepared from alkylated glutaconic esters and ammonia (Ruhemann, *J.*, 1893, **63**, 259, 874; 1899, **75**, 249) but there are advantages to be gained in having the nitrogen atom of the pyridine ring provided by the cyano-group of alkylated cyanoglutaconic esters (Rogerson and Thorpe, *J.*, 1905, **87**, 1685) or by a carbamyl group (cf. Errera, *Ber.*, 1898, **31**, 1241). The tendency for the formation of the dihydroxypyridine in such cases is quite marked, since, for example, an attempt to prepare αβγ-trimethylglutaconic acid (VII) by hydrolysis of diethyl α-cyano-αβγ-trimethylglutacon-



(VII) (VIII) (IX)

ate (VIII) gave 2 : 6-dihydroxy-3 : 4 : 5-trimethylpyridine (IX) in 56% yield (Adams, VanDuuren, and Braun, *J. Amer. Chem. Soc.*, 1952, **74**, 5608; cf. Thorpe, *J.*, 1905, **87**, 1682). Overall yields in these syntheses of alkylated 2 : 6-dihydroxypyridines, however, are rarely good and few have approached that (85%) claimed by Ruzicka and Fornasir (*Helv. Chim. Acta*, 1919, **2**, 344) in their related synthesis of 3-cyano-5-ethyl-2 : 6-dihydroxy-4-methylpyridine.

No 3-aryl derivatives of 2 : 6-dihydroxypyridine appear to have been studied and it seemed more promising to attempt their synthesis directly from cyano- or carbamyl-substituted α-arylglutaconic esters, particularly since better yields of intermediates were to be expected from cyanoacetic acid derivatives than from malonic acid or ester (cf. Rogerson and Thorpe, *loc. cit.*; Ruzicka and Fornasir, *loc. cit.*), rather than to aim at the α-arylglutaconic esters with subsequent imide formation. The general method of Rogerson and Thorpe (*loc. cit.*) for the preparation of 3-alkyl-2 : 6-dihydroxy-4-methylpyridines, involving the condensation of ethyl sodiocyanoacetate with ethyl α-alkylacetoacetic esters, did not appear to us as attractive as a method based on Errera's condensation (*loc. cit.*) of ethyl ethoxymethylenecyanoacetate with ethyl sodiocyanoacetate, in view of our familiarity with alkoxymethylenearylacetonitriles (Chase, Thurston, and Walker, *loc. cit.*; Chase and Walker, *J.*, 1953, 3518), which also offered the possibility of introducing one amino-group directly. This was indeed realised, since methoxymethylene- or *iso*butoxymethylene-phenylacetonitrile (X) underwent smooth condensation with sodiocyanoacetamide to give 2-amino-5-cyano-6-hydroxy-3-phenylpyridine (XI) in good yield, and the 4-methyl derivative of (XI) was obtained from β-*iso*butoxy-α-phenylcrotononitrile. Prolonged treatment, however, was necessary to effect hydrolysis and decarboxylation of (XI) with the result that only moderate yields of 2-amino-6-hydroxy-3-phenylpyridine (XII) were obtained, and the related amide was also isolated when the time of hydrolysis was appreciably curtailed. Conversion of (XII) into 2-amino-6-chloro-3-phenylpyridine (XIII) with phosphoryl chloride required vigorous conditions and so did the conversion of (XIII) into the desired 2 : 6-diamino-3-phenylpyridine (XIV), the overall yield from the alkoxymethylenephenylacetonitrile being ~16%.



As an alternative, (XIV) was sought by way of 2 : 6-dihydroxy-3-phenylpyridine (XV) and this route called for alkoxymethylene derivatives (XVI) of phenylacetic ester. The alkylation of ethyl α-formylphenylacetate has been studied by Wislicenus and von Schrötter (*Annalen*, 1921, **424**, 215) who found *C*-alkylation to occur almost exclusively with methyl and ethyl iodide but *O*-alkylation to take place mainly with methyl and ethyl sulphate. As methylation of the related α-formylphenylacetonitrile with methyl iodide and potassium carbonate in acetone is a convenient method for the preparation of (X; R = Me) (Chase, Thurston, and Walker, *loc. cit.*), the same conditions were applied to ethyl α-formylphenylacetate and, in contrast with Wislicenus and von Schrötter's observations, the major

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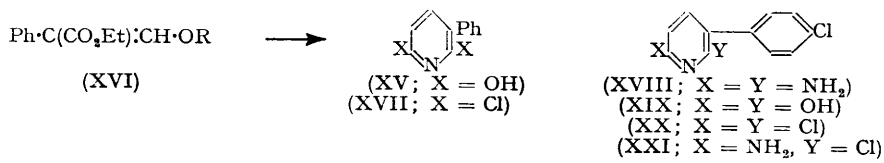
product was ethyl methoxymethylenephenylacetate (XVI; R = Me). The most convenient route to the *O*-alkyl derivatives (XVI) of ethyl α-formylphenylacetate, however, is by acid-catalysed etherification (cf. Chase and Walker, *loc. cit.*). Condensation of either ethyl methoxymethylenephenylacetate or ethyl *iso*butoxymethylenephenylacetate with sodiocyanoacetamide and hydrolysis of the intermediate product gave 2 : 6-dihydroxy-3-phenylpyridine (XV), which was also obtained by ammonolysis of dimethyl α-phenylglutaconate. Subsequent conversion of (XV) into 2 : 6-dichloro-3-phenylpyridine (XVII) with phosphoryl chloride also required vigorous conditions and the addition of phosphorus pentachloride introduced unwanted chlorine atoms, as is well known in the pyridine series (cf. Sell and Dootson, *J.*, 1898, **73**, 432; Ruzicka and Fornasir, *loc. cit.*, p. 346). Amination of (XVII) then gave 2 : 6-diamino-3-phenylpyridine (XIV) in overall yields of ~19% from ethyl alkoxymethylenephenylacetate and ~11% from ethyl α-formylphenylacetate *via* α-phenylglutaconic acid.

Since optimal biological activity would be expected in the *p*-chlorophenyl analogue, 2 : 6-diamino-3-*p*-chlorophenylpyridine (XVIII) was synthesised from ethyl α-*p*-chlorophenyl-α-formylacetate *via* 3-*p*-chlorophenyl-2 : 6-dihydroxypyridine (XIX) and 2 : 6 : 4′-trichloro-3-phenylpyridine (XX) by methods similar to those described above. Difficulty was experienced, however, in the amination of 2 : 6 : 4′-trichloro-3-phenylpyridine (XX) because of the risk of replacing only one or all three chlorine atoms by amino-groups. Only one amino-group was introduced with ethanolic ammonia at 210° in the presence of copper powder or with phenol and ammonium carbonate at 195°, the product being pre-



sumably 6-amino-2-chloro-3(or 5)-*p*-chlorophenylpyridine (XXI), while aqueous ethanolic ammonia at 180—185° in the presence of copper sulphate introduced either two or three amino-groups giving 2 : 6-diamino-3-*p*-chlorophenylpyridine (XVIII) or 2 : 6 : 4′-triamino-3-phenylpyridine.

We are indebted to Miss W. A. F. Webber for kindly carrying out biological tests on compounds (XII), (XIII), (XIV), (XVIII), and (XXI); they were quite toxic and none appeared to be active in tolerated doses against *P. berghei* in the mouse, or against *T. equiperdum*. The high antimalarial activity of (I) therefore is lost when the pyrimidine ring is replaced by a pyridine ring, and toxicity is increased.

Experimental

2-Amino-5-cyano-6-hydroxy-3-phenylpyridine (XI).—(*A*). Cyanoacetamide (8·4 g.) and methoxymethylenephenylacetonitrile (15·9 g.) (Chase, Thurston, and Walker, *loc. cit.*) were added in succession to sodium ethoxide (from 2·3 g. of sodium) in ethanol (100 c.c.). The mixture was boiled under reflux for 2 hr., diluted with water, and extracted with ether. Acidification of the aqueous solution gave *2-amino-5-cyano-6-hydroxy-3-phenylpyridine* (16·4 g., 78%), m. p. 307—310°. Recrystallisation from dimethylformamide–ethanol afforded colourless prisms and raised the m. p. to 320° (decomp.) (Found: C, 67·9; H, 4·2; N, 19·8. $C_{12}H_9ON_3$ requires C, 68·2; H, 4·3; N, 19·9%).

(*B*) A mixture of *iso*butoxymethylenephenylacetonitrile (100·6 g.) (Chase and Walker, *loc. cit.*), cyanoacetamide (42 g.), and sodium ethoxide (from 11·5 g. of sodium) in absolute ethanol (300 c.c.) was boiled under reflux in a slow stream of nitrogen for 6 hr., yielding 2-amino-5-cyano-6-hydroxy-3-phenylpyridine (85·8 g., 81%), m. p. 310°, identical with the preceding product.

Acetylation (of 1·0 g.) with acetic anhydride (5 c.c.) and pyridine (5 c.c.) at the b. p. afforded *2-acetamido-5-cyano-6-hydroxy-3-phenylpyridine*, which separated from methoxyethanol in pale yellow prisms (1·06 g.), m. p. 279—281° (Found: C, 66·6; H, 4·2; N, 16·4. $C_{14}H_{11}O_2N_3$ requires C, 66·4; H, 4·4; N, 16·6%).

2-Amino-6-chloro-5-cyano-3-p henylpyridine.—A mixture of 2-amino-5-cyano-6-hydroxy-3-

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phenylpyridine (1·0 g.) and phosphoryl chloride (3 c.c.) was heated in a sealed tube at 150° for 3 hr. The black residue was poured on ice, maintained just alkaline with aqueous ammonia, and thoroughly extracted with benzene. Removal of the solvent and recrystallisation of the residue from ethyl acetate–light petroleum afforded 2-*amino*-6-*chloro*-5-*cyano*-3-*phenylpyridine* in colourless plates (0·24 g.), m. p. 216—217° (Found : C, 62·9; H, 3·4; N, 18·3. $C_{12}H_8N_3Cl$ requires C, 62·8; H, 3·5; N, 18·3%).

2-*Amino*-6-*hydroxy*-3-*phenylpyridine* (XII).—2-Amino-5-cyano-6-hydroxy-3-phenylpyridine (5 g.) was hydrolysed with concentrated hydrobromic acid (50 c.c.) and glacial acetic acid (50 c.c.) for 21 hr. under reflux. Removal of the solvent under reduced pressure and trituration of the residue with water (50 c.c.) and chloroform (50 c.c.) gave an almost colourless solid (3·9 g.). On crystallisation from aqueous acetic acid, 2-*amino*-6-*hydroxy*-3-*phenylpyridine* separated in colourless needles (1·96 g., 44%), m. p. 235—237° (Found : C, 71·0; H, 5·3; N, 15·2. $C_{11}H_{10}ON_2$ requires C, 71·0; H, 5·4; N, 15·0%). The crude material appeared to contain a considerable proportion of another substance which, however, was not isolated. When the hydrolysis was carried out for only 6 hr., 2-*amino*-6-*hydroxy*-3-*phenylpyridine*-5-*carboxyamide* was also isolated; it separated from aqueous acetic acid in colourless prisms, m. p. 282—284° (Found : C, 62·7; H, 4·8; N, 18·5. $C_{12}H_{11}O_2N_3$ requires C, 62·9; H, 4·8; N, 18·3%). Both compounds acquired a pink to purple colour when kept in the dry state or in solution.

2-*Amino*-6-*chloro*-3-*phenylpyridine* (XIII).—A mixture of 2-amino-6-hydroxy-3-phenylpyridine (2·0 g.) and phosphoryl chloride (5 c.c.) was heated in a sealed tube at 170—175° for 4 hr. The cooled residue was poured on ice and kept alkaline by addition of aqueous ammonia. Extraction with benzene and removal of the solvent left a residue which crystallised from benzene–light petroleum in tan-coloured needles (1·23 g., 56%), m.p. 153—155°. Pure 2-*amino*-6-*chloro*-3-*phenylpyridine*, sublimed at 150°/15 mm., separated from light petroleum in colourless plates, m. p. 155—157° (Found : C, 65·0; H, 4·3. $C_{11}H_9N_2Cl$ requires C, 64·6; H, 4·4%).

2-*Amino*-5-*cyano*-6-*hydroxy*-4-*methyl*-3-*phenylpyridine*.—A mixture of β-*iso*butoxy-α-phenylcrotononitrile (9·2 g.) (Chase and Walker, *loc. cit.*), cyanoacetamide (3·6 g.), and sodium ethoxide (from 1·0 g. of sodium) in absolute ethanol (100 c.c.) was boiled under reflux for 3 hr. The alkali-soluble fraction, isolated in the usual way, afforded 2-*amino*-5-*cyano*-6-*hydroxy*-4-*methyl*-3-*phenylpyridine*, which separated from methoxyethanol in colourless needles (3·1 g.), m. p. 346° (decomp.) (Found : C, 69·6; H, 5·0; N, 18·6. $C_{13}H_{11}ON_3$ requires C, 69·3; H, 4·9; N, 18·7%).

Ethyl α-*Formylphenylacetate*.—Ethyl phenylacetate (142 g.) was formylated as described by Wislicenus (*Annalen*, 1896, **291**, 164), and the colourless product (117 g.), b. p. 89—91°/0·03 mm., n_D^{19} 1·5386, partly solidified on standing. This material was used in the following experiments without separation of the *cis*- and *trans*-(enolic) forms.

Ethyl Methoxymethylenephenylacetate (XVI; R = Me).—A vigorously stirred mixture of ethyl α-formylphenylacetate (100 g.), methyl iodide (111 g.), and anhydrous potassium carbonate (72 g.) in dry acetone (500 c.c.) was boiled under reflux for 6 hr. Most of the acetone was then removed by distillation and the mixture, diluted with ether (500 c.c.), was filtered, the cake being washed with ether (350 c.c.). The combined ethereal solutions were washed with cold N-sodium hydroxide (250 c.c.) and with water (100 c.c.), then dried and evaporated. Fractionation of the residue gave (i) an oil (43 g.), b. p. 60—114°/0·8 mm., doubtless consisting largely of ethyl α-formyl-α-phenylpropionate, and (ii) ethyl methoxymethylenephenylacetate as a colourless oil (60·5 g.), b. p. 114—119°/0·8 mm., n_D^{19} 1·5480 (Found : C, 69·9; H, 6·8; OMe + OEt, 35·6. Calc. for $C_{12}H_{14}O_3$: C, 69·9; H, 6·8; OMe + OEt, 36·9%). Wislicenus and von Schrötter (*loc. cit.*) record b. p. 173—175°/15 mm., m. p. 54—55°, for this substance prepared by using methyl sulphate and aqueous sodium hydroxide.

Ethyl iso*Butoxymethylenephenylacetate* (XVI; R = Bu^i).—A mixture of ethyl α-formylphenylacetate (67 g.), *iso*butanol (37 g.), and toluene-*p*-sulphonic acid (5·9 g.) in benzene (250 c.c.) was boiled under reflux for 4 hr., a conventional Dean and Stark separator being used (cf. Chase and Walker, *loc. cit.*). The benzene solution was washed with cold 0·5N-sodium hydroxide solution (2 × 150 c.c.), and with water, and was then fractionated after addition of a drop of concentrated sulphuric acid, affording *ethyl* iso*butoxymethylenephenylacetate* as a colourless oil (74·8 g., 87%), b. p. 134—138°/2 mm., 126°/0·6 mm., n_D^{19} 1·5251 (Found : C, 72·6; H, 8·1. $C_{15}H_{20}O_3$ requires C, 72·6; H, 8·1%).

2 : 6-*Dihydroxy*-3-*phenylpyridine* (XV).—(*A*) Cyanoacetamide (18·6 g.) and ethyl methoxymethylenephenylacetate (43·5 g.) were added in succession to a solution of sodium ethoxide (from 5·1 g. of sodium) in absolute ethanol (total volume, 175 c.c.). After 4½ hr. at the b. p. under reflux, the mixture was kept at room temperature for 36 hr., then diluted with water (*ca.* 1 l.) and extracted with ether. The aqueous solution was acidified with 10N-hydrochloric acid and

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cooled to 5°. The pale buff precipitate was collected and dried (yield, 30·1 g.). This material (21 g.) was boiled under reflux for 19 hr. with acetic acid (25 c.c.) and hydrobromic acid (150 c.c.; *d* 1·48). After removal of the solvent under reduced pressure, water (75 c.c.) was added, and the insoluble material was filtered off and washed with water and with ether. The resulting 2 : 6-*dihydroxy*-3-*phenylpyridine* separated from aqueous acetic acid, or from *iso*propanol, in needles (11·2 g.), m. p. 214° (deep red melt), which became pink in air (Found : C, 70·3; H, 5·0; N, 7·7. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·9; N, 7·5%). Similar results were obtained on use of ethyl methoxymethylenephenylacetate prepared (without purification) by the action of diazomethane on ethyl α-formylphenylacetate.

(*B*) The use of ethyl *iso*butoxymethylenephenylacetate in the above condensation, hydrolysis of the crude intermediate, and crystallisation from *iso*propanol gave 2 : 6-dihydroxy-3-phenylpyridine (31% yield), identical with the above material.

α-*Phenylglutaconic Acid.*—Ethyl α-formylphenylacetate (38 g.) was treated with malonic acid (22 g.) in pyridine (20 g.) as described by Borsche and Niemann (*Ber.*, 1936, **69**, 1993). The crude product (34 g.) was triturated with carbon tetrachloride to yield α-phenylglutaconic acid (20·5 g., 48%) as a cream-coloured solid, m. p. 153—158°. Addition of piperidine (1 g.) to the reaction mixture raised the yield to 60%. Recrystallisation from water gave clusters of colourless needles, m. p. 165—167°; Borsche and Niemann (*loc. cit.*) record m. p. 166—167°. The acid (10 g.) was refluxed for 5 hr. with 5% methanolic sulphuric acid (100 c.c.), affording the dimethyl ester as a colourless oil (9·9 g., 87%), b. p. 121—122°/0·2 mm., n_D^{25} 1·5309; Borsche and Niemann (*loc. cit.*) record b. p. 180—182°/15 mm.

Pyrolysis of Ammonium α-*Phenylglutaconate.*—A solution of α-phenylglutaconic acid (2·06 g.) in excess of concentrated aqueous ammonia was evaporated under reduced pressure and the residue was twice taken to dryness with ethanol. The resulting ammonium salt was heated to 180—190° (oil-bath) under reduced pressure in a flask fitted with a short air-condenser. When evolution of gas had ceased (after 15 min.) the residue was taken up in 5% aqueous sodium carbonate, and the solution was extracted with ether. The aqueous phase was acidified with hydrochloric acid and again extracted with ether. Removal of the ether from the latter (dried) extract gave 4-phenylbut-3-enoic acid (phenyl*iso*crotonic acid), which separated from light petroleum and from aqueous methanol in colourless needles (1·56 g.), m. p. 85—86° (Found : C, 73·7; H, 6·0. Calc. for $C_{10}H_{10}O_2$: C, 74·0; H, 6·2%). Buchner and Dessauer (*Ber.*, 1892, **25**, 1155) record m. p. 88°.

The product was further characterised as the amide : the methyl ester (prepared by using diazomethane) was set aside at 37° for 48 hr. with concentrated aqueous ammonia, and the resulting amide separated from aqueous ethanol in colourless prisms, m. p. 130—131°. Köhl (*Ber.*, 1903, **36**, 174) records m. p. 130°.

Ammonolysis of Dimethyl α-*Phenylglutaconate.*—Dimethyl α-phenylglutaconate (4·68 g.) and ethanolic ammonia solution (60 c.c., saturated at 0°) were heated in a glass-lined steel bomb-tube at 130° for 4 hr. The solution was cooled to 5° overnight and the resulting 2 : 6-dihydroxy-3-phenylpyridine (1·60 g., 43%; m. p. 208—209°) was collected. Recrystallisation from *iso*propanol gave colourless needles, m. p. 213—214°, identical with the product obtained by the alternative method described above.

2 : 6-*Dichloro*-3-*phenylpyridine* (XVII).—A mixture of 2 : 6-dihydroxy-3-phenylpyridine (4·0 g.) and phosphoryl chloride (8·0 c.c.) was heated in a sealed tube at 200—210° for 4½ hr. The cooled residue was poured on ice with addition of aqueous ammonia to maintain neutrality. The product was recovered by extraction with chloroform and sublimed at 0·5 mm. (bath 90—130°), affording a white crystalline solid (4·15 g., 87%), m. p. 91·5—93·5°. 2 : 6-*Dichloro*-3-*phenylpyridine* separated from light petroleum in large prisms, m. p. 95—96° (Found : C, 59·2; H, 2·9; N, 6·0; Cl, 31·3. $C_{11}H_7NCl_2$ requires C, 59·0; H, 3·2; N, 6·3; Cl, 31·6%).

The dichloro-compound (500 mg.) in ethanol (75 c.c.) containing N-sodium hydroxide (5·6 c.c.) was shaken with 2% palladised strontium carbonate (500 mg.) in hydrogen at room temperature and atmospheric pressure. Uptake of hydrogen was complete in 2 hr. and the mixture was filtered and concentrated under reduced pressure. The product, recovered in ether and washed with water, was isolated and treated with alcoholic picric acid, yielding 3-phenylpyridine picrate (800 mg., 93%), m. p. 159—160°, not depressed on admixture with the specimen obtained from the tetrachloropyridine (below).

2 : 4 : 5 : 6-*Tetrachloro*-3-*phenylpyridine.*—A mixture of 2 : 6-dihydroxy-3-phenylpyridine (1·87 g.), phosphoryl chloride (5 c.c.) and phosphorus pentachloride (5·1 g.) was boiled gently under reflux for 2 hr. The phosphoryl chloride was largely removed under reduced pressure and the residue was treated with ice and dilute aqueous ammonia. Extraction with benzene and

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evaporation of the solvent gave a residue (0·86 g.), which, after passage in benzene through a column of alumina, yielded 2 : 4 : 5 : 6-*tetrachloro*-3-*phenylpyridine* (0·33 g.), separating from light petroleum in colourless needles, m. p. 101—103° (Found: C, 45·3; H, 1·8; N, 5·2; Cl, 48·7. $C_{11}H_5NCl_4$ requires C, 45·1; H, 1·7; N, 4·8; Cl, 48·4%).

The substance (250 mg.) was dechlorinated in the manner described above for 2 : 6-dichloro-3-phenylpyridine, absorption of hydrogen ceasing in 12 hr. 3-Phenylpyridine picrate separated from alcohol in yellow needles (260 mg., 79%), m. p. 159—160°, not depressed on admixture with the previous specimen (Found: C, 53·3; H, 3·1; N, 14·1. Calc. for $C_{11}H_9N,C_6H_3O_7N_3$: C, 53·1; H, 3·1; N, 14·6%). Hey and Walker (*J.*, 1948, 2218) record m. p. 163°.

No pure products could be isolated after 2 : 6-dihydroxy-3-phenylpyridine had been refluxed with phosphoryl chloride (with or without the addition of dimethylaniline), or with thionyl chloride.

2 : 6-*Diamino*-3-*phenylpyridine* (XIV).—(*A*) A mixture of 2-amino-6-chloro-3-phenylpyridine (1·0 g.), aqueous ammonia (20 c.c.; *d* 0·880), ethanol (10 c.c.), and copper sulphate pentahydrate (1 g.) was heated in a glass-lined steel bomb-tube at 180° for 3 hr. The mixture was diluted with water (25 c.c.) and thoroughly extracted with ether. The residue (850 mg.) left on removal of the ether was chromatographed on alumina and elution with chloroform afforded 2 : 6-*diamino*-3-*phenylpyridine* (680 mg., 75%) (Found: C, 71·1; H, 6·2. $C_{11}H_{11}N_3$ requires C, 71·3; H, 6·0%). This specimen crystallised from light petroleum in plates, m. p. 90°, with re-solidification and subsequent melting at 114—115°. After sublimation at 15 mm. only the higher-melting form was obtained, m. p. 114—115°, not depressed on admixture with 2 : 6-diamino-3-phenylpyridine prepared from 2 : 6-dichloro-3-phenylpyridine (below).

(*B*) A mixture of 2 : 6-dichloro-3-phenylpyridine (500 mg.), aqueous ammonia (20 c.c.; *d* 0·880), ethanol (10 c.c.), and copper sulphate pentahydrate (500 mg.) was heated in a glass-lined steel bomb tube at 200° for 6 hr. The cooled solution was thoroughly extracted with ether, and the extract was washed with water, dried, and evaporated. The green residue (400 mg.) was chromatographed on alumina (15 × 1·5 cm.) and elution with chloroform–methanol (9 : 1) afforded 2 : 6-diamino-3-phenylpyridine, separating from light petroleum in colourless plates (290 mg., 70%), m. p. 112—113° (Found: C, 71·6; H, 5·9; N, 22·7. Calc. for $C_{11}H_{11}N_3$: C, 71·3; H, 6·0; N, 22·7%).

Ethyl α-p-*Chlorophenyl*-α-*formylacetate*.—A mixture of ethyl *p*-chlorophenylacetate (90 g.) and ethyl formate (62 c.c.) was added to sodium wire (11·5 g.) in dry ether (450 c.c.) cooled to 5°. The temperature was kept at ~5° during the ensuing vigorous reaction (2—3 hr.) and the mixture was then kept at room temperature overnight. Ice-water was added and the aqueous layer was extracted with ether, acidified with dilute sulphuric acid, and again thoroughly extracted with ether. The ether was removed and the residue (92 g., 83%), dried by azeotropic distillation with benzene, readily solidified. *Ethyl* α-p-*chlorophenyl*-α-*formylacetate* (68 g., 60%) distilled at 120—125°/0·1 mm. and recrystallised from light petroleum, gave colourless needles, m. p. 45—46° (Found: C, 58·0; H, 4·8. $C_{11}H_{11}O_3Cl$ requires C, 58·3; H, 4·9%). Distillation was attended by considerable loss and the substance was used without distillation in the following reactions.

Ethyl α-p-*Chlorophenyl*-α-*ethoxymethyleneacetate*.—A mixture of ethyl α-*p*-chlorophenyl-α-formylacetate (100 g.), ethanol (46 g.) and toluene-*p*-sulphonic acid (5 g.) in benzene (200 c.c.) was boiled under reflux, using the Dean and Stark separator, until no more water was evolved (9 hr.). The benzene solution was washed with cold 0·5N-potassium hydroxide, and with water. Fractionation then afforded: (i) fore-running (12 g.), b. p. 132—142°/1·2 mm., and (ii) *ethyl* α-p-*chlorophenyl*-α-*ethoxymethyleneacetate*, a colourless oil (82 g., 73%), b. p. 142—144°/1·2 mm., 128°/0·2 mm., $n_D^{19\cdot5}$ 1·5488 (Found: C, 61·0; H, 5·7. $C_{13}H_{15}O_3Cl$ requires C, 61·3; H, 5·9%).

Ethyl iso*Butoxymethylene*-p-*chlorophenylacetate*.—In a similar manner, ethyl *p*-chlorophenylformylacetate (10 g.), *iso*butanol (4·0 g.), and toluene-*p*-sulphonic acid (1 g.) in benzene (100 c.c.) afforded *ethyl* iso*butoxymethylene*-p-*chlorophenylacetate* as a colourless oil (10·3 g., 83%), b. p. 137—141°/0·15 mm., n_D^{20} 1·5362 (Found: C, 63·9; H, 6·6; Cl, 12·3. $C_{15}H_{19}O_3Cl$ requires C, 63·7; H, 6·8; Cl, 12·5%).

α-p-*Chlorophenylglutaconic Acid*.—Ethyl *p*-chlorophenylformylacetate (100 g.), malonic acid (49 g.), pyridine (50 c.c.), and piperidine (1 g.) were heated together on the steam-bath for 5 hr. The resulting α-*p*-chlorophenylglutaconic acid (46·3 g., 44%; m. p. 175—179°), isolated as for α-phenylglutaconic acid, was well washed with carbon tetrachloride, and recrystallisation from ethyl acetate–light petroleum afforded colourless needles, m. p. 183—185° (Found: C, 54·6; H, 3·9. Calc. for $C_{11}H_9O_4Cl$: C, 54·9; H, 3·8%). Menon (*J.*, 1936, 1775) records m. p.

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175° for this acid prepared in low yield from ethyl *p*-chlorophenylacetate and diethyl ethoxymethylenemalonate. The *diethyl* ester, prepared by azeotropic distillation in benzene with ethanol and toluene-*p*-sulphonic acid, was a colourless oil, b. p. 149°/0·4 mm., n_D^{22} 1·5275 (Found : C, 61·0; H, 5·8; Cl, 12·3. $C_{15}H_{17}O_4Cl$ requires C, 60·7; H, 5·8; Cl, 11·9%). In one experiment partial decarboxylation took place, yielding approximately equal amounts of the diethyl ester and *ethyl* 4-p-*chlorophenylbut*-3-*enoate*, b.p. 113°/0·15 mm., n_D^{22} 1·5500 (Found : C, 63·8; H, 5·8; Cl, 15·6. $C_{12}H_{13}O_2Cl$ requires C, 64·1; H, 5·8; Cl, 15·8%). Alkaline hydrolysis of the latter ester gave the free acid, which separated from light petroleum in irregular plates, m. p. 109—110° (Found : C, 61·1; H, 4·9; Cl, 17·8. Calc. for $C_{10}H_9O_2Cl$: C, 61·1; H, 4·6; Cl, 18·0%); Erdmann and Schwechten (*Annalen*, 1890, **260**, 65) record m. p. 108—109°.

3-p-*Chlorophenyl*-2 : 6-*dihydroxypyridine* (XIX).—(*A*) A solution of diethyl α-*p*-chlorophenylglutaconate (5·8 g.) in ethanolic ammonia (50 c.c.; saturated at 0°) was heated in a glass-lined steel bomb-tube at 150° for 5 hr. The resulting 3-p-*chlorophenyl*-2 : 6-*dihydroxypyridine* (1·07 g.) was collected and combined with a second crop (0·82 g.; total yield, 44%) obtained on concentration of the alcoholic solution. Recrystallisation from *iso*propanol gave woolly needles, m. p. 216—217° (Found : C, 59·8; H, 3·8; N, 6·0; Cl, 16·0. $C_{11}H_8O_2NCl$ requires C, 59·6; H, 3·6; N, 6·3; Cl, 16·0%).

(*B*) Ethyl *p*-chlorophenylethoxymethyleneacetate (31·8 g.) and cyanoacetamide (10·5 g.) were added to a solution of sodium ethoxide (from 3·0 g. of sodium) in absolute ethanol (100 c.c.); a thick cream-coloured sludge soon separated. More ethanol (100 c.c.) was added and the mixture was boiled under reflux for 8 hr., then poured into water, and the product was collected after acidification with 10N-hydrochloric acid. The moist paste was dehydrated by being suspended in glacial acetic acid (150 c.c.), the mixture being distilled until the b. p. reached 116°, with acetic acid added as required. Concentrated aqueous hydrobromic acid (150 c.c.) was then added and the mixture was boiled under reflux for 48 hr. The solvent was removed under reduced pressure and the residue, triturated with ether (200 c.c.) and water (100 c.c.) and cooled to 5°, was filtered off. Recrystallisation from *iso*propanol afforded woolly needles (5·8 g.) of the required chlorophenyldihydroxypyridine, m. p. 216—217°, alone and in admixture with the previous specimen (above). The mother-liquors and the ethereal washings yielded a further amount (3·3 g.; total yield, 33%) of the same substance, m. p. 214—216°. Similar yields of 3-*p*-chlorophenyl-2 : 6-dihydroxypyridine resulted from the use of the *iso*butyl enol ether.

In one experiment the precaution of dehydrating the pasty intermediate was not observed and hydrolysis was carried out for 18 hr. The product then isolated was 3-p-*chlorophenyl*-2 : 6-*dihydroxypyridine*-5-*carboxyamide*, which crystallised from dimethylformamide–ethanol in pale pink prisms, m. p. 280° (decomp.) (Found : C, 54·4; H, 3·6; N, 10·5. $C_{12}H_9O_3N_2Cl$ requires C, 54·5; H, 3·4; N, 10·6%).

2 : 6 : 4′-*Trichloro*-3-*phenylpyridine* (XX).—The foregoing *p*-chlorophenyldihydroxypyridine (4·0 g.) was heated with phosphoryl chloride (6 c.c.) in a sealed tube at 180° for 4 hr. The cooled residue was poured on ice, made alkaline with aqueous ammonia, and extracted with benzene. The dried solution was passed through a short column of alumina and evaporation then gave 2 : 6 : 4′-*trichloro*-3-*phenylpyridine* as a colourless crystalline mass (4·2 g., 90%), m. p. 135—136°; recrystallisation from light petroleum afforded colourless needles, m. p. 137—138° (Found : C, 51·2; H, 2·2; N, 5·4; Cl, 41·9. $C_{11}H_6NCl_3$ requires C, 51·1; H, 2·3; N, 5·4; Cl, 41·2%).

Ammonolysis of 2 : 6 : 4′-*Trichloro*-3-*phenylpyridine*.—(*A*) 2 : 6 : 4′-Trichloro-3-phenylpyridine (1·2 g.), copper powder (1 g.), and ethanolic ammonia (20 c.c., saturated at 0°) were heated in a glass-lined steel bomb-tube at 210° for 7 hr. After removal of the solvent under reduced pressure the residue was distributed between N-sodium hydroxide (50 c.c.) and chloroform (200 c.c.) and filtered, the chloroform layer then being separated and taken to dryness. The residue was chromatographed on alumina, and elution with benzene gave starting material (0·20 g., 17%), while elution with chloroform yielded a tan-coloured solid (0·90 g.), which proved to be 6-*amino*-2-*chloro*-3(or 5)-p-*chlorophenylpyridine* (XXI), separating from benzene in colourless needles (0·42 g., 45%), m. p. 186—187° (Found : C, 55·2; H, 3·3; N, 12·2. $C_{11}H_8N_2Cl_2$ requires C, 55·3; H, 3·4; N, 11·7%).

(*B*) 2 : 6 : 4′-Trichloro-3-phenylpyridine (1·5 g.), copper sulphate pentahydrate (1·5 g.), concentrated aqueous ammonia (30 c.c.), and ethanol (15 c.c.) were heated together in the glass-lined bomb-tube at 180—185° for 6 hr., the product being worked up as above and chromatographed on alumina. Elution with chloroform gave a tan-coloured solid (240 mg.), separating from benzene in colourless needles (130 mg., 15%), m. p. 185—186°, alone and in admixture with the monoamino-compound obtained above. Further elution with chloroform and with chloroform–methanol (20 : 1), followed by recrystallisation from benzene, afforded 2 : 6-*diamino*-

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3-p-*chlorophenylpyridine* in the form of colourless needles (0·26 g., 20%), m. p. 114—115° (Found: C, 60·3; H, 4·5; N, 19·3. $C_{11}H_{10}N_3Cl$ requires C, 60·1; H, 4·6; N, 19·1%).

In another experiment, elution with chloroform–methanol (20 : 1) followed by recrystallisation from benzene yielded tan-coloured prisms (23%), m. p. 148—152°. Sublimation at 0·05 mm., followed by recrystallisation from benzene, gave colourless rhombs of 2 : 6 : 4′-*triamino*-3-*phenylpyridine*, m. p. 155—157° (Found: C, 66·4; H, 5·8; N, 28·3. $C_{11}H_{12}N_4$ requires C, 66·0; H, 6·0; N, 28·0%). 2 : 6-Diamino-3-*p*-chlorophenylpyridine (15%) was obtained from the mother-liquors.

(*C*) 2 : 6 : 4′-Trichloro-3-phenylpyridine (1·0 g.), phenol (5 g.), and ammonium carbonate (5 g.) were heated together in the bomb tube at 195° for 8 hr. The cooled residue was distributed between ether (500 c.c.) and 2N-sodium hydroxide solution (100 c.c.), and the residue left on evaporation of the ether was chromatographed on alumina. Elution with benzene gave colourless crystals (0·84 g.), m. p. 120—130°, which separated from light petroleum in long needles (0·49 g., 49%), m. p. and mixed m. p. with starting material, 137—138°. Elution with chloroform gave a tan-coloured solid (0·15 g.), separating from benzene in needles (70 mg., 8%), m. p. 185—186°, alone and in admixture with the monoamino-compound described above.

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