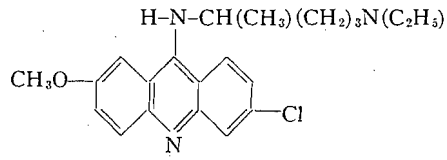
STUDIES IN THE PREPARATION OF ANTIMALARIALS FROM PYRIDINE[1]

By Henry Gilman and John T. Edward[2]

ABSTRACT

The addition of aryllithium compounds to pyridine followed by air oxidation gives satisfactory yields of several 2-arylpyridines. These are readily oxidized by perbenzoic acid to 2-arylpyridine-N-oxides, from which 2-aryl-4- and 6-chloropyridines may be obtained. 2-Arylpyridines and aryllithiums give low yields of 2,6-diarylpyridines. From three different 2-arylpyridines three antimalarials modelled after the plasmoquin type have been prepared.

In earlier investigations in this laboratory (8, 9, 14, 15) it was found that certain "open models" of atebrin (I) such as 2-(3′-chlorophenyl)-4[(α-methyl-δ-diethylaminobutyl)-amino]-6-methoxyquinoline (II) were active against



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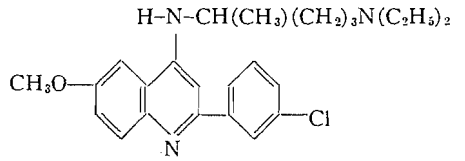
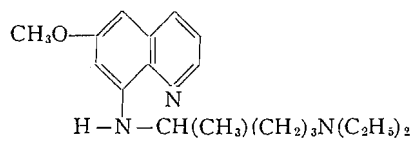


II

experimental avian malarial infections. Consequently, three open models of plasmoquin (III) having the basic side chain on the phenyl group of a 2-phenylpyridine have been prepared. Of these,



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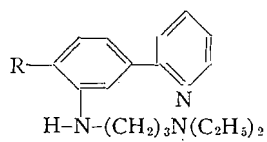

IV

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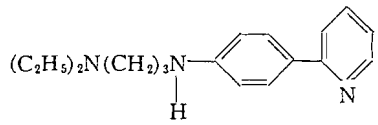


V

2-(3′-[γ-diethylaminopropyl]-amino-4′-methoxyphenyl)-pyridine (IV; R = OCH_3) and 2-(3′-[γ-diethylaminopropyl]-amino-4′-methylphenyl)-pyridine (IV; R = CH_3) proved inactive, while 2-(4′-[γ-diethylaminopropyl]-aminophenyl)-pyridine (V) showed slight activity. Somewhat surprisingly, 2-*p*-tolylpyridine also gave indications of activity. It may be significant that the active compounds are vinylogues of α-picoline and a 2-aminopyridine, in both of which there exists the possibility of a tautomeric shift of hydrogen to the hetero nitrogen atom (19, pp. 32, 91); such a possibility has been suggested in explaining the antimalarial activity of atebrin (23) and other compounds (4).

The general method of synthesis of these plasmoquin models is illustrated by the example below. The aryllithium was prepared in all cases by direct interaction of the appropriate aryl bromide with lithium. It has been observed that *p*-anisyllithium metalates *p*-bromoanisole so that the reaction of the latter with lithium ordinarily yields a mixture of *p*-anisyllithium and 2-methoxy-5-bromophenyllithium (10). However, if the *p*-anisyllithium is prepared very rapidly, the extent of metalation is slight and relatively pure *p*-anisyllithium is obtained.

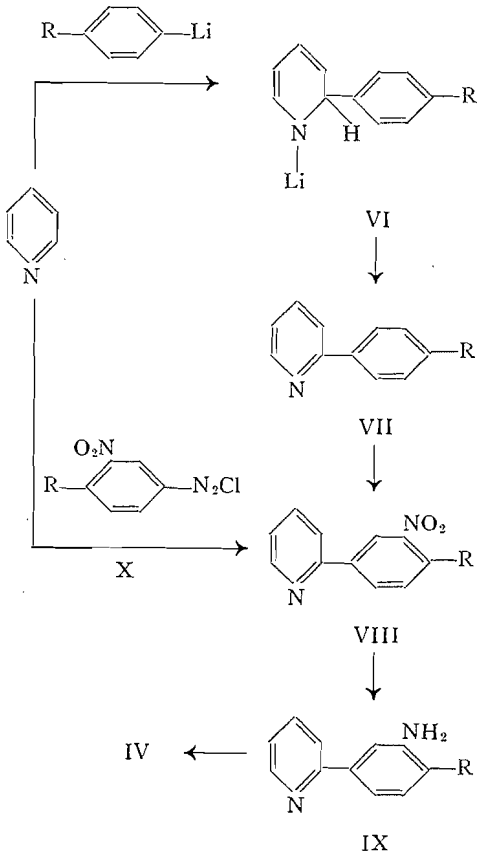
The addition of an aryllithium to pyridine gives an N-lithiodihydropyridine (VI), which hitherto has been converted to the desired 2-arylpyridine (VII) by heating above 100° and splitting out lithium hydride (5, 25, 26, 27). Oxidation of the N-lithiodihydro intermediate with dry air gives, particularly in the cases of 2-*o*-anisyl- and 2-*p*-anisylpyridine, significantly improved yields, though in the case of the *o*-anisyl compound the yield is still low.

Since this work was completed, the preparation of 2-phenylpyridine in 60% yield by oxidation with nitrobenzene of 2-phenyl-1,2-dihydropyridine (produced from (VI; R = H) when the reaction mixture is poured into water) has been reported (7).

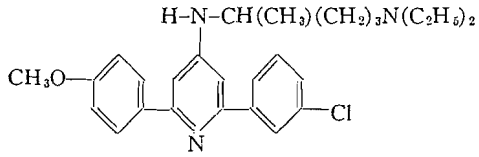
The attempt to prepare 2-phenylpyridine by coupling 2-bromopyridine with phenyllithium gave only a low yield of the desired compound; the isolation of pyridine from the hydrolyzed reaction mixture indicates that a halogen–metal interconversion reaction took place, giving bromobenzene and 2-pyridyllithium. A similar reaction with 3-bromopyridine, using *n*-butyllithium, has been described by Gilman and Spatz (12).

The nitration of 2-phenyl- and 2-*p*-anisylpyridine gave nitro compounds of known orientation (6, 16); however, it was necessary to establish the position of nitration of 2-*p*-tolylpyridine (VII; R = CH_3). This was done by an independent synthesis of the product, 2-(3′-nitro-4′-methylphenyl)-pyridine (VIII; R = CH_3), by the reaction of diazotized 2-nitro-4-aminotoluene (X) with pyridine. This reaction gave, besides (VIII), two other compounds, presumably the isomers formed by substitution at the 3- and 4-positions of pyridine.

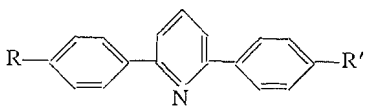
The synthesis of open models of atebrin (e.g. XI) was also envisaged,



through the stages 2,6-diarylpyridine → N-oxide → 4-chloropyridine → 4-(basic alkylamino)-pyridine. However, only low yields of 2,6-diarylpyridines (e.g. XII; R = R′ = H; R = $(CH_3)_2N$, R′ = H; and R = $(CH_3)_2N$, R′ = CH_3) were obtainable from aryllithiums and 2-arylpyridines.



XI



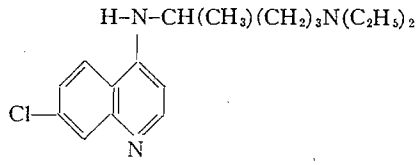
XII

The best yields were obtained by conducting the reaction above 100° and forcing the addition of the aryllithium to the sluggish 2-arylpyridine.

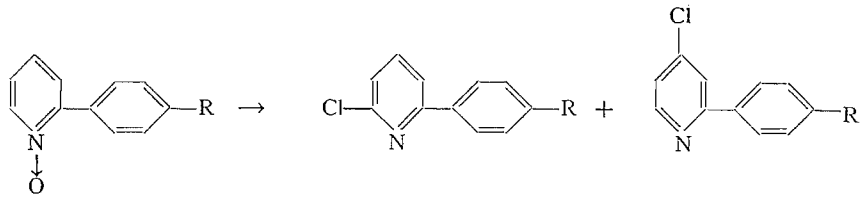
The oxidation of 2,6-diphenylpyridine by a large excess of perbenzoic acid gave a low yield of the N-oxide (cf. 20). On the other hand, 2-phenylpyridine and 2-*p*-anisylpyridine gave good yields of their N-oxides. The introduction of phenyl groups is known to decrease the basicity of the pyridine nucleus (19, p. 71); evidently with two or more of these electron-withdrawing groups

substituted in pyridine the availability of the unshared electron pair of the nitrogen for co-ordination with oxygen is sharply decreased.

The possibility of preparing open models of the highly active 4-(α-methyl-δ-diethylaminobutyl)-amino-7-chloroquinoline (SN 7618) (XIII) was next



XIII



XIV XV XVI

considered. It is known that the N-oxides of pyridine (2), quinoline (1, 20), and similar compounds, on treatment with sulphuryl chloride or phosphorus oxychloride, yield mixtures of the 2- and 4-chloro bases. These may be separated because of the greater basicity of the 4-chloro compounds (e.g. 18). 2-Phenylpyridine-N-oxide (XIV; R = H) and 2-*p*-anisylpyridine-N-oxide (XIV; R = OCH_3) also gave in this way a mixture of chlorinated compounds; the more basic were assumed to be the 4-chloro derivatives (XVI; R = H and OCH_3), and were isolated as picrates; the less basic, which did not form picrates, to be 2-chloro derivatives (XV; R = H and OCH_3). These compounds contain reactive halogen atoms (19, p. 78) which should be easily replaced by the basic side chain to give open models of XIII.

In searching for an alternative synthesis of 2-aryl-6-chloropyridines, 2-chloropyridine was treated with phenyllithium, but no reaction occurred. Evidently the chlorine deactivates the pyridine nucleus (cf. Gilman and Spatz (13)).

EXPERIMENTAL

2-Phenylpyridine

This compound was prepared essentially in accordance with the procedure of Evans and Allen (5), except that the dihydro intermediate was oxidized with air instead of being heated to 110° C. in toluene. Five minutes after addition of slightly more than an equivalent amount of pyridine to phenyllithium, the green color in Gilman's Colour Test I (11), indicative of phenyllithium, had given place to a red color, possibly owing to the dihydro intermediate. The mixture was maintained a further 10 min. under nitrogen, and then dry air was passed over the stirred mixture. The completion of oxidation, indicated when the red color was no longer given, required from 6 to 24 hr.,

depending on the size of the run. Yields, which did not seem to be much affected by varying the temperature of this oxidation between 0° and 35° C., varied from 40% to 57%, about the same as the yields (40–50%) obtained by Evans and Allen.

Reaction of Phenyllithium with 2-Bromopyridine

Phenyllithium (0.065 mole) in 50 cc. of ether was added dropwise over two hours to a stirred solution of 10.2 gm. (0.065 mole) of 2-bromopyridine in 50 cc. of ether. After hydrolysis, the ether layer gave on distillation 3.5 gm. of a yellow liquid boiling at 35–50° C. (20 mm.), which consisted of a water-insoluble liquid and of pyridine, identified by the formation of its picrate (m.p. and mixed m.p.); and 0.5 gm. (5% of theory) of 2-phenylpyridine, b.p. 80° (0.5 mm.), forming a picrate, m.p. 173° to 174° C. (25).

2-(p-[γ-Diethylaminopropyl]-aminophenyl)-pyridine (V)

2-Phenylpyridine was nitrated by a solution of potassium nitrate in sulphuric acid, and the mixture of 2-*m*- and 2-*p*-nitrophenylpyridine separated by the procedure of Forsyth and Pyman (6). Reduction of 2-*p*-nitrophenylpyridine to 2-*p*-aminophenylpyridine was accomplished either with tin and hydrochloric acid (6), or by dissolving in 10 parts of ethanol and heating on the steam bath for seven hours with 10 parts of a saturated aqueous sodium sulphide solution (64% yield). 2-*p*-Aminophenylpyridine (4.1 gm.; 0.024 mole) was heated with 6.7 gm. (0.036 mole) of γ-diethylaminopropyl chloride hydrochloride to 130° C. for four hours, and to 190° C. for 12 hr. The brown glassy melt which formed was dissolved in dilute hydrochloric acid. When the solution was made alkaline a brown oil separated, which was taken up in ether, dried, and distilled. The 2-(*p*-[γ-diethylaminopropyl]-aminophenyl)-pyridine was obtained as a viscous yellow oil, b.p. 185–190° C. (1 mm.), n_D^{25} 1.6166, d_{25}^{25} 1.0482; observed molar refraction R_D (from the Lorenz-Lorentz equation), 94.55. Calc. (from constants of Vogel (24)) 89.35*. The yield was 5.1 gm. or 68%. Calc. for $C_{18}H_{25}N_3$: N, 14.83%. Found: N, 14.90%.

The compound gave with picric acid a red oil which could not be crystallized.

2-m-Aminophenylpyridine

Seven grams of 2-*m*-nitrophenylpyridine dissolved in 70 cc. of ethanol was heated for seven hours on a steam bath with 70 cc. of aqueous saturated sodium sulphide solution. The solution was filtered from a small amount of colored material and diluted with water. The red oil which separated was taken up in benzene, and the extract dried and distilled. Three grams (50% yield) of yellow oil, b.p. 145–147° C. (0.1 mm.), which crystallized on standing to a solid melting at 72–73° C., was obtained. Calc. for $C_{11}H_{10}N_2$: N, 16.48%. Found: N, 16.38%.

Since the completion of this work, this compound has been described by Cook, Heilbron, and Reed (3) who report a m.p. of 72–74° C.

* *The exaltation of molar refraction noted here and in later examples occurs when the pyridine ring is attached to an aromatic nucleus; when it is attached to alkyl groups, the difference between the observed and calculated molar refractions is less than 1%.*

The *picrate*, crystallized from ethanol, melted at 219–220° C. Calc. for $C_{17}H_{13}O_7N_5$: N, 17.54%. Found: N, 17.70%.

p-Anisyllithium

This compound was prepared from the reaction of 18.7 gm. of *p*-bromoanisole with 1.9 gm. of lithium following the conventional techniques, except that the time of addition of *p*-bromoanisole was reduced to 12 min. and the total time of the reaction to 17 min. This was achieved by having the lithium in very small pieces about 0.5 mm. in thickness, and by cooling the reaction flask with ice water once refluxing of ether had commenced. Carbonation with solid carbon dioxide gave anisic acid melting at 175–184° C. (using a Fisher-Johns heated metal block). Pure anisic acid melted at 185° C.; the admixture of 10% of 2-methoxy-5-bromobenzoic acid lowered the m.p. to 150° C. Hence the m.p. of the carbonation product indicated that it contained probably less than 5% of 2-methoxy-5-bromobenzoic acid.

2-p-Anisylpyridine (*VII; R = OCH_3*)

The addition of *p*-anisyllithium to pyridine, followed by air oxidation of the dihydro intermediate, gave an oily solid boiling at 120–135° C. (0.1 mm.). This was crystallized from petroleum ether to give a 35% yield of 2-*p*-anisylpyridine, melting at 47–50° C.; its picrate melted at 189° C. and did not depress the m.p. of an authentic specimen prepared by the method of Haworth, Heilbron, and Hey (16). These authors report a m.p. for the base of 50–51° C. and a m.p. for the picrate of 191–192° C. Their b.p. (160–190° C. at 0.1 mm.) is about 40° higher than ours.

When 2-*p*-anisylpyridine was prepared by the method of Evans and Allen (5), a smaller yield of a more impure product was obtained, which gave on repeated recrystallization from ligroin a 6% yield of base melting at 46–49° C.

2-o-Anisylpyridine

Addition of *o*-anisyllithium to pyridine was very slow, and even after refluxing the ethereal solution for eight hours Colour Test I gave a faint green color. (Gilman and Spatz (14) found the addition of *o*-anisyllithium to quinoline less complete than the addition of other aryllithiums.) The mixture was then air oxidized and worked up in the usual way to give an 18% yield of yellow oil boiling at 120–140° C. (0.1 mm.), which formed a picrate melting at 152–155° C. Haworth, Heilbron, and Hey (16) report a m.p. for the picrate of 155–156° C.; again their b.p. (160–190° C. at 0.1 mm.) appears to be about 40° too high.

When *o*-anisyllithium was allowed to react with pyridine and the reaction mixture then treated according to the procedure of Evans and Allen, no 2-*o*-anisylpyridine was formed. The fraction of the product boiling at 120–140° C. (0.1 mm.), treated with picric acid, gave an unidentified yellow picrate, m.p. 167–175° C., and considerable amounts of tar; none of the other fractions gave any crystalline derivative with picric acid.

2-(3′-Amino-4′-methoxyphenyl)-pyridine (*IX; R = OCH_3*)

2-*p*-Anisylpyridine, nitrated in accordance with the procedure of Haworth,

Heilbron, and Hey (16), gave 2-(3′-nitro-4′-methoxyphenyl)-pyridine (VIII; R = OCH_3). This material was then reduced with aqueous sodium sulphide solution in the same way as 2-*m*-nitrophenylpyridine. After removal of most of the ethanol by distillation, a 95% yield of 2-(3′-amino-4′-methoxyphenyl)-pyridine crystallized out. The crude material melted at 92–94° C.; recrystallization from methanol–water gave pale tan needles melting at 94–95° C. Calc. for $C_{12}H_{12}ON_2$: N, 14.00%. Found: N, 14.25%. The *picrate*, crystallized from methanol, melted at 219–220° C. Calc. for $C_{18}H_{15}O_8N_5$: N, 16.32%. Found: N, 16.29%.

2-(3′-[γ-Diethylaminopropyl]-amino-4′-methoxyphenyl)-pyridine (IV; R = OCH_3)

Six grams (0.030 mole) of 2-(3′-amino-4′-methoxyphenyl)-pyridine and 8.4 gm. (0.045 mole) of γ-diethylaminopropyl chloride hydrochloride were heated together at 150° C. for nine hours. The glassy melt was worked up in the manner described above for V. A heavy yellow oil, reddening slowly on contact with air, and almost setting to a glass at room temperature, was obtained; b.p. 195–200° C. (0.5 mm.), n_D^{25} 1.5859. The yield was 4.3 gm. (46%). Calc. for $C_{19}H_{27}ON_3$: N, 13.42%. Found: N, 13.65%. No crystalline picrate could be formed.

2-p-Tolylpyridine (VII; R = CH_3)

This compound was prepared in 62% yield by the action of *p*-tolyllithium on pyridine, using the air oxidation method as described for 2-phenylpyridine. It was a yellow oil, b.p. 93–98° C. (1 mm.), d_{25}^{25} 1.055, n_D^{25} 1.6107. R_D observed 55.66, calc. 53.02. Calc. for $C_{12}H_{11}N$: N, 8.28%. Found: N, 8.14%.

The picrate melted at 181–182° C. Calc. for $C_{18}H_{14}O_7N_4$: N, 14.07%. Found: N, 14.28%.

2-(3′-Nitro-4′-methylphenyl)-pyridine (VIII; R = CH_3)

A. *By the Nitration of 2-p-Tolylpyridine*

To a stirred solution of 42 gm. (0.25 mole) of 2-*p*-tolylpyridine in 35 cc. of sulphuric acid, cooled by an ice bath, was added dropwise a solution of 25 gm. (0.25 mole) of potassium nitrate in 100 cc. of sulphuric acid. The mixture was stirred for 10 min. at room temperature, and for 30 min. at 100° C. It was cooled, poured on ice, and neutralized with ammonium hydroxide. The brown flocculent precipitate, on crystallization from methanol, gave 38.9 gm. (73%) of brownish needles, melting at 58–61° C. and a second crop of 3.5 gm. (6.5%), m.p. 55–59° C. Recrystallization from methanol, after decoloration with Norit, gave white needles, m.p. 60–61° C. Calc. for $C_{12}H_{10}O_2N_2$: N, 13.09%. Found: N, 13.40%. The *picrate* crystallized from methanol in small, yellow prisms, m.p. 184–184.5° C. Calc. for $C_{18}H_{13}O_9N_5$: N, 15.80%. Found: N, 16.24%.

B. *By the Action of Diazotized 2-Nitro-4-aminotoluene (X; R = CH_3) on Pyridine*

2-Nitro-4-aminotoluene (7.6 gm.; 0.05 mole), prepared by a modification of the procedure of Nölting and Collin (21), was dissolved in 25 cc. (0.25 mole) of concentrated hydrochloric acid and 12 cc. of water, and diazotized by

3.4 gm. (0.05 mole) of sodium nitrite in 10 cc. of water. The solution of diazotized amine was then added dropwise with stirring to 100 cc. (1.24 mole) of pyridine, over a period of 45 min. A mildly exothermic reaction maintained the temperature at 40–45° C. The reaction mixture was stirred for 30 min. while being heated on a steam bath, and then worked up by the methods employed in similar reactions by Haworth, Heilbron, and Hey (16). Three grams of a yellow oil boiling at 155–160° C. (0.1 mm.) was obtained. This was treated with picric acid in methanol, and the yellow solid obtained was subjected to systematic fractional crystallization from acetone and from ethanol to yield three different picrates. The least soluble, m.p. 217–219° C., crystallized from ethanol–acetone (4: 1) in lemon-yellow, woolly tufts of fine needles, and was probably the picrate of *4-(3′-nitro-4′-methylphenyl)-pyridine*. Calc. for $C_{18}H_{13}O_9N_5$; N, 15.80%. Found: N, 15.65%.

The more soluble fraction was separated into a small amount of a yellow solid, m.p. 240–250° C., probably the impure picrate of 3-(3′-nitro-4′-methylphenyl)-pyridine, and hard canary-yellow prisms melting at 183–185° C., which were shown by mixed m.p. to be identical with the picrate of the *2-(3′-nitro-4′-methylphenyl)-pyridine* prepared by the nitration of 2-*p*-tolylpyridine.

2-(3′-Amino-4′-methylphenyl)-pyridine (*IX; R = CH₃*)

Reduction of the nitro compound with sodium sulphide was accomplished in the same manner as the reduction of 2-*m*-nitrophenylpyridine. A yield of 88.5% of long yellowish needles, m.p. 109–110° C., was obtained. Recrystallization from methanol failed to raise the melting point. Calc. for $C_{12}H_{12}N_2$: N, 15.22%. Found: N, 15.43%. The *picrate* crystallized from methanol in tufts of needles, m.p. 186–187° C. Calc. for $C_{12}H_{15}O_7N_5$: N, 16.95%. Found: N, 17.10%.

2-(3′-[γ-Diethylaminopropyl]-amino-4′-methylphenyl)-pyridine (*IV; R = CH₃*)

2-(3′-Amino-4′-methylphenyl)-pyridine (4.5 gm.; 0.024 mole) and 6.9 gm. (0.037 mole) of γ-diethylaminopropyl chloride hydrochloride were fused together at 160° C. for four hours, and the glassy melt was worked up in the same way as for V. A yellow oil was obtained, b.p. 185–190° C. (0.5 mm.), d_{25}^{25} 1.0272, n_D^{25} 1.5887, R_D observed 97.54, calc. 94.00, weighing 4.6 gm. (63% yield). Calc. for $C_{19}H_{27}N_3$: N, 14.14%. Found: N, 14.38%. No crystalline picrate could be formed.

2,6-Diphenylpyridine (*XII; R = R′ = H*)

When 2-phenylpyridine was allowed to react with an equivalent amount of phenyllithium in ethereal solution at 35° C. under nitrogen, addition was still incomplete after 80 min., as shown by a pale blue color given by the reaction mixture in Colour Test I. Air oxidation and working up in the usual manner gave a large recovery of 2-phenylpyridine, boiling at 85–90° C. (0.1 mm.), and identified by forming the picrate melting at 174° C. (25), and some 2,6-diphenylpyridine distilling at 195–200° C. (1 mm.). Crystallization of the latter from petroleum ether gave a 13.5% yield of solid melting at 79–81° C.; by repeated recrystallization from ethanol the melting point was raised to 81° C.;

m.p. of picrate 169° C. Scholtz (22) reports the same melting points for the base and picrate.

On attempting to force addition of phenyllithium to 2-phenylpyridine by refluxing the mixture in ether–toluene at 60° C. under nitrogen it was found that even after 90 min. Colour Test I was pale blue. The mixture was air oxidized and worked up as before to give a 16% recovery of 2-phenylpyridine (isolated as pure picrate from the fraction boiling at 85–100° C. (0.1 mm.)) and 30% yield of impure 2,6-diphenylpyridine; after one crystallization from methanol the yield was 24%, m.p. 79–81° C.

When 2-phenylpyridine was reacted with phenyllithium and the procedure of Evans and Allen (5) followed, a 34% yield of crude 2,6-diphenylpyridine was obtained, but still about 10% of 2-phenylpyridine was recovered.

2,6-Diphenylpyridine-N-oxide

A 350 cc. chloroform solution of 20 gm. (0.087 mole) of 2,6-diphenylpyridine and 0.176 mole of perbenzoic acid was kept in an ice box for 18 hr., and at room temperature for three days. Titration then showed that only 0.031 mole of perbenzoic acid remained. The chloroform solution was extracted with sodium hydroxide solution and dried over sodium sulphate. Evaporation of the solution at reduced pressure gave a yellow oil. On addition of a small amount of ether–ligroin to the oil, 7 gm. of white crystals, m.p. 80–115° C., separated out; the filtrate on being cooled to −10° C. gave a further 5 gm., m.p. 60–70° C. These crops were extracted twice with ether, which served to remove 2,6-diphenylpyridine, of which 3.3 gm. (16%) was recovered in this manner. The extracted solid melted at 105–123° C.; crystallization twice from chloroform – petroleum ether gave 1.2 gm. (5.6%) of pure 2,6-diphenylpyridine-N-oxide, m.p. 125–126° C.; and a second crop (1.8 gm.; 8.4%) melting at 121–126° C. Calc. for $C_{17}H_{13}ON$: N, 5.67%. Found: N, 5.84%. The *picrate* crystallized from ethanol in yellow prisms, m.p. 161–162° C. Calc. for $C_{25}H_{16}O_8N_4$: N, 11.75%. Found: N, 11.92%.

2-p-Dimethylaminophenylpyridine (VII; R = $(CH_3)_2N$)

This compound was prepared from the reaction of *p*-dimethylaminophenyllithium with pyridine essentially in accordance with the procedure of Evans and Allen (5). It distilled as a yellow oil, b.p. 160–162° C. (0.1 mm.), which set to a solid melting at 87–92° C. (63% yield). Repeated recrystallization from ligroin and from aqueous acetone gave white crystals, m.p. 97–98.5° C. Calc. for $C_{13}H_{14}N_2$: N, 14.15%. Found: N, 13.96%. The *picrate* crystallized from acetone in long fibrous orange needles, m.p. 194–195° C. Calc. for $C_{19}H_{27}O_7N_5$: N, 16.39%. Found: N, 16.30%.

2-p-Dimethylaminophenyl-6-phenylpyridine (XII; R = $(CH_3)_2N$, R′ = H)

The reaction of *p*-dimethylaminophenyllithium with slightly more than an equivalent amount of 2-phenylpyridine according to the method of Evans and Allen (5) gave 2-*p*-dimethylamino-6-phenylpyridine, b.p. 230–240° C. (0.1 mm.). After crystallization from benzene and from benzene–methanol, a 13% yield of white needles melting at 172–173° C. was obtained. Calc. for

$C_{19}H_{18}N_2$: N, 10.22%. Found: N, 10.22%. The *picrate* was more soluble in methanol than the free base and separated as fluffy, orange crystals, m.p. 143–144° C., with one molecule of methanol of crystallization. Calc. for $C_{25}H_{21}O_7N_5.CH_4O$: N, 13.09%. Found: N, 12.93, 13.15%.

2-p-Dimethylaminophenyl-6-p-tolylpyridine (*XII; R* = $(CH_3)_2N$, *R'* = CH_3)

The reaction of *p*-tolyllithium with 2-*p*-dimethylaminophenylpyridine, following the procedure of Evans and Allen (5), gave a 23% yield of impure solid, b.p. 257° C. (0.5 mm.). Decolorization in benzene solution with Norit followed by recrystallization from benzene and benzene–methanol gave a 9% yield of white crystals, m.p. 196–197° C. Calc. for $C_{20}H_{20}N_2$: N, 9.72%. Found: N, 9.78%. The *picrate* was more soluble in methanol than the free base. It crystallized as a fluffy, orange solid melting at 157–158° C.

2-Phenylpyridine-N-oxide (*XIV; R* = *H*)

A 350 cc. chloroform solution containing 20 gm. (0.13 mole) of 2-phenylpyridine and 0.167 mole of perbenzoic acid was left in the refrigerator for 40 hr. It was then extracted with sodium hydroxide solution, dried over sodium sulphate, and evaporated down to a volume of 60 cc. On dilution with 50 cc. of petroleum ether and cooling, 10.7 gm. (48% yield) of white needles melting at 153–155° C. separated. Concentration of the mother liquors gave a further 4.2 gm. (19% yield) melting at 145–155° C. Recrystallization from benzene raised the m.p. to 155–155.5° C. Calc. for $C_{11}H_{19}ON$: N, 8.19%. Found: N, 8.4%.

When the mole ratio of perbenzoic acid to base was increased from 1.28 to 1.66, the total yield rose from 67% to 77%.

The *picrate* of 2-phenylpyridine-N-oxide crystallized in yellow prisms from benzene, m.p. 150–152° C. Calc. for $C_{17}H_{12}O_8N_4$: N, 14.00%. Found: N, 13.95%.

Chlorination of 2-Phenylpyridine-N-oxide

2-Phenylpyridine-N-oxide (4.2 gm.; 0.025 mole) protected from moisture and cooled in an ice bath was treated with 46 gm. (0.34 mole) of sulphuryl chloride. The amine oxide dissolved almost immediately. After standing for a few minutes at room temperature, the solution was refluxed gently for five hours. It was then cooled, added to 200 gm. of cracked ice, and made strongly alkaline with ammonia. The oil separating was taken up in ether and treated with alcoholic picric acid to give the picrate of *2-phenyl-4-chloropyridine* (XVI; R = H), m.p. 177–182° C. The yield was 4.5 gm. (43%). Crystallization from methanol gave yellow prisms, m.p. 180–182° C. Calc. for $C_{17}H_{11}O_7N_4Cl$: N, 13.39%. Found: N, 13.73%.

The solvent was removed from the filtrate of the picrate, and the resultant oil treated with 30 cc. of 5% sodium hydroxide solution to remove excess picric acid. It was then taken up in ether and distilled to give 1.7 gm. (35%) of 2-phenyl-6-chloropyridine (XV; R = H), b.p. 124–125° C. (0.1 mm.), m.p. 31° C. Leben (17) reports a m.p. of 34° C.

When 4.2 gm. (0.025 mole) of 2-phenylpyridine-N-oxide was boiled with

30.7 gm. (0.20 mole) of phosphorus oxychloride for 30 min., the yield of 2-phenyl-4-chloropyridine picrate was 3.0 gm. (29%), and of 2-phenyl-6-chloropyridine 1.4 gm. (29%).

2-p-Anisylpyridine-N-oxide (XIV; R = OCH_3)

This compound was prepared in essentially the same manner as 2-phenylpyridine-N-oxide from the reaction of 30.5 gm. (0.165 mole) of 2-*p*-anisylpyridine with 0.275 mole of perbenzoic acid. A first crop of 17.0 gm. (51.5% yield) of the amine oxide, m.p. 132–136° C., and a second crop of 8.0 gm. (24%), m.p. 127–136° C., were obtained. Recrystallization from benzene gave white needles, m.p. 135–136° C. Calc. for $C_{12}H_{11}O_2N$: N, 6.97%. Found: N, 7.16 and 7.30%.

The *picrate* crystallized from methanol in long silky yellow needles, m.p. 136–138° C. Calc. for $C_{18}H_{14}O_9N_4$: N, 13.02%. Found: N, 13.10 and 13.31%.

Chlorination of 2-p-Anisylpyridine-N-oxide

Phosphorus oxychloride (24.5 gm.; 0.16 mole) was added to 4.0 gm. (0.02 mole) of 2-*p*-anisylpyridine-N-oxide. After standing for 10 min. at room temperature, the mixture was refluxed for 30 min. It was hydrolyzed with 200 gm. of cracked ice and made barely acid to Congo red. A pale tan solid, assumed to be 2-*p*-anisyl-6-chloropyridine (XV; R = OCH_3), melting at 87–100° C. was filtered off. It crystallized from methanol in pale tan flakes, m.p. 99–100° C. weighing 1.5 gm. (30% yield). A second crop (0.2 gm.; 4% yield) melted at 92–97° C. Calc. for $C_{12}H_{10}ONCl$: N, 6.38%. Found: N, 6.35%.

Both the aqueous and methanolic mother liquors of the solid, on being made strongly alkaline, became turbid. However, the compound which separated did not solidify on standing, and so was extracted with ether and treated with picric acid. A yellow solid, believed to be the *picrate of 2-p-anisyl-4-chloropyridine* (XVI; R = OCH_3) separated. It crystallized from methanol in tiny rods forming a feltlike mat, m.p. 167–168° C. The yield was 0.5 gm. (5%). Calc. for $C_{18}H_{13}O_8N_4Cl$; N, 12.48%. Found: N, 12.44%.

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