[Contribution from the Chemical Laboratory of Iowa State College]

PYRIDYLLITHIUM COMPOUNDS

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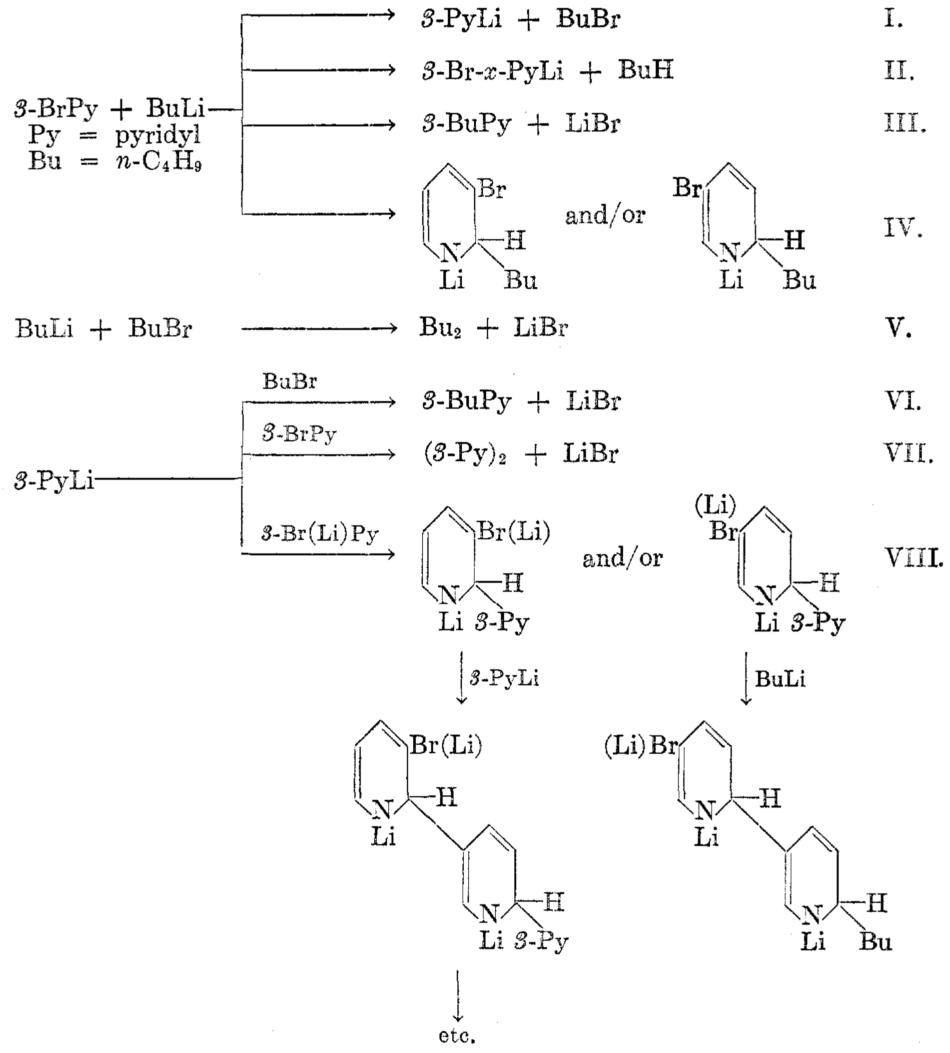
Functionally active pyridyl- and quinolyl-metallic compounds have been made available in recent years by the halogen-metal interconversion reaction (1, 2), a modified "entrainment" method (3), and the classical reaction between a metal, such as lithium or magnesium, and a pyridyl halide (4). The limited scope of the classical procedure in the formation of the pyridylmetallic



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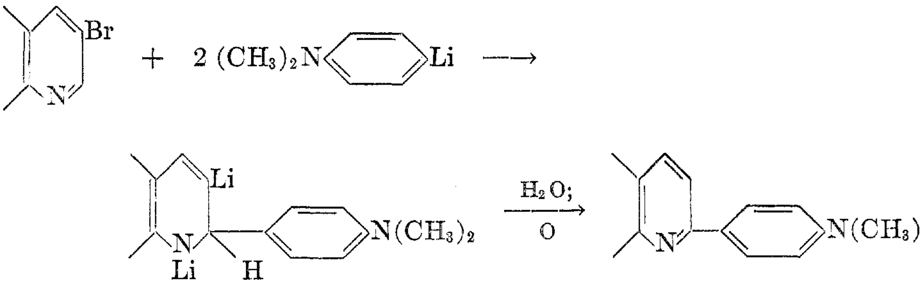
compounds has been established by numerous workers (4, 5); on the other hand, the versatility of the X-M interconversion reaction[2] (6) has been extended to the preparation of the 2-pyridyl-, the 3-pyridyl-, the 6-bromo-2-pyridyl-, and the 5-bromo-3-pyridyl-lithium compounds, and of several quinolyllithium compounds (1b).

The entrainment technique, providing only a 40–55% yield of 2-pyridylmagnesium bromide from 2-bromopyridine, magnesium, and ethyl bromide as the "auxiliary" agent, is suggestive of an X-M interconversion reaction. However, the slight yield difference observed with marked deficiences of the auxiliary content does not support an X-M interconversion mechanism (3).

Preliminary failures (7) to prepare pyridyl- and quinolyl-lithium compounds by X-M interconversion (reaction I) at 30–35° for twenty hours are understandable in the light of our present knowledge. Under these conditions, the —N═C linkage has ample opportunity to add not only the interconverting agent (reaction IV) but also the pyridyl- or quinolyl-lithium product as it is formed (reaction VIII). Failure to curb the activity of the azomethine function accounts in considerable, if not in complete, measure for the negative results obtained hitherto (5, 7). Subsequently, the application of the interconversion technique at low temperature (−35° to 0°) and short reaction time (5 to 15 minutes) was established as the most suitable means for suppressing the —N═C activity (1). The simultaneous occurrence of X-M interconversion and RLi addition is reflected in the isolation of 2-*p*-dimethylaminophenylquinoline from the reaction between 3-bromoquinoline and *p*-dimethylaminophenyllithium, subsequent to the customary hydrolysis and air-oxidation (8):



Competition from nuclear metalation (reaction II) may in large part be ignored since this reaction is conspicuously slower than reactions I, IV, and VIII (1b). The well-known lateral metalations of α-picoline and quinaldine (9) do not apply to the problem under discussion, but even this type of metalation is slow. On the other hand, the RLi addition to the azomethine linkage in pyridine and quinoline is rapid (10). A striking illustration is the 93.5% yield of 2-*n*-butylquinoline from a 15-minute reaction between *n*-butyllithium and quinoline at −35° (1b). Indeed, the action of various alkyllithiums on 2-bromo-, 3-bromo-, 3-iodo-, 2,6-dibromo-, 3,5-dibromo-, and 2-bromo-3,4,6-triphenylpyri-

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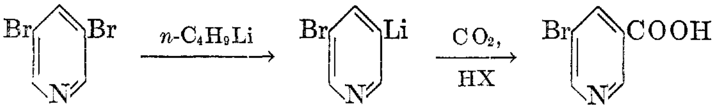
[2] For a review of the mechanism, scope, and experimental use of the halogen-metal interconversion reaction, see Jones and Gilman, *Org. Reactions*, **6**, 339–366 (1951).

dines (2), as well as on 3-bromoquinoline (1) and 2-iodolepidine (1b), which, incidentally, contains an active lateral hydrogen, failed to yield detectable quantities of metalation products.

The interconversion yields may, however, be diminished by a variety of coupling reactions (III, V, VI, and VII). Both the inorganic and an organic coupling product have been isolated. The latter, 2,2′-bipyridyl from a 2-pyridyllithium preparation (11), tags the occurrence of reaction VII. As yet, little is known about the relative magnitude of the several coupling reactions. Further aspects of the coupling reactions are presented in the experimental part.

The 63–69% yield of 2-pyridyllithium, estimated by its condensation with benzaldehyde, is in contrast with the 30–35% yield of the 3-isomer, determined by carbonation. Substitution of the 3-bromopyridine by the iodo compound increased the yield of 3-pyridyllithium to 40–46%. But the reactions of 3-bromopyridine with a variety of interconverting agents (Table I) did not effect any yield improvement, and thus failed to disclose any noteworthy RLi agent capable of slow addition to the —N=C group and of rapid interconversion with the halogen atom. It should be noted that the decreasing X-M reactivities of *sec*-C_4H_9Li, *n*-C_3H_7Li, C_2H_5Li, *tert*-C_4H_9Li, *n*-C_4H_9Li, *n*-$C_5H_{11}Li$, C_6H_5Li, and CH_3Li toward α-bromonaphthalene (12) did not correlate exactly with the interconversion yields from 3-bromopyridine. For example, *n*-propyllithium gave a 16.8% yield of 3-pyridyllithium in contrast to the 24.5% yield obtained with the relatively sluggish *n*-amyllithium. The yield reversal may arise from a greater reactivity of the propyllithium for the —N=C bond. The steric factor expected from the substitution of the *sec*- and *tert*-butyllithiums for the *n*-butyllithium did not decrease anil addition (Table I, expts. 5, 6, and 7).

In contrast to the dihalogenated carbazoles (1b), the 2,6- and 3,5-dibromopyridines undergo monointerconversion:



In conjunction with the carbazole studies, these facts suggest a stepwise mechanism for multiple interconversions in polyhalogenated compounds. Interestingly, the application of the modified entrainment method to 2,6-dibromopyridine yields the dimagnesium compounds (3).

To date, only the bromo- and iodo-pyridines and -quinolines have responded to the X-M interconversion. Compounds containing α- and γ-chlorine atoms, recognized for their increased reactivity toward hydrolysis, ammonolysis, and etherification by alkoxides, have not yet been found capable of the X-M interconversion reaction (1b, 13).

EXPERIMENTAL

3-Pyridyllithium from 3-bromopyridine. Of the several experiments summarized in Table I, only experiment 1 is described in detail. A solution of 10 g. (0.063 mole) of 3-bromopyridine in 50 cc. of ethyl ether was added dropwise under nitrogen to a rapidly stirred solution of

0.07 mole of *n*-butyllithium in 150 cc. of ether at −5° to 0° over a period of 25 minutes. Each addition of the 3-bromopyridine formed a yellow flocculent precipitate which gradually changed to a more compact red-brown body with the simultaneous coloration of the solution to brick red. When all of the bromopyridine had been added, agitation of the mixture was stopped and the precipitate allowed to settle for five minutes. The supernatant liquid was carbonated by decantation into an ether slush[3] of freshly powdered Dry Ice. The dark red-

TABLE I

3-PYRIDYLLITHIUM

EXP. NO.	STARTING MATERIAL*	INTERCONVERTING REAGENT	SOLVENT	TEMP., °C.	TIME (MIN.)	YIELD OF 3-PyLi, %
1	3-BrPy 0.063 m. in 50 cc.	*n*-C$_4$H$_9$Li 0.07 m. in 150 cc.	Ethyl ether[a]	−5 to 0°	30	30.8
2	3-BrPy 0.063 m. in 100 cc.	*n*-C$_4$H$_9$Li 0.07 m. in 150 cc.	Ethyl ether[b]	−14°	15	16.8
3	3-BrPy 0.045 m. in 50 cc.	*n*-C$_3$H$_7$Li 0.052 m. in 100 cc.	Ethyl ether[c,d]	−20°	15	16.9
4	3-BrPy 0.057 m. in 50 cc.	*n*-C$_5$H$_{11}$Li 0.067 m. in 100 cc.	Ethyl ether[c,d]	−20°	15	24.5
5	3-BrPy 0.057 m. in 40 cc.	*sec*-C$_4$H$_9$Li 0.065 m. in 140 cc.	Petroleum ether (b.p. 20–28°)[d]	−20 to −15°	15	35.7
6	3-BrPy 0.047 m. in 40 cc.	*tert*-C$_4$H$_9$Li 0.056 m. in 140 cc.	Petroleum ether[d]	−20 to −15°	15	32.9
7	3-BrPy 0.055 m. in 40 cc.	*n*-C$_4$H$_9$Li 0.062 m. in 140 cc.	Petroleum ether[d]	−20 to −15°	15	34.3
8	3-IPy 0.017 m. in 30 cc.	*n*-C$_4$H$_9$Li 0.027 m. in 80 cc.	Ethyl ether[e]	−20 to −15°	41	41.3
9	3-IPy 0.02 m. in 35 cc.	*n*-C$_4$H$_9$Li 0.027 m. in 100 cc.	Ethyl ether[e]	−20 to −15°	26	42.2
10	3-IPy 0.02 m. in 35 cc.	*n*-C$_4$H$_9$Li 0.027 m. in 100 cc.	Ethyl ether[c,d]	−20 to −15°	15	46.3
11	3-IPy 0.013 m. in 25 cc.	*n*-C$_4$H$_9$Li 0.018 m. in 75 cc.	Ethyl ether[e]	−20 to −15°	33	40.2

* Legend: BrPy = Bromopyridine; IPy = Iodopyridine; PyLi = Pyridyllithium; cc. refers to quantity of solvent.

[a] The initially yellow, flocculent precipitate gradually changed to a dark, red-brown, amorphous or gummy precipitate. Only the supernatant solution was carbonated. [b] In this experiment, the customary addition of the halogenated pyridine to the alkyllithium reagent was reversed. [c] The alkyllithium compound was prepared in unsaturate-free petroleum ether (b.p. 20–28°); the solvent was distilled off under nitrogen to within a volume of about 8–10 cc. and replaced with ethyl ether. [d] The color and consistency of the voluminous, cream-colored precipitate did not change materially by the end of the reaction. The entire contents were carbonated, since separation of the liquid from the precipitate was attended with difficulties. [e] The quantity of dark, red-brown, gummy precipitate which formed by the end of the reaction was considerably smaller than those of experiments 1 and 2.

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[3] The technique of carbonating organolithium compounds by pouring onto a slush of Dry Ice and ether was reported previously by Gilman and Spatz, *J. Am. Chem. Soc.*, **63**, 1553 (1941).

brown residue was hydrolyzed to a thick oil, but except for the isolation of a minute amount of pyridine, the rest of the oily material remains to be identified. It did not contain any 3-bromopyridine.

After hydrolysis of the carbonation mixture with 1% potassium hydroxide solution, the alkaline layer was boiled with Norit, filtered, acidified with hydrochloric acid, and boiled to remove odor traces of valeric acid. The solution, neutralized to litmus, yielded *via* the copper salt (14) 2.4 g. (30.8%) of nicotinic acid, melting at 231–232° (15). The picrate melted at 214–215°, which agrees with the reported value (16). The octadecylamine salt of this acid, prepared by Dr. B. A. Hunter (17), melted at 78–79°, and a mixture melting point with an authentic specimen showed no depression.

Examination of the ether layers of experiments 3 and 4, subsequent to carbonation and hydrolysis, yielded 0.07 g. and 0.04 g. of pyridine, respectively, but no 3-bromopyridine.

The preparation of the *n*-amyllithium (12b) for experiment 4 was effected in 84% yield from 8.5 g. (0.08 mole) of *n*-amyl chloride in 50 cc. of petroleum ether (b.p. 20–28°) and 1.25 g. (0.18 g.-atom) of lithium in 60 cc. of the same solvent.

The *sec*-butyllithium (12b) for experiment 5 was prepared in 65% yield from 0.1 mole of *sec*-butyl chloride and 0.22 g.-atom of lithium. The *tert*-butyllithium for experiment 6 was prepared by Dr. W. F. Moore from *tert*-butyl chloride (12b).

In experiments 5 and 7, one-half to one-cc. samples of the reaction mixture were withdrawn just prior to carbonation for Color Tests I (18) and IIa (19). In both experiments, the former test was positive (deep, dark green) and the latter negative, indicating that the organolithium compound was not an alkyllithium compound. *sec*-Butyllithium itself in petroleum ether gave a red-violet Color Test I and a bright salmon red Color Test IIa.

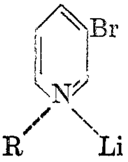

FIG. 1

The 3-bromopyridine for experiments 2 and 4 was provided by the kindness of Dr. S. A. Harris of Merck & Co. Eastman's 3-bromopyridine was employed in the other experiments.

Unlike the preparation of the other pyridyllithium compounds, that of the 3-pyridyllithium is accompanied by precipitate formation, presumably originating from either simple or multiple RLi additions to the —N=C< group (reactions IV and VIII). The absence of precipitate formation does not necessarily infer the absence of anil addition. For example, the reaction between *o*-anisyllithium and quinoline may or may not precipitate the intermediary 1-lithio-2-*o*-anisyl-1,2-dihydroquinoline without affecting materially the ultimate isolation of 2-*o*-anisylquinoline (13). Since the alkyllithium compound is consumed completely within 15 minutes, the occurrence of the rapid reactions I, IV, and VIII is strongly suggested. The product of reaction I, as already indicated, is dissolved in the solvent. The insoluble body, since it yielded neither pyridine nor 3-bromopyridine subsequent to hydrolysis, is neither 3-pyridyllithium nor an addition complex (Fig. 1) of the type postulated for pyridine and phenylmagnesium bromide (20); the insoluble body must, therefore, have resulted from reactions IV and/or VIII.

3-Pyridyllithium from 3-iodopyridine. In experiment 8, Table I, the ethereal solution of iodopyridine[4] was added dropwise over a 36-minute period to a vigorously stirred solution of *n*-butyllithium. The pale yellow, voluminous precipitate gradually changed to a compact body. The solution darkened from yellow through orange to brick red. When all of the iodopyridine had been added, stirring was arrested to permit settling of the dark red precipi-

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[4] Provided through the courtesy of the late Dr. F. C. Schmelkes, Wallace and Tiernan Co., Belleville, N. J.

tate; this was accomplished within five minutes. Also, from the clear supernatant liquid a white, crystalline material settled out in increasing amount toward the end of the reaction period. The supernatant solution was easily decanted upon Dry Ice and processed for the nicotinic acid.

In experiment 11, the white, crystalline material was rinsed off the dark red gum with dry ether. After one recrystallization from water, it was identified as lithium iodide, the inorganic product of coupling. Its chronological appearance, largely toward the end of the reaction period, suggests that the primary coupling (reaction III) is of minor significance. Of the three secondary coupling reactions, VI and/or VII appear to be the dominant ones since the color test IIa (19) for alkyllithium compounds is negative long before the major portion of the lithium iodide has precipitated.

It is interesting to note that the pyridyllithium solution from 3-iodopyridine and *n*-butyllithium in ethyl ether is more easily decanted than the pyridyllithium solution from 3-bromopyridine in the same solvent.

2-Pyridyllithium and pyridyl-2-phenylcarbinol. A solution of 12.6 g. (0.08 mole) of 2-bromopyridine[5] in 50 cc. of ether was added slowly over a three-minute period to 0.09 mole of *n*-butyllithium in 200 cc. of ether at −18°, and the red solution stirred for seven minutes. To the solution of 2-pyridyllithium was added, over a five-minute period, 10.6 g. (0.1 mole) of freshly purified benzaldehyde in 50 cc. of ether. When most of the aldehyde had been added, the red color suddenly disappeared and a gray precipitate formed which gradually turned to yellow by the end of 30 minutes. The temperature was kept at −18° throughout. At the end of this time, a sample of the reaction contents gave a negative color test (18). After hydrolysis with an ice-cold solution of ammonium chloride, the ether layer was filtered from a small amount of insoluble residue and extracted with 10% hydrochloric acid. Neutralization of the acid extract gave a dark oil, which was dissolved in ether and the solution dried over potassium carbonate. Fractional distillation gave a pale yellow oil (b.p. 143°/2 mm.) which gradually solidified to a white, crystalline mass, melting at 68–74°. The yield of crude carbinol was 10.1 g. or 68.7% on the basis of the 2-bromopyridine used.

A sample of the crude product, dissolved in 95% ethanol, gave a picrate, melting at 169°, which is in agreement with the value reported by Ashworth, *et al.* (21).

Recrystallization of the carbinol from an ether-ligroin mixture gave heavy, white crystals, melting at 76–78°. Ashworth reported the melting point as 78°. The yield of pure product was 9.3 g. (62.7%).

5-Bromo-3-pyridyllithium. A solution of 10 g. (0.042 mole) of 3,5-dibromopyridine (Eastman) in 100 cc. of ether, cooled to −30°, was added with stirring over a two-minute period to a filtered, similarly cooled solution of *n*-butyllithium (0.11 mole) in 160 cc. of ether. The reactants were stirred for ten more minutes at −30° and for five minutes with the cooling bath removed. After carbonation, 4.35 g. of crude acid was isolated from the alkaline layer. The acidic material was redissolved in dilute base and then acidified with glacial acetic acid, which precipitated 0.1 g. of a yellow colored product, melting at 213–217°. Further acidification of the filtrate with dilute hydrochloric acid yielded 3.5 g. (41%) of 5-bromonicotinic acid, melting, as reported (22, 23), at 182–183°.

When 9.9 g. (0.4 mole) of 3,5-dibromopyridine[3] in 150 cc. of ether was added gradually to 0.12 mole of *n*-butyllithium in 200 cc. of ether and stirred at −16° for 50 minutes, the transparent orange colored solution gave, subsequent to carbonation, a 64.1% yield of crude 5-bromonicotinic acid. The yield of pure product was 46.3%.

Another 9.9 g. of the 3,5-dibromopyridine[3] and 0.11 mole of *n*-butyllithium was kept at −35° for ten minutes, and then refluxed for 30 minutes in an attempted di-interconversion. After carbonation, only a minute quantity of highly impure acidic material was isolated.

Substitution of *n*-propyl- for *n*-butyl-lithium also failed to effect di-interconversion. A solution of 0.04 mole of the pyridine compound in 150 cc. of ether was treated with 0.12 mole of *n*-propyllithium in 200 cc. of the same solvent for 25 minutes at −35 to −10° to yield,

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[5] Provided through the courtesy of Dr. E. C. Britton, Dow Chemical Co.

subsequently, 4.0 g. (47.2%) of crude 5-bromonicotinic acid. The yield of pure product was 2.7 g. (32.1%).

Methyl 5-bromonicotinate. The methyl ester was prepared quantitatively by the action of excess diazomethane on an ethereal solution of 0.1 g. of the acid. The ester melted at 98–99°, as reported (23).

6-Bromo-2-pyridyllithium. In this case, (10 g., 0.042 mole) of 2,6-dibromopyridine was treated with 0.11 mole of *n*-butyllithium in the manner described for the preparation of the 5-bromo-3-pyridyllithium. The purified acid, isolated after carbonation, melted at 192–194°. Obtained in a yield of 3.85 g. (45.2%), the compound gave satisfactory bromine and nitrogen analyses for 6-bromopicolinic acid, as yet unreported in the literature. Likewise, the methyl ester derivative was found to have the correct nitrogen content. However, the acid itself gave unsatisfactory neutral equivalent data when titrated with dilute alkali against phenolphthalein as indicator.

Anal. Calc'd for $C_6H_4BrNO_2$: Br, 39.57; N, 6.95; Neut. equiv., 202.
Found: Br, 39.13, 39.34; N, 6.88, 6.82; Neut. equiv., 181, 182.2.

An attempted di-interconversion between 12.4 g. (0.05 mole) of 2,6-dibromopyridine in 150 cc. of ether and 0.16 mole of *n*-butyllithium, maintained at −16° for 55 minutes, gave, instead, a 39.8% yield of 6-bromopicolinic acid. In a run carried out at the temperature of the refluxing ether, no acidic material was isolated after carbonation.

Methyl 6-bromopicolinate. Methylation of 6-bromopicolinic acid with diazomethane gave a crystalline ester, which softened at 92–93° and melted at 93–94°.

Anal. Calc'd for $C_7H_6BrNO_2$: N, 6.41. Found: N, 6.49.

DISCUSSION

The yield estimation of a non-isolatable RMgX or RLi compound varies not only with the characterizing agent employed, but also with the ease of isolation of the resulting derivative. This statement takes into account the variation in side reactions incurred with different functional groups. Only recently, French and Sears demonstrated a yield variation of 15 to 70% for 3-pyridyllithium, depending on the method of derivatization (24). The respective 69 and 35% yields of the 2- and 3-pyridyllithiums, reported in this paper, are, therefore, not strictly comparable, since the former was estimated by a condensation with benzaldehyde and the latter by reaction with carbon dioxide, although both reagents are highly reactive toward RLi and RMgX compounds. However, in subsequent studies (25) an 83–86% yield of 2-pyridyllithium was effected by a condensation with *p*-methoxybenzonitrile, a type of molecule which is low in the Entemann-Johnson series of reactivities with RMgX compounds (26). It is, therefore, our opinion that 2-pyridyllithium is obtainable in better yield than the 3-isomer from the X-M interconversion reaction with the corresponding halogenated pyridines. This opinion is justified further by the following considerations.

The yield difference can be explained simply in terms of the socalled greater reactivity of the 2- over the 3-positioned halogen in the pyridine (and quinoline) series. However, it is to be noted that the reactivity difference has been established from a variety of metathetic reactions with amines, sodium alkoxides, etc. (27), not one of which is capable of adding to the azomethine function, even under the conditions essential for metathesis. Accordingly, it is perhaps possible to consider the yield variations of X-M interconversions in the pyridine series in terms of the deactivating influence of the electronegative halogen on the competitive azomethine function.

In 2-bromopyridine, the electron density at the nitrogen atom must be less than that of its counterpart in 3-bromopyridine by virtue of the unequal inductive effects ($-I_s$) of the halogens. Hence, the former nitrogen will have a weaker affinity for the electrophilic lithium in the process of anil addition, resulting in an increased availability of the RLi reagent for X-M interconversion. The deactivating effect of an electron-attracting group on the azomethine function is supported by the large recovery of α-chloroquinoline from an attempted reaction with methyllithium (1b). Likewise, organolithium compounds have been found to add much less readily to 2-aryl- and to 2-chloro-pyridines than to pyridine itself as evidenced by the slower rate of addition, the lower yield of product, or the complete absence of reaction (11). In these examples, geometric hindrance may also play a significant role. Decisive evidence for the geometric hindrance of the methyl radical of α-picoline in the reaction with trimethylboron has been established recently by Brown and Barbaras (28). In the case of the bromopyridines, the 2-bromine atom conceivably creates a greater steric hindrance toward RLi loss by anil addition than the 3-bromine atom, providing thereby a greater X-M interconversion yield.

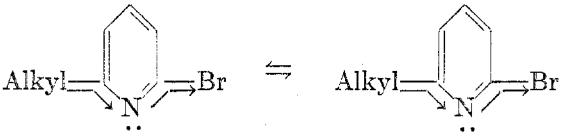

FIG. 2

Likewise, 3,5-dibromopyridine, endowed with two electron-attracting sources, should be characterized by less RLi addition and more interconversion than 3-bromopyridine, which is in accord with the experimental data.

Finally, the $-I_s$ effect of the —CH=CH—CH=CH— group, deducible from the ionization constants of quinoline and pyridine (1×10^{-9} and 2.3×10^{-9} at 25°, respectively) and of α-naphthylamine, β-naphthylamine, and aniline (9.9×10^{-11}, 2×10^{-10}, and 4.6×10^{-10} at 25°, respectively) (29), suggests that 3-bromoquinoline, like 3,5-dibromopyridine, should undergo less anil addition than 3-bromopyridine. The X-M interconversion yields conform with these contentions.

Possibly, the X-M interconversion reaction of bromopyridines with alkyllithium compounds provides an additional tool for the relative estimation of the geometric *versus* electronic influences in sterically hindered reactions (28). In the consideration of certain alkylbromopyridines (Fig. 2), a predominance of the electronic influence should be reflected by a diminished X-M interconversion yield over that obtained with 2-bromopyridine, since the $-I_s$ effect of the halogen atom is partially counteracted by the $+I_s$ effect of the alkyl group which thus enhances the electron availability of the nitrogen for RLi addition. Conversely, a proportionately larger share of the geometric influence should be reflected by less anil addition and accordingly more X-M interconversion in the molecule represented by Fig. 2 than in 2-bromopyridine.

The superior X-M interconversion yield from 3-iodopyridine, compared to that from 3-bromopyridine, is in accord with the greater polarizability of the iodine atom (− I > − Br > − Cl > − F).[6]

SUMMARY

The preparation of 2-pyridyl-, 3-pyridyl-, 6-bromo-2-pyridyl-, and 5-bromo-3-pyridyl-lithium compounds is described.

The mono-interconversion behavior of the dibromopyridines contrasts with the di-interconversion behavior of the bromocarbazoles.

The variation of interconversion yields with molecular structure is discussed.

AMES, IOWA

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