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350. 1-Pyridylisoquinolines.

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Several 1-3'- and 1-4'-pyridylisoquinolines have been prepared by the application of the Bischler-Napieralski reaction, or modifications thereof, to the appropriate nicotin- or *iso*nicotin-amides, followed by dehydrogenation. Observations have been made on the facility of the cyclisation and dehydrogenation stages in the synthesis of the compounds studied. An abortive attempt to obtain a pyridylisoquinoline, in which the pyridyl group is attached to the carbocyclic nucleus, is described.

THE long-known spasmolytic action of papaverine, coupled with the recently discovered antispasmodic activity in certain pyridylquinolines (Coates, Cook, Heilbron, Hey, Lambert, and Lewis, J., 1943, 401 and subsequent papers), suggested that members of the pyridylisoquinoline series might be worthy of study. The significance of this suggestion was emphasised by the claim that 3-methyl-6: 7-methylenedioxy-1-3'-pyridylisoquinoline had in fact been prepared and was described as an excellent substitute for papaverine (Merck, D.R.-P. 549,967). No further members of this series, however, appear to have been prepared, although it has been reported that the synthesis of the closely related 6: 7-methylenedioxy-1-2'-picolylisoquinoline has been attempted (Clemo, McIlwain, and Morgan, J., 1936, 610; Bills and Noller, J. Amer. Chem. Soc., 1948, 70, 957) but failed because the corresponding 3: 4-dihydroisoquinoline could not be dehydrogenated. The preparation of 3: 4-dihydro-6: 7-dimethoxy-1-3'-pyridyliso-quinoline has been reported by Sugusawa and Kuriyagawa (Ber., 1936, 69, 2068) and it would appear that attempts to dehydrogenate this compound were also unsuccessful.

By means of the Bischler-Napieralski reaction (*Ber.*, 1893, 26, 1903), or modifications thereof (*e.g.*, Decker and Kropp, *Ber.*, 1909, 42, 2075; Decker, Kropp, Hoyer, and Becker, *Annalen*, 1913, 395, 299), a series of 1-pyridylisoquinolines (III) should result from the ring closure of *N*-acyl-2-phenylethylamines (I), in which the acyl group is derived from one of the pyridine-carboxylic acids, by the series of reactions represented as follows:



It was found, however, that neither N-nicotinoyl-2-phenylethylamine nor N-isonicotinoyl-2-phenylethylamine could be converted into the dihydroisoquinoline (II) by the action of phos-

phoric oxide or phosphorus oxychloride in boiling toluene or xylene, but when decalin was used as solvent the formation of the dihydroisoquinolines took place in low yield with much simultaneous decomposition. Excellent yields of the dihydroisoquinolines were obtained when the modified procedure due to Decker and Kropp (*loc. cit.*) was used. In this method the imidochloride (IV), formed by the action of phosphorus pentachloride on the acyl-2-phenylethylamine, is treated with aluminium chloride. In addition to 3:4-dihydro-1-3'- and -1-4'-pyridylisoquinoline, the 3- and 4-methyl derivatives of each of these were prepared in this manner with the use of 1-phenyl-2-propylamine or 2-phenyl-*n*-propylamine in place of 2-phenylethylamine. The six dihydroisoquinolines were dehydrogenated by heating them with palladium-charcoal to give the corresponding isoquinolines.

N-Nicotinoyl- and N-isonicotinoyl-2-(3: 4-methylenedioxyphenyl)ethylamine were converted into the corresponding 3: 4-dihydro-1-pyridylisoquinolines in the normal manner by the action of phosphorus pentachloride in boiling xylene, the reaction being facilitated in these compounds by the strong activating influence of the methylenedioxy-group. The resulting compounds have been assigned the structures of 3: 4-dihydro-6: 7-methylenedioxy-1-3'- and -1-4'-pyridylisoquinoline by analogy with the formation of 3: 4-dihydro-6: 7-methylenedioxy-1-3'- and -1-4'-pyridylquinoline from benzoyl-2-(3: 4-methylenedioxyphenyl)ethylamine as described by Decker Kropp, Hoyer, and Becker (*loc. cit.*). On the other hand, *N*-nicotinoyl- and *N*-isonicotinoyl-2-p-chlorophenylethylamine required conversion to the imidochloride and subsequent treatment with aluminium chloride in order to obtain the corresponding dihydroisoquinolines. The attempted dehydrogenation of these four substituted 3: 4-dihydroisoquinolines by heating them with palladium-charcoal led to complete disintegration, but it was found possible to convert 3: 4-dihydro-6: 7-methylenedioxy-1-3'-pyridylisoquinoline into 6: 7-methylenedioxy-1-3'-pyridylisoquinoline by the action of bromine in dioxan solution.

Harwood and Johnstone (J. Amer. Chem. Soc., 1934, 56, 468) have reported the facile dehydrogenation of 3:4-dihydro-6:7-dimethoxy-1-phenylisoquinoline-3-carboxylic acid by the action of thionyl chloride, and the presence of a group in the 3-position may account for the successful preparation of 3-methyl-6:7-methylenedioxy-1-3'-pyridylisoquinoline as reported in D.R.-P. 549,967. The failures at the dehydrogenation stage reported above, together with similar observations recorded elsewhere (Clemo, McIlwain, and Morgan, and Bills and Noller, locc. cit.), led to a repetition of the synthesis of 3-methyl-6:7-methylenedioxy-1-3'-pyridylisoquinoline. Apart from discrepancies in the physical constants of the intermediate compounds the synthesis has been confirmed and both the dihydroisoquinoline and the isoquinoline have been further characterised as the picrates.

In an attempt to obtain an *iso*quinoline derivative with a pyridyl group attached to the carbocyclic ring, attention was directed to the possibility of the cyclisation of the amino-acetals of suitable pyridylbenzaldehydes following the general procedure of Pomeranz (*Monatsh.*, 1893, 14, 116; 1894, 15, 299). Methyl o-3-pyridylbenzoate (V), prepared by the action of diazotised



methyl anthranilate on pyridine, was converted by the method of McFadyen and Stevens (J., 1936, 584) into the corresponding aldehyde (VI). An attempt to establish the constitution of the ester (V) by hydrolysis and decarboxylation led only to the production of a ketonic product regarded as 2: 2'-di-(3-pyridyl)benzophenone, but its constitution was finally established by its synthesis from 3-o-aminophenylpyridine (VII) (Coates *et al., loc. cit.*) by way of 3-2'-cyanophenylpyridine (VIII) and o-3-pyridylbenzoic acid. o-3-Pyridylbenzylideneaminoacetal, prepared from o-3-pyridylbenzaldehyde and aminoacetal, could not be cyclised by treatment with concentrated sulphuric acid, phosphorus oxychloride, or anhydrous hydrogen fluoride. Similar attempts to effect the cyclisation of 4-phenylbenzylideneaminoacetal were also abortive.

EXPERIMENTAL.

Preparation of Bases.—2-(3: 4-Methylenedioxyphenyl)ethylamine was prepared by the method of Decker et al. (Annalen, 1913, **395**, 291), and 2-p-methoxyphenylethylamine by the method of Barger and Walpole (J., 1909, 95, 1724).

2-Phenyl-n-propylamine. To β -phenyl-n-butyric acid (27 g.) at room temperature an excess of thionyl chloride was added, and after the vigorous reaction had subsided the mixture was heated for a

further 2 hours at 60°. The excess of thionyl chloride was then removed under reduced pressure and the residual oil kept overnight in a desiccator (KOH). A solution of the acid chloride in dry acetone (25 c.c.) was added dropwise during 30 minutes to a vigorously stirred solution of sodium azide (18 g.) in water (30 c.c.) and acetone (30 c.c.) kept below 0° during the addition. After a further 20 minutes' stirring water and crushed ice were added and the azide was extracted from the mixture with benzene. The benzene extract was washed once with cold water and then dried (CaCl₂). The dry solution was cautiously heated on a water-bath until the evolution of nitrogen had ceased. The mixture was cooled and concentrated hydrochloric acid (30 c.c.) added. The benzene layer was separated and washed with water. The combined aqueous extracts were made strongly alkaline with aqueous potassium hydroxide (40%), and the liberated amine extracted with benzene. After removal of the benzene from the dried (K₂CO₃) extract, the residue was distilled under reduced pressure to give 2-phenyl-*n*-propylamine (19·5 g.; b. p. 102-103°/17 mm.). Von Braun, Grabowski, and Kirschbaum (*Ber.*, 1913, **46**, 1280) obtained this amine by means of a Hofmann reaction on β -phenyl-*n*-butyramide and record b. p. $104^{\circ}/21 \text{ mm}$.

2-p-Chlorophenylethylamine. β -p-Chlorophenylpropionic acid (10 g.; Skraup and Schwamberger, Annalen, 1928, **462**, 147), treated under identical conditions to those given above, proportional quantities being used, gave 2-p-chlorophenylethylamine (7.5 g.; b. p. 114—116°/15 mm.). The hydrochloride crystallised from concentrated hydrochloric acid in plates, m. p. 215° (Found : C, 49.9; H, 6.0. C₈H₁₀NCl,HCl requires C, 50.0; H, 5.8%).

1-3': 4'-Methylenedioxyphenyl-2-propylamine. a-Piperonylpropionic acid (27 g.; Lorenz, Ber., 1880, 13, 760) was treated with an excess of phosphorus trichloride and after the vigorous reaction had subsided the mixture was heated to 60° for 2 hours. The excess of phosphorus trichloride was distilled from the mixture under reduced pressure, and the acid chloride extracted from the residue with dry ether and added with shaking to aqueous ammonia ($d \ 0.88$) in large excess. The mixture was heated on a water-bath to remove the ether and then chilled. The amide (26 g.) was filtered off from the solution. A sample separated from aqueous alcohol in plates, m. p. 121° (Found : C, 63·3; H, 6.6. C₁₁H₁₃O₃N requires C, 63·4; H, 6·3%). A cold solution of alkaline sodium hypochlorite was prepared by absorbing chlorine (5·5 g.) in a solution of sodium hydroxide (20 g.) in water (50 c.c.) and crushed ice (100 g.). To this mechanically stirred solution was added the above powdered crude amide (25·5 g.). After 10 minutes the temperature was slowly raised to 50° and a solution of potassium hydroxide (36 g.) in water (200 c.c.) was slowly added. When all the amide had dissolved the mixture was again heated to 70° and kept at 70—80° for half an hour, during which an oil commenced to separate from the solution. The mixture was cooled and extracted with benzene. After removal of benzene from the dried (K₂CO₃) extract, the residue was distilled under reduced pressure to give 1-3': 4'-methylenedioxyphenyl-2-propylamine (9·5 g.; b. p. 149—150°/14 mm.). Merck (D.R.-P. 274,350) describes the preparation of this amine by the addition of hydrogen bromide to safrole followed by amination, and records b. p. 153°/19 mm.

Nicotinoyl and isoNicotinoyl Chloride Hydrochlorides.—The preparation of the hydrochlorides of nicotinoyl and isonicotinoyl chloride has been described by Späth and Spitzer (Ber., 1926, 59, 1477). In the present work these acid chloride hydrochlorides were freshly prepared before use by heating a mixture of the acid and thionyl chloride under reflux for 2 hours. The excess of thionyl chloride was distilled from the mixture, and the acid chloride hydrochloride purified by sublimation under reduced pressure.

Preparation of the Amides.—The powdered nicotinoyl (or isonicotinoyl) chloride hydrochloride (0.03 mol.) was added during 2 minutes to a solution of the base (0.09 mol.) in dry chloroform (50 c.c.). A vigorous reaction commenced almost immediately, which was completed by boiling the mixture under reflux for 2 hours on the water-bath. When cold, the mixture was shaken with water (25 c.c.), and the chloroform layer separated. After removal of the solvent the residue was crystallised. A quantity of the base was recovered from the aqueous extract. The amides prepared by this general procedure are listed in the following Table. The yields obtained varied from 60 to 85% calculated on the acid chloride hydrochloride.

N-Substituted nicotin- and isonicotin-amides.

	Cryst.		Found, %.		Reqd., %.		
Amide.	M. p.	form.	Formula.	С.	Ĥ.	C.	Ĥ.
N-Nicotinoyl-2-phenylethylamine	79°	needles ª	$C_{14}H_{14}ON_{2}$	74.1	6.0	74.3	$6 \cdot 2$
N-isoNicotinoyl-2-phenylethylamine	123	needles »	,,	74.0	$6 \cdot 1$,,	,,
N-Nicotinoyl-1-phenyl-2-propylamine	98	needles ^c	$C_{15}H_{16}ON_2$	75.1	6.6	75.0	6.6
N-isoNicotinoyl-1-phenyl-2-propylamine	109	needles ^b	,,	$75 \cdot 1$	6.6	,,	,,
N-Nicotinoyl-2-phenyl-n-propylamine	73	needles ^d	$C_{15}H_{16}ON_2$	$75 \cdot 2$	6.5	75.0	6.6
N-isoNicotinoyl-2-phenyl-n-propylamine	83	needles d	,,	$75 \cdot 1$	6.4	,,	,,
N-Nicotinoyl-2-p-methoxyphenylethylamine	116	needles ^b	$C_{15}H_{16}O_2N_2$	70.3	6.7	70.3	6.3
N-isoNicotinoyl-2- p -methoxyphenylethylamine	130	plates °	,,	70.2	$6 \cdot 4$,,	
N-Nicotinoyl-2-(3: 4-methylenedioxyphenyl)-							
ethylamine	129	needles ^f	$C_{15}H_{14}O_{3}N_{2}$	66.7	$5 \cdot 6$	66·7	$5 \cdot 2$
N-isoNicotinoyl-2-(3: 4-methylenedioxy-							
phenyl)ethylamine	138	needles ^f	,,	66.7	$5 \cdot 4$,,	,,
N-Nicotinoyl-I-(3: 4-methylenedioxyphenyl)-							
2-propylamine	120 *	needles *	$C_{16}H_{16}O_{3}N_{2}$	67.5	5.6	67.6	5.7
<i>N</i> -Nicotinoyl-2- <i>p</i> -chlorophenylethylamine	133	plates •	$C_{14}H_{13}ON_2CI$	64.9	4.7	64.5	5.05
<i>N-iso</i> Nicotinoyl-2- <i>p</i> -chlorophenylethylamine	108	needles *	,,	64·8	4 ·9	••	.,
Solvents : a , light petroleum (b. p. 80—10	$(0^{\circ}); b_{1}$	benzene-li	ght petroleum	(b. p.	60-8	$)^{\circ}): c.$	ether ;

d, ether-light petroleum (b. p. 40-60°); *e*, benzene-light petroleum (b. p. 80-30°); *f*, benzene. * D.R.-P. 549,967 records m. p. 99-100° for this amide.

3: 4-Dihydro-1-3'-pyridylisoquinoline.—A mixture of N-nicotinoyl-2-phenylethylamine (4.4 g.) and phosphorus pentachloride (5.1 g.) was warmed whereupon a vigorous reaction set in. The mixture was gently heated on a water-bath for a further 20 minutes. Thiophen-free benzene (25 c.c.) was then added and the mixture shaken until the yellow oil had dissolved. Aluminium chloride (5 g.) was then added in one portion. When the vigorous reaction had subsided the mixture was heated on a water-bath for 3 hours. The dark brown resulting mixture was poured on crushed ice, and the aqueous solution extracted with ether. Concentrated hydrochloric acid (20 c.c.) was added and the mixture boiled under reflux for 12 hours in order to hydrolyse any unchanged starting material. After being boiled with reliand to the house of hydrolyse any unchanged starting material. After being coned when animal charcoal and filtered, the colourless filtrate was made strongly alkaline with aqueous sodium hydroxide (20%). The liberated oil was extracted with ether and dried (K_2CO_3). After removal of the ether distillation under reduced pressure gave 3:4-*dihydro*-1-3'-*pyridylisoquinoline* (2.7 g.; b. p. 118°/8.3 × 10⁻³ mm.) (Found : N, 13.2. C₁₄H₁₂N₂ requires N, 13.45%). The *dipicrate*, prepared in the normal manner, separated from acetone-methyl alcohol in fine yellow needles, m. p. 192° after having first sintered at 160° (Found : C, 46.7; H, 2.9. C₁₄H₁₂N₂, 2C₆H₃O₇N₃ requires C, 46.8; H, 2.7%).

3:4-Dihydro-1-4'-pyridylisoquinoline.—N-isoNicotinoyl-2-phenylethylamine (5.4 g.) was cyclised under conditions identical with those described above, using phosphorus pentachloride (6^{+} g.; was cyclused aluminium chloride (6 g.) in benzene (30 c.c.). 3: 4-Dihydro-1-4'-pyridylisoquinoline (3.5 g.; b. p. 132–135°/1.3 × 10⁻² mm.) was obtained as a viscous oil (Found : N, 12.9%). The dipicrate separated from dioxan in orange needles, m. p. 146–147° (decomp.) (Found : C, 46.4; H, 3.1%).

The following preparations are analogous: 3: 4-Dihydro-3-methyl-1-3'-pyridylisoquinoline (2.5 g.), from N-nicotinoyl-1-phenyl-2-propylamine (3.1 g.), phosphorus pentachloride (3.5 g.), and aluminium chloride (4 g.) in benzene (25 c.c.), had b. p. $106-108^{\circ}/3 \times 10^{-3}$ mm. (Found : N, 12.9. C₁₈H₁₄N₂ requires N, 12.6%). The dipicrate separated from acetone in yellow needles, m. p. $161-162^{\circ}$ (Found : C, 47.6; H, 2.9. C₁₆H₁₄N₂, 2C₆H₃O₇N₃ requires C, 47.7; H, 3.0%).

3: 4-Dihydro-3-methyl-1-4'-pyridylisoquinoline (2.9 g.), from N-isonicotinoyl-1-phenyl-2-propylamine (3.5 g.), phosphorus pentachloride (4 g.), and aluminium chloride (4.3 g.) in thiophen-free benzene (30 c.c.), had b. p. $122-125^{\circ}/3 \times 10^{-3}$ mm., and solidified on cooling and separated from light petroleum (b. p. $60-80^{\circ}$) in fine needles, m. p. 58° (Found : N, $12\cdot2\%$). The *dipicrate* separated from acetone in fine needles, m. p. $126-127^{\circ}$ (Found : C, $47\cdot5$; H, $3\cdot2\%$).

3: 4-Dihydro-4-methyl-1-3'-pyridylisoquinoline (3.1 g.), from N-nicotinoyl-2-phenyl-n-propylamine (6.8 g.), phosphorus pentachloride (7.75 g.), and aluminium chloride (9 g.) in benzene (40 c.c.), had b. p. 136-138°/9.3 \times 10⁻³ mm. (Found : N, 12.2%). The *dipicrate* separated from acetone-methyl alcohol in fine needles, m. p. 151° (decomp.) (Found : C, 47.3; H, 3.1%).

3: 4-Dihydro-4-methyl-1-4'-pyridylisoquinoline (2.9 g.), from N-isonicotinoyl-2-phenyl-n-propylamine (6.5 g.), phosphorus pentachloride (7.5 g.), and aluminium chloride (8.8 g.) in benzene (40 c.c.), had b. p. 138°/1.5 \times 10⁻² mm. and crystallised when kept and separated from light petroleum (b. p. 60-80°) in hard needles, m. p. 82° (Found : N, 12.2%). The *dipicrate* separated from acetone-methyl alcohol in fine needles, m. p. 172° (decomp.) (Found : C, 47.8; H, 3.1%).

1-3'-Pyridylisoquinoline.—3: 4-Dihydro-1-3'-pyridylisoquinoline (2.6 g.) was dehydrogenated by heating it at $240-250^{\circ}$ for 30 minutes with palladium-charcoal (0.3 g.; 10%). The mixture was extracted with benzene and filtered. After removal of the solvent the solid residue was recrystallised from light petroleum (b. p. 40–60°). 1-3'-Pyridylisoquinoline (2·1 g.) separated in fine needles, m. p. 58° (Found : C, 81·6; H, 5·3. $C_{14}H_{10}N_2$ requires C, 81·5; H, 4·9%). The *dipicrate* separated from acetone-methyl alcohol in plates, m. p. 192–193° (Found : C, 46·7; H, 2·4. $C_{14}H_{10}N_2, 2C_6H_3O_7N_3$ requires C, 47.0; H, 2.4%).

Similar dehydrogenations led to the following : 1-4'-Pyridylisoquinoline (2.9 g. from 3.3 g.) separated from light petroleum (b. p. 80—100°) in fine needles, m. p. 89° (Found : C, 81.4; H, 5.1%). The picrate separated from dioxan in fine needles, m. p. 205° after having sintered at 170° (Found : C, 55.5; H, **3.1.** $C_{14}H_{10}N_2, C_6H_3O_7N_3$ requires C, 55.2; H, 3.0%).

3-Methyl-1-3'-pyridylisoquinoline (1.9 g. from 2.3 g.) separated from light petroleum (b. p. 60–80°) in fine needles, m. p. 94° (Found : C, 82·1; H, 5·35. $C_{15}H_{15}N_2$ requires C, 81·8; H, 5·5%). The dipicrate separated from methyl alcohol in fine needles, m. p. 172° after having sintered at 156° (Found : C, 48.1; H, 2.7. C₁₅H₁₂N₂, $2C_{6}H_{3}O_{7}N_{3}$ requires C, 47.8; H, 2.8%).

3-Methyl-1-4'-pyridylisoquinoline (2·1 g. from 2·8 g.) separated from light petroleum (b. p. 80-100°) in needles, m. p. 117° (Found: C, 82·0; H, 5·4%). The picrate separated from dioxan-cyclo-hexanone in fine needles, m. p. 251-254° after having sintered at 210° (Found: C, 56·2; H, 3·6. $C_{18}H_{12}N_2, C_8H_3O_7N_3$ requires C, 56·1; H, 3·4%).

4-Methyl-1-3'-pyridylisoquinoline (2.5 g. from 3 g.) had b. p. $128^{\circ}/5 \times 10^{-3}$ mm. (Found : C, 81·1; H, 6·1%). The *picrate* separated from dioxan in needles, m. p. $123-124^{\circ}$ (Found : C, 56·2; H, 3·2%). 4-Methyl-1-4'-pyridylisoquinoline (1·1 g. from 1·5 g.) had b. p. $136-137^{\circ}/2 \cdot 5 \times 10^{-3}$ mm. and separated from light petroleum (b. p. $80-100^{\circ}$) in fine needles, m. p. 113° (Found : C, $82 \cdot 1$; H, $5 \cdot 2^{\circ}$). The *picrate* separated from dioxan in needles, m. p. $235-237^{\circ}$ after having sintered at 185° (Found : C, $82 \cdot 1$; H, $5 \cdot 2^{\circ}$). C, 56.1; H, 3.1%).

7-Chloro-3: 4-dihydro-1-3'-pyridylisoquinoline.—N-Nicotinoyl-2-p-chlorophenylethylamine could not be cyclised with phosphoric oxide in boiling xylene. The amide (2·1 g.) was, however, cyclised by conversion into the imidochloride with phosphorus pentachloride (2·0 g.), followed by treatment with aluminium chloride (2·0 g.) in benzene (50 c.c.). 7-Chloro-3: 4-dihydro-1-3'-pyridylisoquinoline (1·1 g.; b. p. 151--155°/2·7 × 10⁻³ mm.) separated from ether-light petroleum (b. p. 40--60°) in cubic crystals, m. p. 92° (Found : C, 69·0; H, 4·65. C₁₄H₁₁N₂Cl requires C, 69·3; H, 4·6%). The dipicrate separated from acetone-methyl alcohol in fine needles, m. p. 175° having sintered at 145° (Found : C, 44·7; H, 2·9. C. H. N. Cl 2C. H.O. N. requires C, 44.5; H 2·4%) $C_{14}H_{11}N_2Cl_2C_6H_2O_7N_3$ requires C, 44.5; H, 2.4%).

7-Chloro-3: 4-dihydro-1-4'-pyridylisoquinoline (0.9 g. from 2.1 g.), prepared and purified similarly, formed cubic crystals, m. p. 113° (Found : C, 69.3; H, 4.7%). The dipicrate separated from alcohol in needles, m. p. 151° (decomp.) (Found : C, 44.5; H, 3.0%).

3 : 4-Dihydro-6 : 7-methylenedioxy-1-3'-pyridylisoquinoline.—N-Nicotinoyl-2-(3 : 4-methylenedioxyphenyl)ethylamine (3.5 g.) and phosphorus pentachloride (3.0 g.) were warmed together on a water-bath for 10 minutes. Pure xylene (30 c.c.) was then added and the mixture boiled under reflux in an oil-bath for 1 hour. The cold mixture was shaken with water (50 c.c.), and the aqueous layer separated from the xylene fraction. The base was liberated from the aqueous solution by the addition of aqueous sodium hydroxide and extracted with benzene. After removal of the solvent the residue crystallised and repeated crystallisation from benzene gave 3 : 4-dihydro-6 : 7-methylenedioxy-1-3'-pyridylisoquinoline (1.3 g.) in rectangular prisms, m. p. 130° (Found : N, 10.8. $C_{15}H_{12}O_2N_2$ requires N, 11.1%). The dipicrate separated from acetone in needles, m. p. 183—184° (Found : C, 46-1; H, 2.7. $C_{15}H_{12}O_2N_2, 2C_{6}H_{3}O_{7}N_{3}$ requires C, 45.6; H, 2.5%). An attempt to dehydrogenate this compound with palladium-charcoal at 220° led to complete disintegration.

3: 4-Dihydro-6: 7-methylenedioxy-1-4'-pyridylisoquinoline.—N-isoNicotinoyl-2-(3: 4-methylenedioxy-phenyl)ethylamine (3.5 g.) was cyclised under identical conditions to the dihydroisoquinoline (1.1 g.), which separated from ether in fine needles, m. p. 101—102° (Found: N, 11.5%). The dipicrate separated from acetone-methyl alcohol in needles, m. p. 210° after having sintered at 160° (Found: C, 45.4; H, 2.8%). Attempted dehydrogenation of this compound by palladium-charcoal led to complete disintegration.

3: 4-Dihydro-3-methyl-6: 7-methylenedioxy-1-3'-pyridylisoquinoline.—N-Nicotinoyl-1-(3: 4-methylene dioxyphenyl)-2-propylamine (4 g.) and phosphorus pentachloride (3·3 g.) were warmed together and then heated in an oil-bath for 1 hour in xylene (30 c.c.). The dihydroisoquinoline (1·7 g.; b. p. 165–167°/7 × 10⁻² mm.) was isolated in the normal manner and separated from ether in needles, m. p. 135° (Found: C, 72·3; H, 5·0. Calc. for $C_{16}H_{14}O_{2}N_{2}$: C, 72·2; H, 5·3%). The dipicrate separated from alcohol in needles, m. p. 200° after having sintered at 190° (Found: C, 46·0; H, 2·8. $C_{16}H_{14}O_{2}N_{2}.2C_{6}H_{3}O_{7}N_{3}$ requires C, 46·4; H, 2·8%).

6 : 7-Methylenedioxy-1-3'-pyridylisoquinoline.—To a boiling solution of 3 : 4-dihydro-6 : 7-methylenedioxy-1-3'-pyridylisoquinoline (0.5 g.) in dioxan (20 c.c.), bromine (0.1 c.c.) was added in one portion. The mixture was boiled for a further 20 seconds and then rapidly cooled. After cooling at 5° for 1 hour the crystalline 6 : 7-methylenedioxy-1-3'-pyridylisoquinoline hydrobromide was filtered off and decomposed with aqueous ammonia. The liberated base was extracted with benzene and after removal of the solvent the solid residue crystallised from light petroleum (b. p. 80—100°), containing a trace of benzene, in fine needles, m. p. 186° (Found : C, 72.4; H, 3.9. C₁₈H₁₀O₂N₂ requires C, 72.0; H, 4.0%). The dipicrate separated from acetone-methyl alcohol in fine needles, m. p. 200° after having sintered at 180° (Found : C, 45.6; H, 2.3. C₁₅H₁₀O₂N₂, 2C₆H₃O₇N₃ requires C, 45.7; H, 2.3%).

3-Methyl-6: 7-methylenedioxy-1-3'-pyridylisoquinoline.—3: 4-Dihydro-3-methyl-6: 7-methylenedioxy-1-3'-pyridylisoquinoline was dehydrogenated with palladium-charcoal as described in D.R.-P. 549,967. The base was purified by sublimation under reduced pressure, followed by recrystallisation from light petroleum (b. p. $80-100^{\circ}$), from which solvent it separated in fine needles, m. p. $190-191^{\circ}$ (Found : C, 72.5; H, 4:3. Calc. for $C_{14}H_{12}O_{2}N_{3}$: C, 72.7; H, 4:6%). The dipicrate separated from acetone-methyl alcohol in fine needles, m. p. 192° (Found : C, 46.7; H, 2:3. $C_{16}H_{12}O_{2}N_{2}$, $2C_{6}H_{3}O_{7}N_{3}$ requires C, 46.5; H, 2:5%). D.R.-P. 549,967 records m. p. 192° for the free base.

Methyl o-3-Pyridylbenzoate.—A mixture of methyl anthranilate (15 g.), suspended in concentrated hydrochloric acid (30 c.c.) and crushed ice (25 g.) and externally cooled by ice-salt, was diazotised with aqueous sodium nitrite (16 g.), and the resulting solution was dropped as rapidly as possible into stirred pyridine (150 c.c.) at $40-50^{\circ}$. The temperature of the mixture was then gradually raised to 70° and kept at this temperature for 0.5 hour for completion of the reaction. An aqueous solution of sodium carbonate (16 g.; anhydrous) was then added and the excess of pyridine removed with steam. The cooled mixture was extracted with ether, the ethereal extract was dried (K_2CO_3), and after removal of the ether the residue was distilled under reduced pressure. The fraction (10.5 g.), b. p. 110–120°/1.3 × 10⁻² mm., was dissolved in acetone (300 c.c.) and to the hot solution picric acid (12 g.) was added. When cold a mixture of methyl o-3-pyridylbenzoate picrates (12 g.) separated in clusters of fine needles, m. p. 188–189°. After a number of crystallisations from the same solvent the *picrate* of methyl o-3-pyridylbenzoate methed at 192–193° (Found : C, 51.8; H, 3.4. C₁₃H₁₁O₂N, C₆H₃O,N₃ requires C, 51.6; H, 3.2%). The picrate (10 g.) was decomposed by adding it to a hot, mechanically stirred mixture of aqueous sodium hydroxide (5%) and benzene. The benzene extract was dried (K_2CO_3) and, after removal of the benzene, the residue was distilled under reduced pressure to give methyl o-3-pyridylbenzoate (4 g.; b. p. 114–117°/1.3 × 10⁻² mm.). A sample (0.5 g.) was hydrolysed in boiling alcoholic sodium hydroxide. After removal of the alcohol under reduced pressure, the residue was ground with soda-lime and strongly heated in an attempt to effect decarboxylation. The neutral product which distilled from the mixture was converted into its picrate and recrystallisation from alcohol gave the dipicrate of 2 : 2'-(di-3-pyridylbenzohenone, which separated in fine needles, m. p. 197° (Found : C

3-o-Cyanophenylpyridine.—3-o-Aminophenylpyridine (4 g.; b. p. $128^{\circ}/6 \times 10^{-2}$ mm.; m. p. 52° ; Coates et al., loc. cit.) was diazotised in concentrated hydrochloric acid (10 c.c.) and water (10 c.c.) at $0-5^{\circ}$ with aqueous sodium nitrite (2 g.) in water (5 c.c.). The solution of the diazonium salt was slowly added to a well-stirred suspension of nickel cyanide (7-5 g.) in water (20 c.c.) to which potassium cyanide (20 g.) had been added. After the addition the mixture was heated on a steam-bath for 20 minutes. The hot solution was filtered from tar and cooled, whereupon a small quantity of the nitrile separated. The tar was extracted with methyl alcohol and the solution boiled with animal charcoal and filtered. Concentration of the filtrate and dilution with water gave a further quantity of the crude nitrile. 3-o-Cyanophenylpyridine (2·2 g.) separated from methyl alcohol in fine needles, m. p. 89° (Found : C 80-0; H, 4·6. $C_{12}H_8N_2$ requires C, 80-0; H, 4·5%).

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o-3-Pyridylbenzoic Acid.—3-o-Cyanophenylpyridine (2·1 g.) was hydrolysed in boiling alcoholic potassium hydroxide under reflux for 12 hours. The alcohol was distilled from the mixture on a waterbath, and the solid residue dissolved in the minimum of hot water. The free acid liberated from this solution on acidification with acetic acid was recrystallised from aqueous methyl alcohol, to give 2-3'-pyridylbenzoic acid (2·1 g.) in needles, m. p. 185°. Skraup (Monatsh., 1884, 4, 450) records m. p. 185° for this acid, obtained by the decarboxylation of 3-o-carboxyphenylpyridine-2-carboxylic acid. The methyl ester was prepared by heating a mixture of the acid (1 g.), methyl alcohol.(20 c.c.) and concentrated sulphuric acid (3 g.) on a steam-bath for 4 hours. The mixture was poured on crushed ice, and the ester extracted with ether after neutralisation with aqueous ammonia. After evaporation of the ether, the residual oil was dissolved in acetone (50 c.c.) and to the hot solution, a hot solution of picric acid (1 g.) in acetone (10 c.c.) was added. On cooling, the picrate of methyl o-3-pyridylbenzoate separated in clusters of fine needles, m. p. 191—192°, not depressed when mixed with a sample of the picrate prepared as described above.

A mixture of methyl 2-3'-pyridylbenzoate (4 g.), alcohol (4 c.c.), and hydrazine hydrate (2 c.c.; 90%) was heated on a water-bath for 1 hour. Removal of the alcohol under reduced pressure left a viscous residue (3.6 g.), which solidified in a desiccator (CaCl₂). o-3-*Pyridylbenzoylhydrazide*, which was obtained in almost quantitative yield, separated from alcohol in plates, m. p. 138° (Found : C, 67.4; H, 5.4. $C_{12}H_{11}ON_3$ requires C, 67.6; H, 5.2%).

To a solution of the hydrazide (3.5 g.) in pyridine (10 c.c.) was added toluene-*p*-sulphonyl chloride (3.5 g.), and the mixture was heated to 80° for 1 hour. When the mixture was poured into water N-o-3-*pyridylbenzoyl*-N-*toluene*-p-sulphonhydrazide was precipitated in almost quantitative yield as a white crystalline compound, which separated from alcohol in fine needles, m. p. 220° (Found : C, 61.8; H, 5.4. $C_{19}H_{17}O_3N_3S$ requires C, 62.1; H, 4.6%).

o-3-Pyridylbenzaldehyde.—To a solution of the above toluene-p-sulphonyl derivative (5.5 g.) in glycol (50 c.c.) at 150°, anhydrous sodium carbonate (5.5 g.) was added in one portion, and the mixture kept at 150° for 3 minutes. After rapid cooling, the mixture was poured on crushed ice and extracted with chloroform (4 × 30 c.c.). After removal of the solvent from the dried extract (K₂CO₃), the residue was distilled under reduced pressure to give o-3-pyridylbenzaldehyde (1.85 g.; b. p. 117°/7.28 × 10⁻² mm.), which separated from light petroleum (b. p. 60—80°) in fine needles, m. p. 63° (Found : C, 78.65; H, 5.0%).

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