[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

SUBSTITUTIONS AT THE α- OR γ-POSITIONS IN PYRIDYL RING SYSTEMS BY BASIC REAGENTS[1]

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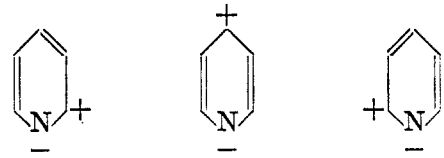
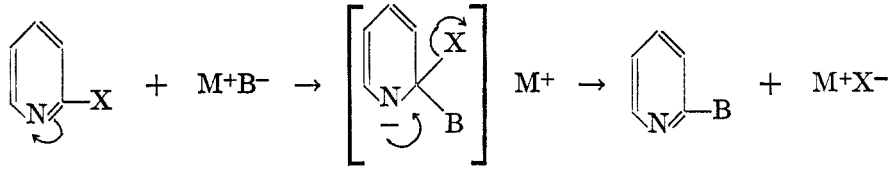
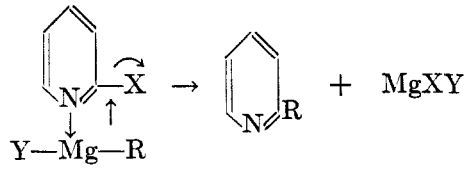
Pyridine may exhibit certain typical aromatic substitutions of the electrophilic type such as bromination and nitration to form the β-derivative, but these reactions take place with some difficulty. Pyridine and especially α- or γ-halopyridines have a greater tendency to undergo nucleophilic substitutions with certain basic reagents to form the α- or γ-derivative. This is not surprising since the following ionic resonance structures having positive charges at the α or γ positions appear to make significant contributions to the structure of the molecule (1, 2).



In contrast to electrophilic substitutions in which hydrogen is removed as a proton, nucleophilic substitutions involve the displacement of hydride (2) or halide ion (3). In certain cases methoxide ion or the sulfonic acid group may be displaced (4). As might be expected, halide ion may be displaced by certain bases which are too weak to displace hydride ion; even with certain relatively strong bases, it is sometimes expedient to facilitate the displacement of hydride ion by the presence of oxidizing agents (2). The mechanism of the displacement of X^- (hydride ion, halide ion, etc.) by a basic anion, B^-, may be represented by the following general equation.



It is not clear whether the addition complex is actually formed (5) or whether X^- is displaced directly from the pyridine ring system (2). With Grignard reagents or organolithium compounds the displacement may take place within a coordination complex, thus



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[2] Eli Lilly Fellow, 1947-1948.

Displacements of hydride ion. Hydride ion may be displaced from pyridyl ring systems by amide ion (5). Generally the 2-amino derivative is formed. With pyridine, for example, 2-aminopyridine is produced, the product being converted in the reaction mixture to its anion.

Although this reaction with alkali amides is quite general, the corresponding reaction with metallic derivatives of amines has seldom been realized. Bergstrom and co-workers (6) have introduced certain primary aliphatic amine groups into pyridine rings under special conditions, but the reaction has failed with secondary aliphatic amines or aniline. Chichibabin and Seide (7) reported only a slight yield of 2-anilinopyridine from sodium anilide and pyridine. We have been unable to effect the reaction with sodium methylanilide and pyridine, with diethylaminomagnesium bromide and quinoline, or with lithium dibutylamide and pyridine or quinoline.

Hydride ion may be displaced even by hydroxide ion but a relatively high temperature appears to be required. Thus, quinoline and potassium hydroxide react at about 300° to form 2-hydroxyquinoline and hydrogen (8).

Hydride ion may be substituted by the potential carbanions of Grignard reagents and organolithium compounds such as phenylmagnesium bromide (8) and phenyllithium (8). Thus, with pyridine and phenyllithium, 2-phenylpyridine is formed. However, Bergmann and Rosenthal (9) were unable to condense sodium diphenylmethide with pyridine, quinoline, or isoquinoline, although they did realize condensation with acridine. We have been unable to condense potassium diphenylmethide or potassium quinaldide with pyridine.

Displacements of halide ion. Halogen at the α- or γ-position of pyridyl ring systems may be displaced as halide ion by various basic reagents including hydroxide ion, phenoxide ion, ethoxide ion, and even ammonia and primary and secondary amines (10). Also Gilman and co-workers (11) have displaced halide ion from 2-chloroquinoline with lithium diethylamide. However, earlier workers (12) failed to obtain the 2-amino derivative from 2-bromopyridine or 2-chloroquinoline and potassium amide.

We have effected this type of reaction not only with sodium and potassium amide but also with sodium methylanilide, di-*n*-butylaminomagnesium bromide, and certain related basic reagents. Our results are summarized in Table I. The yields are not necessarily the optimum obtainable. Sodium methylanilide and similar reagents were prepared from sodium amide and the appropriate aromatic amine.

$$C_6H_5NHCH_3 + NaNH_2 \rightarrow C_6H_5N(Na)CH_3 + NH_3$$

Di-*n*-butylaminomagnesium bromide and other magnesium derivatives were prepared from standardized ethylmagnesium bromide solution and the appropriate aromatic or aliphatic amine (13).

$$C_2H_5MgBr + (n\text{—}C_4H_9)_2NH \rightarrow (n\text{—}C_4H_9)_2NMgBr + C_2H_6$$

In general the reactions between the alkali amides and the halogen compounds were first carried out in liquid ammonia or in liquid ammonia followed by reflux-

TABLE I

RESULTS WITH BASIC REAGENTS AND 2-BROMOPYRIDINE (2-BrP), 2-CHLOROQUINOLINE (2-ClQ), AND 4,7-DICHLOROQUINOLINE (DCQ)

HALOGEN COMPOUND	MOLES	BASIC REAGENT	MOLES	SOLVENT (REFLUX TEMP.)	TIME (HRS.)	PRODUCT	B.P., °C	MM.	YIELD (%)
2-BrP	.06	$NaNH_2$	.12	Liq. NH_3	4	2-Aminopyridine	120–121[a]	36.5	67
2-BrP	.03	KNH_2	.06	Liq. NH_3	6	2-Aminopyridine	118–120[a] 55–57[b] (m.p.)	36	77
2-BrP	.06	KNH_2	.12	Liq. NH_3	0.5	2-Aminopyridine	54–57[b] (m.p.)		49
2-ClQ	.06	$NaNH_2$	.15	Liq. NH_3	5	2-Aminoquinoline	127–128[c] (m.p.)		22
2-ClQ	.06	KNH_2	.15	Liq. NH_3	4	2-Aminoquinoline	123[c] (m.p.)		15
				Ethyl ether	12[d]				
2-ClQ	.025	C_6H_5NHNa	.05	Liq. NH_3	3	2-Anilinoquinoline	93–96 (m.p.)		20
				Ethyl ether	12	Di - α - quinolylphenylamine	200 *ca.* (m.p.)		20
2-ClQ	.025	$C_6H_5NHMgBr$	.05	Butyl ether	12	2-Anilinoquinoline	96–97 (m.p.)		28(43)[e]
2-BrP	.10	$C_6H_5N(CH_3)Na$	.10	Liq. NH_3	1.5	2 - Methylanilinopyridine	147–148	10	57(62)[e]
				Ethyl ether	2				
2-ClQ	.06	$C_6H_5N(CH_3)Na$	.07	Liq. NH_3	1.5	2 - Methylanilinoquinoline	165–175	1.5	47
				Ethyl ether	4				
2-ClQ	.09	$C_6H_5N(CH_3)MgBr$	.10	Ethyl ether	6 + 12[d]	2 - Methylanilinoquinoline	172–182	3	43(61)[e]
DCQ	.05	$C_6H_5N(CH_3)Na$	.05	Liq. NH_3	4	7 - Chloro - 4 - methylanilinoquinoline	194–205	1	46
				Ethyl ether	10[d]				
2-BrP	.045	$(C_6H_5)_2NNa$	.06	Butyl ether[f]	3	2 - Diphenylaminopyridine	95–99 (m.p.)		17

2-ClQ	.025	n-$C_4H_9NHMgBr$	.05	Butyl ether[g]	20	Di - α - quinolyl - n - butylamine	90–92 (m.p.)		54
2-ClQ	.10	$(n$-$C_4H_9)_2NMgBr$	.11	Ethyl ether	6 + 10[d]	2 - Di - n - butylamino-quinoline	168–169	1.5	48(60)[e]
DCQ	.045	$(n$-$C_4H_9)_2NMgBr$	.10	Butyl ether[h]	12	7 - Chloro - 4 - di - n - butylaminoquinoline	185 *ca.*	7	3
2-BrP	.05	$(n$-$C_4H_9)_2NMgBr$	.05	Ethyl ether	12	2 - Di - n - butylamino-pyridine	155[i]	20	11(19)[e]
2-ClQ	.09	C_6H_5MgBr	.09	Ethyl ether	9	2-Phenylquinoline	82.5–83 (m.p.)		40

[a] Ref. 26 reports 117–120° at 36 mm.

[b] Lange (Handbook of Chemistry, 3rd edition, 1939, p. 279) lists 56°.

[c] Footnote b lists 129°.

[d] At room temperature.

[e] Yield is based on halogen compound used minus that recovered.

[f] When the reaction was carried out in liquid ammonia for one hour and in refluxing ethyl ether for four hours, 61% of the 2-BrP was recovered.

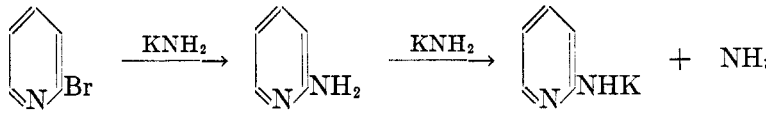
[g] When the reaction was carried out in ethyl ether for fourteen hours, 81% of the 2-ClQ was recovered.

[h] When the reaction between equimolecular amounts was carried out in ethyl ether for ten hours at reflux and for thirty-six hours at room temperature, 80%, of the DCQ was recovered.

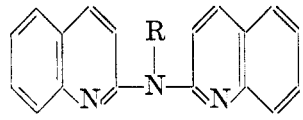
[i] Reported b.p. 163° at 20 mm. (22).

ing diethyl ether; if the reaction failed under these conditions it was repeated in refluxing di-*n*-butyl ether. The reactions with the magnesium derivatives were usually carried out first in refluxing diethyl ether, and if the reaction failed it was repeated in refluxing di-*n*-butyl ether.

It can be seen from Table I that, with sodium or potassium amide in liquid ammonia, 2-bromopyridine gave a good yield of 2-aminopyridine but that a considerably lower yield of 2-aminoquinoline was obtained from 2-chloroquinoline.



With sodium anilide or anilinomagnesium bromide and 2-chloroquinoline a fair yield of 2-anilinoquinoline was obtained. With the sodium anilide another compound, apparently the disubstituted product (I, R = C_6H_5), also was formed.



(I)

With sodium methylanilide, 2-bromopyridine, 2-chloroquinoline and 4,7-dichloroquinoline gave fair to good yields of 2-methylanilinopyridine, 2-methylanilinoquinoline and 7-chloro-4-methylanilinoquinoline, respectively. A fairly good yield of 2-methylanilinoquinoline was also obtained from 2-chloroquinoline and methylanilinomagnesium bromide. With sodium diphenylamide in refluxing di-*n*-butyl ether, 2-bromopyridine gave a 17% yield of 2-diphenylaminopyridine.

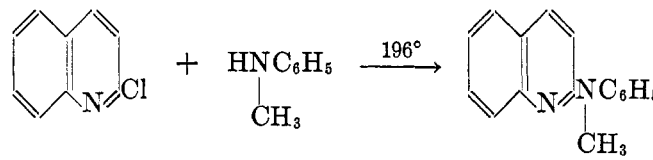
Since aliphatic amines are not readily converted to alkali metal amides, only the bromomagnesium derivatives of these amines were used. With *n*-butylaminomagnesium bromide in refluxing di-*n*-butyl ether, 2-chloroquinoline gave the di-substituted product (I, R = *n*-C_4H_9). The reaction failed in ethyl ether. With di-*n*-butylaminomagnesium bromide, 2-chloroquinoline gave a satisfactory yield of 2-di-*n*-butylaminoquinoline but 2-bromopyridine and 4,7-dichloroquinoline failed to give satisfactory yields.

With the potential carbanion of phenylmagnesium bromide, 2-chloroquinoline gave 2-phenylquinoline in 40% yield. Walter and McElvain (14) have condensed sodio-ethylmalonic ester with 2-bromopyridine to form ethyl-2-pyridylmalonic ester. However, we have been unable to condense satisfactorily the sodium salts of ethyl isobutyrate (15), acetone[3] (16) and methyl isobutyl ketone (16) with 2-bromopyridine. Potassium diphenylmethide (17) also failed to condense with 2-bromopyridine. It is of interest that when this reaction was carried out in liquid ammonia, 2-aminopyridine was obtained in 64% yield, which is approximately the same yield obtained with potassium amide alone. Apparently the amide ion, which is in equilibrium with the diphenylmethide ion, reacted

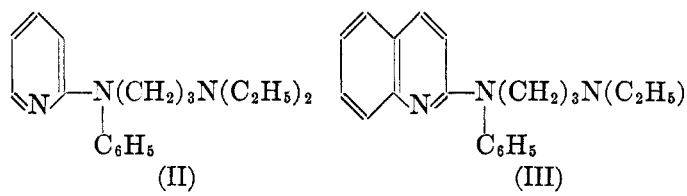
[3] Unsuccessful attempts have been made to condense acetone with 2-bromo-pyridine in the presence of boron trifluoride.

much more rapidly with the 2-bromopyridine than did the relatively large diphenylmethide ion. Similarly, with potassium diphenylmethide and 2-chloroquinoline, 2-aminoquinoline was obtained, although the yield was only 11%.

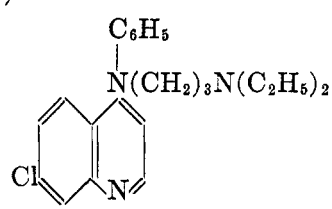
As it has been pointed out above, even free primary and secondary amines may be coupled with α- or γ-halopyridyl compounds, although the reaction generally appears to require higher temperatures. Actually, this reaction is used in the synthesis of the well known antimalarials, quinacrine and SN 7618; the latter is obtained by coupling 4-diethylamino-1-aminopentane with 4,7-dichloroquinoline at 160–170° (18). Since an example with a secondary aromatic amine could not be found in the literature, we have coupled methylaniline with 2-chloroquinoline; the product was obtained in 87% yield which is considerably higher than the yields with the metallic derivatives of methylaniline (see Table I).



In connection with this study, it seemed of interest to synthesize compounds (II), (III), and (IV), which are somewhat related to the well known antimalarials, quinacrine and SN 7618.



(II) (III)



(IV)

Compounds (II) and (IV) were prepared by reacting the potassium salt of the diamine, N-(γ-diethylaminopropyl)aniline (V), with 2-bromopyridine and 4,7-dichloroquinoline, respectively. Compound (III) was obtained from the magnesium derivative of the diamine and 2-chloroquinoline. The diamine was prepared from aniline by the following series of reactions.

$$C_6H_5NH_2 + p\text{-}CH_3C_6H_4SO_2Cl \rightarrow C_6H_5NHSO_2C_6H_4CH_3\text{-}p \xrightarrow[+\ K_2CO_3]{Cl(CH_2)_3N(C_2H_5)_2}$$

$$C_6H_5N(CH_2CH_2CH_2N(C_2H_5)_2)SO_2C_6H_4CH_3\text{-}p \xrightarrow{HCl} C_6H_5NHCH_2CH_2CH_2N(C_2H_5)_2 \quad (V)$$

The direct condensation of γ-diethylaminopropyl chloride with aniline gave a mixture which consisted presumably of the mono- and the di-alkylated products.

2-Methylanilinoquinoline, 2-di-*n*-butylaminoquinoline, and compounds (II), (III), and (IV) were tested as potential antimalarials at the Lilly Research Laboratories of Eli Lilly and Company, Indianapolis, Indiana. The tests were carried out in ducks infected with *P. lophurae*. The compounds were, however, all inactive. Four of these compounds were also tested for activity against tuberculosis. The tuberculosis tests were carried out *in vitro* using avirulent human strain No. 599. 2-Methylanilinoquinoline showed activity at a minimum dosage of 0.2 mg. per 10 ml. of culture. Compounds (III) and (IV) were active at a minimum dosage of 2 mg., and compound (II) was active at a minimum dosage of 20 mg.

EXPERIMENTAL[4,5]

Halogen compounds. 4,7-Dichloroquinoline (m.p. 86–87°) and 2-chloroquinoline (b.p. 152–154° at 22 mm.) were commercial products. 2-Bromopyridine (b.p. 88–89° at 24 mm.) was prepared in 85% yield from 200 g. of 2-aminopyridine and the corresponding amounts of sodium nitrite, bromine and 48% hydrobromic acid essentially by the method of Craig (19).

Preparation of metallic bases. Sodium or potassium amide was made in the usual manner (16, 17) in a three-necked flask (ground glass joints) fitted with a mercury-sealed stirrer, dropping-funnel, and a condenser having an attached Drierite drying tube. Sodium anilide and sodium methylanilide were prepared by the addition of the redistilled amine, dissolved in an equal volume of anhydrous ether, to an equivalent of sodium amide suspended in liquid ammonia. The anilide and the methylanilide, which were both soluble in liquid ammonia, were formed almost immediately.

Sodium diphenylamide was prepared in a similar manner except that, after all the diphenylamine (m.p. 54°) had been added, the ammonia was replaced by anhydrous di-*n*-butyl ether (b.p. 141°) and the suspension stirred and refluxed for two hours to ensure complete conversion to the salt.

The magnesium bases were prepared using the apparatus described above, by the dropwise addition of an equivalent of the redistilled amine, dissolved in anhydrous ether, to a stirred 0.2 molar solution of ethylmagnesium bromide (13). The reaction was considered complete after twenty to thirty minutes. Di-*n*-butylaminomagnesium bromide, *n*-butylaminomagnesium bromide, and methylanilinomagnesium bromide were all soluble in ether. Anilinomagnesium bromide was insoluble in ether.

Reactions of halogen compounds with metallic bases. The proportions of reactants, the general conditions, the yields and the physical constants of the products are summarized in Table I. The procedures with the various metallic bases are described below.

(A). *With sodium or potassium amide.* A solution of 2-bromopyridine or 2-chloroquinoline in an equal volume of anhydrous ether was added dropwise to a liquid ammonia suspension of sodium amide or a solution of potassium amide and the reaction mixture was allowed to reflux (a Dry-Ice reflux condenser with attached Drierite tube was used). The salts were decomposed by the careful addition of excess solid ammonium chloride. The ammonia was allowed to evaporate and about 50 ml. of 5% sodium hydroxide solution for each 0.1 mole of amide ion used was then carefully added.

2-Aminopyridine was isolated by saturating the sodium hydroxide solution with sodium hydroxide pellets in an ice-bath, followed by extraction with ether. After drying over Drierite the ether was removed and the residue was distilled *in vacuo*; usually there was no forerun.

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[4] Analyses were done by Oakwold Laboratories, Alexandria, Va.

[5] Boiling points are uncorrected; melting points, unless otherwise stated, are also uncorrected.

2-Aminoquinoline was isolated from the tar, which was formed after the alkali treatment, by several extractions with boiling distilled water. The water solution was evaporated to about 75 ml., treated with Norit, and chilled to give fine white crystals.

(B). *With sodium anilide.* To a stirred solution of sodium anilide in liquid ammonia was added dropwise a solution of 2-chloroquinoline in anhydrous ether. Some heat was evolved and a black solid soon formed. After three hours the ammonia was replaced by ether and the ether was refluxed. Potassium carbonate solution was then added, producing a red solid, and the mixture was extracted several times with ether. The portion of the solid which did not dissolve in ether was suction-filtered, washed with water, and dried *in vacuo* (see below). The combined ether extracts were dried over anhydrous potassium carbonate and the solvent distilled. The residue was fractionated *in vacuo* through an eleven-cm. Vigreux column up to 81° at 21.5 mm., and the remainder distilled through a von Braun head, giving a 46% yield of crude 2-anilinoquinoline boiling at 200–205° at 3.5 mm. and melting at 75–87°. Two recrystallizations from ligroin (b.p. 70–90°) using Norit gave crystals (20% yield) melting at 93–96°; a third recrystallization raised the melting point to 96–98°; reported m.p. 98° (20).

The ether-insoluble material mentioned above, after several recrystallizations from ethyl acetate, melted at approximately 200°, a constant melting point being difficult to obtain. A sample analyzed for di-α-quinolylphenylamine (I, R = C_6H_5).

Anal. Calc'd for $C_{24}H_{17}N_3$: N, 12.10. Found: N, 11.88.

(C). *With sodium methylanilide.* The reactions of 2-bromopyridine, 2-chloroquinoline and 4,7-dichloroquinoline with this basic reagent were carried out as described above for sodium anilide. At the conclusion of the refluxing period the ether solution was decanted and the solid washed with anhydrous ether till the washings were practically colorless. The solvent was removed from the combined ether solutions and the residue was distilled *in vacuo* through an eleven-cm. Vigreux column.

2-Methylanilinopyridine was redistilled, b.p. 147° at 10 mm. and analyzed as the free base.

Anal. Calc'd for $C_{12}H_{12}N_2$: C, 78.22; H, 6.57; N, 15.21.
Found: C, 78.17; H, 6.23; N, 15.52.

2-Methylanilinoquinoline was converted to its hydrobromide salt by adding 34% hydrobromic acid to a solution of the free base in ether until no more white crystals formed. The crystals were suction-filtered, washed with a small amount of acetone and recrystallized from a mixture of 95% ethanol and isopropyl ether to give a product melting at 260° corr.

Anal. Calc'd for $C_{16}H_{14}N_2 \cdot HBr$: C, 60.96; H, 4.80; Br^-, 25.35; N, 8.89.
Found: C, 60.45; H, 4.69; Br^-, 25.41; N, 9.37.

7-Chloro-4-methylanilinoquinoline was obtained as a heavy red oil which crystallized after several days standing at room temperature. This compound (m.p. 68–73°) was converted to its monohydrochloride salt by passing hydrogen chloride gas through an ether solution of it, and recrystallizing the precipitated salt four times from a mixture of ethanol and ethyl acetate. The salt (pale orange yellow needles) melted at 192–193° corr. and analyzed as the monohydrate.

Anal. Calc'd for $C_{16}H_{13}ClN_2 \cdot HCl \cdot H_2O$: C, 59.45; H, 4.99; Cl^-, 10.97; N, 8.67.
Found: C, 59.58; H, 4.95; Cl^-, 10.88; N, 8.96.

(D). *With sodium diphenylamide.* 2-Bromopyridine was added to a stirred suspension of sodium diphenylamide in di-*n*-butyl ether and the reaction mixture was refluxed on a Wood's metal-bath. After cooling, the salts were decomposed with a few ml. of water and the butyl ether solution was then extracted several times with 6 *N* hydrochloric acid solution. The combined acid extracts after separation from a large amount of black solid were saturated with potassium carbonate, extracted several times with ether and the combined ether solutions were dried over anhydrous sodium sulfate. After the ether was removed, the residue was fractionated through an eleven-cm. Vigreux column at 6 mm. yielding two fractions, b.p. 152–193° (partially solid) and b.p. 193° (m.p. 83–93°). The combined fractions were recrystallized from ethanol-water (Norit) to give 2-diphenylaminopyridine as

white crystals melting at 95–99°. Further recrystallization raised the melting point to 102–103.5°; reported m.p. 104° (21).

(E). *With the magnesium bases.* To a solution or suspension of the magnesium base was added the halogen compound, dissolved in anhydrous ethyl ether, and the mixture refluxed. In certain cases the ethyl ether was replaced by di-*n*-butyl ether and the reaction mixture was then stirred and refluxed. An aqueous ammonium chloride solution was added slowly with stirring; the two layers were separated and the aqueous layer, after saturation with ammonium chloride, was thoroughly extracted with ether. In some cases solids or oils formed during the course of the reaction; these experiments were, however, worked up in the same way as the others.

In the experiments carried out in ethyl ether the combined ether extracts were dried over potassium carbonate, the ether was removed and the residue was distilled *in vacuo* through an eleven-cm. Vigreux column.

In the experiments carried out in di-*n*-butyl ether the combined ether extracts were extracted several times with 6 *N* hydrochloric acid solution. After the combined acid solutions were saturated with potassium carbonate, the mixture was extracted several times with ether. The combined ether solutions were dried, the solvent distilled and the residue fractionated.

Di-α-quinolyl-*n*-butylamine (I, R = $n-C_4H_9$) was obtained, after evaporation of the ether, as a red oil which solidified after several days in the refrigerator. One recrystallization from methanol-water gave white crystals melting at 90–92°. Two additional recrystallizations raised the melting point to 91–92°.

Anal. Calc'd for $C_{22}H_{21}N_3$: C, 80.70; H, 6.47; N, 12.83.
Found: C, 80.49; H, 6.10; N, 13.21.

The monopicrate after three recrystallizations from methyl isobutyl ketone melted at 181–182° corr.

Anal. Calc'd for $C_{28}H_{24}N_6O_7$: C, 60.43; H, 4.35; N, 15.10.
Found: C, 60.80; H, 4.37; N, 15.54.

2-Di-*n*-butylaminopyridine was characterized as the monopicrate, which after three recrystallizations from 95% ethanol melted partly at 130–132° and partly at 134–135°; reported m.p. 136–137° (22).

Anal. Calc'd for $C_{19}H_{25}N_5O_7$: C, 52.41; H, 5.79; N, 16.09.
Found: C, 52.14; H, 5.57; N, 16.12, 16.14.

2-Di-*n*-butylaminoquinoline was carefully redistilled through a fifteen-cm. Vigreux column and a mid-fraction boiling at 172–173° at 2.5 mm. was analyzed as the free base.

Anal. Calc'd for $C_{17}H_{24}N_2$: C, 79.63; H, 9.44; N, 10.93.
Found: C, 79.50; H, 9.33; N, 11.00.

7-Chloro-4-di-*n*-butylaminoquinoline was characterized as the monopicrate, which after four recrystallizations from ethanol-dioxane melted at 178–180° after much sintering.

Anal. Calc'd for $C_{23}H_{26}ClN_5O_7$: N, 13.47. Found: N, 13.29.

2-Anilinoquinoline was obtained crude in 40% yield (b.p. 207° at 4 mm.; m.p. 87–95°). One recrystallization from ligroin (b.p. 70–90°) gave a product (28% yield) melting at 96–97°; reported m.p. 98° (20).

2-Phenylquinoline was obtained from 2-chloroquinoline and phenylmagnesium bromide, which was prepared in the usual manner. The crude product (b.p. 172–182° at 3.5 mm., m.p. 71–75°) was obtained in 52% yield by distillation through an eleven-cm. Vigreux column. A fair amount of higher-boiling material was also present. Two recrystallizations of the crude product from a mixture of ethanol and water gave white crystals melting at 82.5–83° (23). Further recrystallization did not raise the melting point.

Reaction of 2-chloroquinoline with methylaniline. A solution of 9.2 g. (0.085 mole) of methylaniline and 7.0 g. (0.043 mole) of 2-chloroquinoline was refluxed for nine hours on a Wood's metal-bath maintained at 250°. The reaction mixture was allowed to cool and was then poured into potassium carbonate solution. After the combined ether extracts of this mixture had been dried over potassium carbonate, the ether was distilled and the residue

was fractionated through a fifteen-cm. Vigreux column to give 3.7 g. (40% recovery) of methylaniline and 8.8 g. (87% yield) of 2-methylanilinoquinoline (b.p. 204–214° at 10 mm.) A portion of this product was converted to the hydrobromide salt as described in (C). A mixed melting point of this salt with the salt obtained in (C) showed no depression.

Derivatives of N-(γ-diethylaminopropyl)aniline (V). *p*-Toluenesulfonanilide (m.p. 99–101°) was prepared in 96% yield from aniline and *p*-toluenesulfonylchloride in pyridine. The product after two recrystallizations from ethanol-water melted at 101°; reported m.p. 103° (24).

To a solution of 94 g. (0.38 mole) of *p*-toluenesulfonanilide (m.p. 99–101°) and 66.8 g. (0.45 mole) of γ-diethylaminopropyl chloride (25) in 325 ml. of commercial absolute ethanol was added 52.5 g. (0.38 mole) of anhydrous potassium carbonate. After the reaction mixture had been refluxed for seventeen hours, about 200 ml. of ethanol was distilled off, the residue was poured into 300 ml. of 6 *N* hydrochloric acid and the small amount of insoluble material was filtered off. The acid solution was made alkaline with sodium carbonate and the resulting mixture was thoroughly extracted with chloroform. The chloroform was distilled leaving crude N-(γ-diethylaminopropyl)-*p*-toluenesulfonanilide. This crude alkylated sulfonanilide was hydrolyzed as described below. It was isolated from a small scale experiment starting with 10 g. of *p*-toluenesulfonanilide in 78% yield as a viscous yellow oil boiling at 252–256° at 7.5 mm. The picrate melting at 144–145° corr. after recrystallization from a mixture of ethanol and dioxane was analyzed.

Anal. Calc'd for $C_{26}H_{31}N_5O_9S$: C, 52.96; H, 5.30; N, 11.88; S, 5.44.
Found: C, 52.60; H, 5.27; N, 11.72; S, 5.63.

The hydrolysis of the crude alkylated sulfonanilide was carried out by refluxing it for seventeen hours in 900 ml. of 20% hydrochloric acid. The solution was cooled, saturated with sodium carbonate, and extracted several times with ether. After drying the combined ether extracts over potassium carbonate, the ether was distilled and the residue was fractionated *in vacuo* through a fifteen-cm. Vigreux column, yielding, after a slight forerun, 44.8 g. (59% overall yield from aniline) of N-(γ-diethylaminopropyl)aniline as a colorless oil boiling at 160–161° at 12.5 mm. A portion of this product was carefully redistilled and a portion of the mid-fraction boiling at 156.5° at 11 mm. was submitted for analysis.

Anal. Calc'd for $C_{13}H_{22}N_2$: C, 75.67; H, 10.75; N, 13.58.
Found: C, 75.13; H, 10.69; N, 13.67.

γ-Diethylaminopropylphenyl-α-quinolylamine (III). An ethyl ether solution containing 4.1 g. (0.025 mole) of 2-chloroquinoline and N-(γ-diethylaminopropyl)anilinomagnesium bromide, prepared from 5.1 g. (0.025 mole) of the diamine, was refluxed for thirty hours and allowed to stand at room temperature for twelve hours. The reaction mixture was then worked up as described above in (E), except that the product was distilled from a 50-ml. Claisen distilling flask to give 4.2 g. (51% yield) of crude γ-diethylaminopropylphenyl-α-quinolylamine as a yellow oil boiling at 175–193° at 2 mm.

A similar experiment carried out by refluxing the reaction mixture for 120 hours gave only a 42% yield of product.

The product was converted to its dihydriodide salt by the addition of an excess of a 47% hydriodic acid solution to the free base dissolved in isopropyl alcohol. The alcohol solution was heated to reflux and isopropyl ether was added till the solution became cloudy. On cooling, an oil formed, which solidified after twenty-four hours in the refrigerator. Four recrystallizations from isopropyl alcohol gave pale yellow needles melting at 185–186° corr.

Anal. Calc'd for $C_{22}H_{27}N_3 \cdot 2HI$: I^-, 43.07; N, 7.13.
Found: I^-, 42.69; N, 7.51.

γ-Diethylaminopropylphenyl-α-pyridylamine (II). The potassium salt of N-(γ-diethylaminopropyl)aniline was prepared according to the general procedure described above for alkali metal salts. In order to ensure satisfactory conversion, the ammonia was replaced by anhydrous ethyl ether and the ether suspension was stirred and refluxed for six hours, nitrogen being passed over the mixture during the last three hours. To the ether suspension of this salt was added an equivalent of 2-bromopyridine (4.7 g.; 0.029 mole), dissolved

in anhydrous ether. The mixture was refluxed and stirred for twenty-eight hours and the reaction mixture was then worked up as in (C), except that the product was distilled from a 50-ml. Claisen flask, to give 3.1 g. of recovered N-(γ-diethylaminopropyl)aniline and 2.8 g. (35%) of γ-diethylaminopropylphenyl-α-pyridylamine as a red oil boiling at 185–195° at 5 mm.; the yield was 70% when based on the N-(γ-diethylaminopropyl)aniline used, minus that recovered. When this compound was prepared by the magnesium salt method with a reflux period of 120 hours the yield was only 21%; the yield was 35% when based on the 2-bromopyridine and the N-(γ-diethylaminopropyl)aniline used minus that recovered. The product was converted to its dihydriodide salt by the dropwise addition of a 64% hydriodic acid solution to an ether solution of the free base. The oil which first formed soon crystallized on standing in the refrigerator. The salt was recrystallized four times from a mixture of commercial absolute ethanol and isopropyl ether, yielding white crystals melting at 187–188.5° corr.

Anal. Calc'd for $C_{18}H_{25}N_3 \cdot 2HI$: C, 40.09; H, 5.05; I^-, 47.07; N, 7.79.
Found: C, 40.61; H, 5.01; I^-, 47.27; N, 7.88.

γ-Diethylaminopropylphenyl-(7-chloro-4-quinolyl)amine (IV). This compound (b.p. 228° at 3 mm.) was prepared in 47% yield from 4,7-dichloroquinoline and the potassium salt of N-(γ-diethylaminopropyl)aniline. The reaction mixture was stirred and refluxed for 96 hours.

The product was converted to its dihydriodide salt as described for the salt of (IV). Three recrystallizations from a mixture of commercial absolute ethanol and isopropyl ether gave orange crystals melting at 192.5–193° corr.

Anal. Calc'd for $C_{22}H_{26}ClN_3 \cdot 2HI$: I^-, 40.70; N, 6.74.
Found: I^-, 40.91; N, 6.83.

SUMMARY

The scope, limitations, and mechanism of nucleophilic substitutions in pyridyl ring systems have been considered. α- and γ-Halopyridyl rings have been substituted with sodium and potassium amide, sodium methylanilide, di-*n*-butylaminomagnesium bromide and certain related basic reagents. Methylaniline has been coupled with 2-chloroquinoline.

Certain potential antimalarials have been synthesized.

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REFERENCES

(1) SCHOMAKER AND PAULING, *J. Am. Chem. Soc.*, **61**, 1769 (1939).
(2) See DEASY, *J. Org. Chem.*, **10**, 141 (1945).
(3) BANKS, *J. Am. Chem. Soc.*, **66**, 1127 (1944).
(4) BERGSTROM, *J. Org. Chem.*, **3**, 233 (1938).
(5) LEFFLER, "Organic Reactions"; John Wiley and Sons (New York); 1942, Vol. I; p. 92.
(6) BERGSTROM, STURZ, AND TRACY, *J. Org. Chem.*, **11**, 239 (1946).
(7) CHICHIBABIN AND SEIDE, *J. Russ. Phys.-Chem. Soc.*, **46**, 1216 (1914); *Chem. Abstr.*, **9**, 1901 (1915).
(8) See BERGSTROM, *Chem. Rev.*, **35**, 111 (1944).
(9) BERGMANN AND ROSENTHAL, *J. prakt. Chem.*, [2] **135**, 267 (1932).
(10) See ref. 8, p. 140, 168.
(11) GILMAN, CROUNSE, MASSIE, BENKESER, AND SPATZ, *J. Am. Chem. Soc.*, **67**, 2106 (1945)
(12) BERGSTROM AND HORNING, *J. Org. Chem.*, **11**, 334 (1946).
(13) HAUSER AND WALKER, *J. Am. Chem. Soc.*, **69**, 295 (1947).
(14) WALTER AND MCELVAIN, *J. Am. Chem. Soc.*, **57**, 1891 (1935).
(15) LEVINE, BAUMGARTEN, AND HAUSER, *J. Am. Chem. Soc.*, **66**, 1230 (1944).

(16) ADAMS AND HAUSER, *J. Am. Chem. Soc.*, **66,** 1220 (1944).
(17) YOST AND HAUSER, *J. Am. Chem. Soc.*, **69,** 2325 (1947).
(18) DRAKE AND CO-WORKERS, *J. Am. Chem. Soc.*, **68,** 1214 (1946).
(19) CRAIG, *J. Am. Chem. Soc.*, **56,** 232 (1934).
(20) FRIEDLÄNDER AND WEINBERG, *Ber.*, **18,** 1532 (1885).
(21) CHICHIBABIN, *J. Russ. Phys.-Chem. Soc.*, **50,** 497 (1918).
(22) SLOTTA AND FRANCKE, *Ber.*, **63,** 690 (1930).
(23) DOEBNER AND VON MILLER, *Ber.*, **16,** 1665 (1883).
(24) MÜLLER AND WEISINGER, *Ber.*, **12,** 1548 (1879).
(25) BRESLOW, WALKER, YOST, AND HAUSER, *J. Am. Chem. Soc.*, **67,** 1472 (1945).
(26) Ref. 5, p. 100.