of cyclohexanone diisopropyl ketal were absent. In the spectrum after 130 min. weak absorption bands due to the cyclohexanone ketal had appeared and the absorption bands of cyclohexanone and the acetone ketal had become weaker. These trends continued in the same direction in the spectrum of the 190-min. sample, in which the concentration of cyclohexanone diisopropyl ketal was estimated at about 10%.

b. Cyclohexanone isopropyl methyl ketal and cyclohexanone diisopropyl ketal. A solution of cyclohexanone (98 g., 1.0 mole), isopropyl alcohol (264 g., 4.40 moles), 2,2-dimethoxypropane (125 g., 1.20 mole), benzene (250 ml.), and *p*-toluenesulfonic acid (0.05 g.) was distilled on a good fractionating column at a pressure of 270 mm. with automatic controls set to remove distillate when the temperature in the still head was below 34°. After about 24 hr. this temperature could not be maintained with a 50:1 reflux ratio, so the distillation was stopped. The volume of the distillate was 226 ml. and contained 109 ml. of water-soluble material. The reaction solution was made basic by adding a solution of 0.1 g. of sodium in 20 ml. of isopropyl alcohol. Infrared analysis showed that less than 2% of the cyclohexanone remained unchanged. Distillation was resumed and after 412 ml. of forerun had distilled, 99 g. (57.5%) of cyclohexanone isopropyl methyl ketal was obtained in the boiling range 47–70° (8 mm.), n_D^{24} 1.4388. The residue was identified by infrared spectroscopy as practically pure cyclohexanone diisopropyl ketal, yield 34 g. (17%). Similar yields were obtained using hexane as solvent instead of benzene.

Hydrolytic degradation. Equimolar amounts of acetone di-*sec*-butyl ketal (11.5 g.) and water (1.10 g.) were mixed and acidified with a tiny crystal of *p*-toluenesulfonic acid introduced on the bulb of a thermometer. The temperature began to decrease and the mixture suddenly became homogeneous. The infrared spectrum of the solution, determined after 30 min., indicated the presence of 29% (vol.) acetone and 70% *sec*-butyl alcohol (calcd., 29% and 71%). None of the absorption bands of the ketal was present.

Cyclohexanone dicyclohexyl ketal was hydrolyzed in an equal weight of purified dioxane with a 10% excess of water, and the infrared spectrum of the solution was determined. Absorption bands characteristic of cyclohexanol and cyclohexanone were present, but the bands of the ketal were absent.

Acknowledgment. The authors are grateful to J. H. Brown, Jr., Professor Otis C. Dermer, and Professor Lewis F. Hatch for their advice and help.

FREEPORT, TEX.

[CONTRIBUTION NO. 1054 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Synthesis of Nitrogen-Containing Ketones. X. The Mechanism of the Acylation of Pyridine Derivatives[1,2]

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A new mechanism is proposed for the course of the acylation of pyridine derivatives. Evidence in its support is presented.

As a result of previous work from this laboratory,[4–7] the following series of reactions was proposed, using a 2-alkylpyridine as an example, to rationalize the results which were obtained when 2-picoline and certain related 2-alkylated tar bases were acylated with esters in the presence of the basic condensing agent, BM.

$$\underset{\text{I}}{2\text{-}C_5H_4NCH_2R} + BM \longrightarrow \underset{\text{II}}{(2\text{-}C_5H_4NCHR)^-\,M^+} + HB \quad (1)$$

$$\text{II} + R'CO_2C_2H_5 \longrightarrow \underset{\text{III}}{2\text{-}C_5H_4NCHR(COR')} + MOC_2H_5 \quad (2)$$

$$\text{III} + \text{II} \begin{cases} \xrightarrow{a} \underset{\text{IV}}{[2\text{-}C_5H_4NCR(COR')]^-M^+} + \text{I} \\ \xrightarrow{b} \underset{\text{V}}{(2\text{-}C_5H_4NCHR)_2C(OM)R'} \end{cases} \quad (3)$$

An acid-base reaction occurs between I and the basic condensing agent, BM, to give the metalated pyridine derivative, II (equation 1). *Then it is assumed* (Equation 2) *that the free ketone,* III, *is formed by the reaction of* II *with the ester.* Finally, III may react with II in two ways: (1) III and II may undergo an acid-base reaction to give the anion of the ketone, IV, and I (Equation 3a) and (2) a carbinol may be formed as its metallic salt, V, by the addition of II across the carbonyl group of III (Equation 3b). Thus, when the lithium derivatives of 2-picoline,[4,5] quinaldine,[5] 2,6-lutidine,[5] 2-ethylpyridine,[7] and 2-isobutylpyridine[7] were acylated with esters only ketones of type III (where R′ is aromatic or heterocyclic) or mixtures of ketones and carbinols of type V (where M = H and R′ is aliphatic) were obtained. When

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(1) For paper IX in this series, see S. Raynolds and R. Levine, *J. Am. Soc.*, in press.

(2) This paper is based on part of the thesis presented by S. R. to the Graduate Faculty of the University of Pittsburgh in partial fulfillment of the requirements for the Ph.D. degree.

(3) Monsanto Chemical Co. Research Fellow for the academic year 1958–59.

(4) N. N. Goldberg, L. B. Barkley, and R. Levine, *J. Am. Chem. Soc.*, **73**, 4301 (1951).

(5) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **74**, 5217 (1952).

(6) N. N. Goldberg and R. Levine, *J. Am. Chem. Soc.*, **77**, 4926 (1955).

(7) C. Osuch and R. Levine, *J. Org. Chem.* **21**, 1099 (1956).

TABLE I

ACYLATION OF 2-PICOLINE AND 2-BENZYLPYRIDINE TO GIVE KETONES, $2-C_5H_4NCHRCOR'$, AND CARBINOLS, $(2-C_5H_4NCHR)_2C(OH)R'$, USING 2:2:1 MOLAR RATIO OF TAR BASE: CONDENSING AGENT: ETHYL ESTER

Run No.	R	R'	Condensing Agent	Solvent	Temp.	Ketone, % Yield	M.P. or B.P.	mm.	Carbinol, % Yield	M.P. or B.P	Mm.	K/C
1	H	CH_3	C_6H_5Na	C_6H_6	5	59	75–78[a,b]	2	28	148–152[a,c]	2	2.1
2	H	C_2H_5	C_6H_5Na	C_6H_6	5	55	83–86[a,d]	2	33	153–156[a,e]	1	1.7
3	H	C_2H_5	SDIA[f]	C_6H_6	5	48	73–75	0.77	22	135–140	0.68	2.2
4	H	C_2H_5	C_6H_5Li	$(C_2H_5)_2O$	35[g]	62	83–86	2	12	153–156	1	5.2
5	H	C_2H_5	LDIA[h]	$(C_2H_5)_2O$	35[g]	62	83–86	2	2	135–140	0.68	31.0
6	H	C_2H_5	C_6H_5Li	C_6H_6	5	64	83–86	2	4	153–155	1	16.0
7	H	C_2H_5	C_6H_5Na	$(C_2H_5)_2O$[i]	35[g]	34	83–85	2	24	153–156	1	1.4
8	H	C_6H_5	C_6H_5Na	C_6H_6	5	80	148–155[a]	2	0			∞
9	H	C_6H_5	C_6H_5Li	$(C_2H_5)_2O$	35[g]	80	149–155	2	0			∞
10	C_6H_5	CH_3	C_6H_5Li	$(C_2H_5)_2O$	35[g]	93	145–150[j]	2.74	0			∞
11	C_6H_5	C_2H_5	C_6H_5Li	$(C_2H_5)_2O$	35[g]	22	128–132 76–78[k,l]	0.28	60	146–147[m,n]		0.37
12	C_6H_5	C_2H_5	SDIA[f]	C_6H_6	5	82	128–132	0.27	0			∞
13	C_6H_5	C_2H_5	C_6H_5Na	C_6H_6	5	81	128–132	0.28	0			∞
14	C_6H_5	C_2H_5	LDIA[h]	$(C_2H_5)_2O$	35[g]	54	128–132	0.28	37	146–147		1.5
15	C_6H_5	C_2H_5	C_6H_5Li	C_6H_6	5	64	128–132	0.28	0			∞
16	C_6H_5	C_2H_5	C_6H_5Na	$(C_2H_5)_2O$[i]	35[g]	68	128–132	0.28	0			∞
17	C_6H_5	$(CH_3)_2CH$	C_6H_5Li	$(C_2H_5)_2O$	35[g]	81	133–135[o,p]	0.30	0			∞
18	C_6H_5	C_6H_5	C_6H_5Li	$(C_2H_5)_2O$	35[g]	60	190–195 125.0–125.7[p,q]	0.5	16	137.8–138.8[r,s]		3.75
19	C_6H_5	C_6H_5	C_6H_5Na	C_6H_6	5	62	180–185	0.25	0			∞
20	C_6H_5	C_6H_5	SDIA[f]	C_6H_6	5	82	180–185	0.25	0			∞

[a] See ref. 4. [b] Picrate, m.p. 134–135° (from 95% ethanol); lit.[4] m.p. 140–141°; *Anal.* Calcd. for $C_{14}H_{12}N_4O_8$: C, 46.16; H, 3.82. Found: C, 46.46; H, 3.63. [c] Dipicrate, m.p. 213–214°. [d] Picrate, m.p. 143.2–143.6°. [e] Dipicrate, m.p. 193.5–195°. [f] SDIA = sodium diisopropylamide. [g] Reaction effected in refluxing ether. [h] LDIA = lithium diisopropylamide. [i] The sodium derivative of the tar base was prepared in benzene, which was then replaced by ether. [j] *Anal.* Calcd. for $C_{14}H_{13}NO$: C, 79.60; H, 6.20. Found: C, 79.20; H, 6.30. Picrate, m.p. 133.8–134.5° (from 95% ethanol). *Anal.* Calcd. for: $C_{20}H_{16}N_4O_8$: C, 54.55; H, 3.66. Found: C, 54.18; H, 3.50. [k] From 95% ethanol. *Anal.* Calcd. for $C_{15}H_{15}NO$: C, 79.96; H, 6.71. Found: C, 79.98; H, 6.70. [l] Picrate, m.p. 117.5–119.2° (from a 60–70° petroleum ether-benzene mixture). *Anal.* Calcd. for $C_{21}H_{18}N_4O_8$: C, 55.51; H, 3.99. Found: C, 55.28; H, 4.05. [m] Recrystallized from 95% ethanol. *Anal.* Calcd. for: $C_{27}H_{26}N_2O$: C, 82.20; H, 6.64. Found: C, 82.51; H, 6.77. [n] Picrate, m.p. 133.0–133.5° (from 95% ethanol). *Anal.* Calcd. for $C_{39}H_{32}N_8O_{15}$: C, 63.56; H, 4.69. Found: C, 63.78; H, 5.12. [o] *Anal.* Calcd. for $C_{16}H_{17}NO$: C, 80.32; H, 7.16. Found: C, 80.74; H, 7.49. [p] From 60–70° petroleum ether. *Anal.* Calcd. for $C_{19}H_{15}NO$: C, 83.49; H, 5.53. Found: C, 83.27; H, 5.92. [q] Picrate, m.p. 139.2–139.9° (from 95% ethanol). *Anal.* Calcd. for $C_{25}H_{18}N_4O_8$: C, 59.76; H, 3.61. Found: C, 59.62; H, 3.71. [r] From a 60–70° petroleum ether-benzene mixture. *Anal.* Calcd. for $C_{31}H_{26}N_2O$: C, 84.13; H, 5.92. Found: C, 83.80; H, 5.86. [s] Attempts to prepare a crystalline picrate failed.

TABLE II

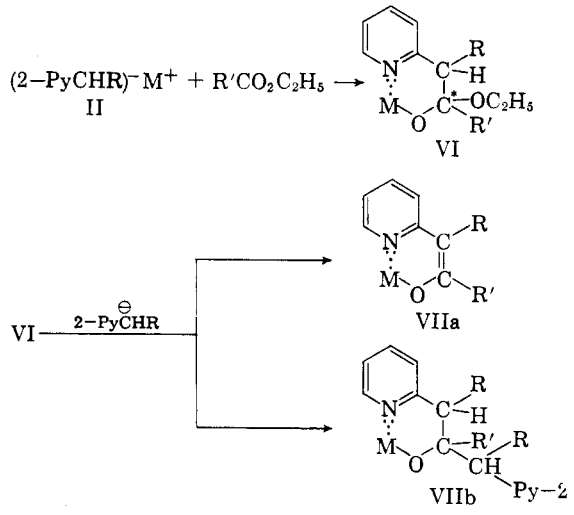
REACTIONS OF KETONES, 2-$C_5H_4NCHR(COC_2H_5)$, I, WITH TAR BASES, 2-$C_5H_4NCH_2R$, II, IN THE PRESENCE OF CONDENSING AGENTS, C_6H_5M, III, TO GIVE CARBINOLS, $(2\text{-}C_5H_4NCHR)_2C(OH)C_2H_5$, IV

R	M	Molar Ratio III:II:I	Solvent	Temp.	Carbinol, IV % Yield	Ketone, I % Recovered
H	Na	1:1:1	C_6H_6	5	13	81
H	Na	2:2:1	C_6H_6	5	23	73
C_6H_5	Li	1:1:1	$(C_2H_5)_2O$	35[a]	0	73
C_6H_5	Li	2:2:1	$(C_2H_5)_2O$	35[a]	3	94

[a] Reaction effected in refluxing ether.

mixtures were formed, the ketone was found to be the major product.

In the present paper new data are presented which necessitate a revision of the mechanism which has just been described. *It is now suggested that when* II *and the ester react they do not give the free ketone directly. Instead, they react to give the adduct,* VI. Intermediate VI can then react with the anion II in two ways: (1) elimination of ethanol gives directly the enol derivative, VIIa, of the ketone and (2) displacement of ethoxide ion at C* by the anion II gives the metallic derivative, VIIb, of the carbinol. When the reaction is processed, VIIa and VIIb give the free ketone and carbinol, respectively.



A consideration of the following seven factors lends support to the revised mechanism.

1. Interaction of Metalated Pyridine Derivatives with Free Ketones. The original mechanism of Levine et al.[4–7] implies that, in those reactions where mixtures of ketones and carbinols are obtained, comparable amounts of the products should be obtained when either the metalated pyridine derivative is treated with an ester or the free ketone is treated with the metalated pyridine derivative. To test this argument several experiments were performed. From the interaction of two equivalents of 2-picolylsodium (prepared from 2-picoline and phenylsodium in benzene) and one equivalent of ethyl propionate (Table I, Run 2) there were isolated 1-(2-pyridyl)-butanone-2, VIII (55%, III where R = hydrogen and R′ = ethyl) and ethyl-di-(2-picolyl)carbinol, IX (33%, V where R = hydrogen, R′ = ethyl and M = hydrogen). In addition, treatment of the free ketone, VIII, with one and two equivalents or 2-picolylsodium (Table II, Runs 1 and 2) gave 13% and 23% yields respectively of carbinol, IX. Thus, the 13% yield of IX which was obtained from the interaction of equivalents of VIII and 2-picolylsodium was only about one-third as much (33%) as would be expected from the reaction of 2-picolylsodium (two equivalents) with ethyl propionate (one equivalent) if IX arises exclusively from the interaction of VIII with 2-picolylsodium. It is not too surprising that a higher yield (23%) of IX (Table II, Run 2) was obtained when a 2:1 molar ratio of 2-picolylsodium:VIII was employed than when a 1:1 molar ratio of reactants was used as in the former reaction more 2-picolylsodium is available for reaction with VIII.

That a ketone is not necessarily the intermediate from which the total amounts of the carbinols are formed in the reactions of 2-picoline and its derivatives with esters is even more forcibly supported by the following results. When 2-benzylpyridine (two equivalents) was acylated with ethyl propionate (one equivalent) using phenyllithium (two equivalents) as the condensing agent (Table I, Run 11), there was obtained a mixture of 1-phenyl-1-(2-pyridyl)-butanone-2, X, (22%, III where R = phenyl and R′ = ethyl) and 1,3-di-(2-pyridyl)-1,3-diphenyl-2-ethylpropanol-2, XI (60%, V where R = phenyl, R′ = ethyl and M = hydrogen). However, when the free ketone, X, was treated with the lithium derivative of 2-benzylpyridine, no more than 3% of carbinol, XI, was obtained (Table II, Runs 3 and 4).

The data which have just been presented suggest that although part of the carbinols, IX and XI, may have been formed by the reactions of the free ketones VIII and X with 2-picolylsodium and the lithium derivative of 2-benzylpyridine, respectively, the major amounts of these products are formed in some other way.

2. The Effects of the Size of the Alkyl Group, R′, in the Acylating Ester, $R'CO_2C_2H_5$. The ketone to carbinol ratio (K/C) which is found in the acylation of a tar base anion with an ester appears to result from a competition between the elimination and substitution reactions which were mentioned above. The size of R′ in the acylating ester and thus in the adduct VI might be expected to have definite

effects on the K/C ratio. It might be anticipated that *the elimination reaction would be aided by bulky R′ groups*, as the acetal-like carbon atom (C*) of VI is bonded to four other atoms in this adduct and to only three other atoms in the free ketone, III. The elimination is thus accompanied by a relief of steric strain. It might also be anticipated that *the substitution reaction would be hindered by the presence of bulky R′ groups*, as they would increase the crowding around C*, and it should be more difficult for substitution to take place by a backside attack of the tar base anion at this carbon atom. *Thus, it can be concluded that the K/C ratio should be increased as the steric requirements of R′ are increased.*

This mechanistic picture is of use in understanding the earlier results which were obtained in this laboratory. Thus, it is not surprising that when an ether solution of 2-picolyllithium[4] was acylated with a series of ethyl esters, $RCO_2C_2H_5$, the K/C ratio increased from 1.29 to 7.40 when R was increased[8] in size from methyl to ethyl to isopropyl to isobutyl. Similar results were obtained in the acylation of 2,6-lutidyllithium.[5]

In the present study it was found that the acylation of an ether solution of the lithium derivative of 2-benzylpyridine with three aliphatic ethyl esters of increasing steric requirements gave results (Table I, Runs 10, 11 and 17) which were unexpected from a consideration of the above discussion concerning the K/C ratios which were found in the acylation of 2-picoline[4] and 2,6-lutidine.[5] These experiments show that as R′ is increased in size from methyl to ethyl to isopropyl a minimum in ketone formation and a maximum in carbinol formation occur when R′ is of intermediate size, *i.e.*, when R′ is ethyl (Table I, Run 11). These results suggest that two opposing factors are in operation, one of which is primarily responsible for preventing carbinol formation in the case of ethyl acetate (Table I, Run 10) and the other which prevents carbinol formation in the case of ethyl isobutyrate (Table I, Run 17). A molecular model of the adduct which is formed between the lithium derivative of 2-benzylpyridine and ethyl isobutyrate (VI, where R = phenyl, R′ = isopropyl and M = lithium) shows that the approach of another molecule of the lithium derivative of 2-benzylpyridine to the backside of the acetal-type carbon, C*, would be very difficult and hence it might be anticipated that little or no carbinol should be formed. It is not too surprising that a slight change in the steric situation as occurs in changing the acylating ester from ethyl isobutyrate (Table I, Run 17, K/C = ∞) to ethyl propionate (Table I, Run 11, K/C = 0.37) would have a very pronounced effect on the K/C ratio, as C* of VI is very crowded in both cases.[9]

From the above considerations it might be anticipated that a very low K/C ratio,*i.e.*, a high yield of carbinol, should be obtained in the acylation of 2-benzylpyridine with ethyl acetate, as C* in the initially-formed adduct (VI, R = phenyl, R′ = methyl and M = lithium) should be less sterically hindered than C* in the adduct which is formed between the lithium derivative of 2-benzylpyridine and ethyl propionate. However, contrary to these expectations, no carbinol was obtained in the acylation of 2-benzylpyridine with ethyl acetate (Table I, Run 10, K/C = ∞).

The following theory is presented to rationalize the results which have been obtained. It is suggested that the lithium derivative of 2-benzylpyridine reacts with ethyl acetate to give the chelated structure VI (R = phenyl, R′ = methyl, and M = lithium), which is sufficiently stable[10] to resist rupture and subsequent backside attack by the 2-benzylpyridine anion at C*—hence no carbinol is produced. When ethyl propionate is used as the acylating ester, a less stable chelate ring is formed, which does not interfere appreciably with the substitution reaction by which carbinol is formed. Finally, if a chelate is formed when ethyl isobutyrate is used as the acylating ester, the chelate is less stable than that which is formed in the ethyl propionate reaction and carbinol formation does not occur because of steric crowding at C*. Thus, in the acylation of the lithium derivative of 2-benzylpyridine, the K/C ratio appears to depend on a delicate balance between the importance of the stability of the initially-formed chelate VI and the steric situation at C*.[11]

3. The Importance of Pyridine Ring Substitution. It is important to stress that in the present investigation and in previous studies which were performed in this laboratory[4-7], when mixtures of ketones and carbinols were obtained from the reaction of a tar base with an ester, the tar base is always 2-picoline or a derivative of 2-picoline. Thus, the reactions of the anions of 3-picoline,[12,13] 4-picoline,[13,14] and cer-

(8) These results were originally[4] explained as being due to the increase in steric interference in the reactions between the initially-formed free ketones and 2-picolyllithium as R′ increases in size.

(9) The same changes in the relatively unstrained adducts which are believed to be present when 2-picolyllithium is acylated with ethyl propionate and ethyl isobutyrate[4] would be expected to result in the relatively small changes in the K/C ratios which were observed, *viz.*, 2.28 and 3.75, respectively.

(10) It is not unreasonable to assume the formation of this stable chelate, as it has been shown [G. A. Guter and G. S. Hammond, *J. Am. Chem. Soc.*, **78**, 5166 (1956)] that lithium ions can be separated from sodium and potassium ions by their preferential chelation with the beta-diketone, dipivaloylmethane.

(11) Numerous examples are known in the field of chelate chemistry in which large differences in ring stability are caused by small structural changes [A. E. Martell and M. Calvin, *Chemistry of the Metal Chelate Compounds*, Prentice-Hall Inc. (1952)].

(12) A. D. Miller, C. Osuch, N. N. Goldberg, and R. Levine, *J. Am. Chem. Soc.*, **78**, 674 (1956).

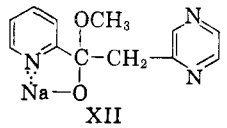
(13) S. Raynolds and R. Levine, *J. Am. Chem. Soc.*, **82**, 472 (1960).

tain of their derivatives[13,14] with esters give only ketones. Why carbinol formation should be so critically dependent on the location of the side chain in the pyridine ring is not apparent from the previously reported[4] mechanism for these acylations, which was summarized at the start of this paper.

However, if it is assumed that most of the carbinol produced in any reaction arises from structure VI, the results which were obtained can be explained. That the acylations of 2-picoline and 2-benzylpyridine give higher yields of carbinols than the corresponding reactions in which the free ketones, 1-(2-pyridyl)-butanone-2 and 1-(2-pyridyl)-1-phenylbutanone-2 are treated with metallic derivatives of 2-picoline and 2-benzylpyridine (see the discussion of factor 1 above) is not unreasonable, for the necessary intermediate adduct VI, from which most of the carbinols are subsequently formed, cannot be produced in the reactions of ketones with the organometallic compounds. It is also suggested that the adducts which are formed from the metallic derivatives of 3- and 4-picoline and their derivatives with esters have open chain rather than chelated structures analogous to VI, as such chelated structures would involve the formation of highly strained seven- and eight-membered rings.

The following results of Behun and Levine[15] lend further support to the argument that pyridine ring substitution plays an important role in carbinol formation. Thus, the acylation of pyrazylmethylsodium with a series of aliphatic, aromatic, and heterocyclic[16] esters gave good to excellent yields of ketones in all cases. Only one reaction, *viz.*, when the acylating ester was methyl picolinate, gave a mixture of ketone (2-pyridyl pyrazylmethyl ketone, 42.6%) and carbinol (2-pyridyl-bis(pyrazylmethyl) carbinol, 22.8%).

The intermediate XII, which is comparable to VI, can be formed when the acylating ester is methyl picolinate; hence some carbinol is formed in this reaction. Because of the strain which would be involved it is very unlikely that structures comparable to XII would be produced when the acylating ester is methyl nicotinate or isonicotinate; thus only ketones are formed in these reactions. It is also important to stress that a chelated structure comparable to VI would be very unlikely to involve the nitrogen atoms of the pyrazine ring when methylpyrazine is acylated, as these atoms are only weakly basic.[17]



XII

It is also important to note that when 2-pyridyl pyrazylmethyl ketone was treated with pyrazylmethylsodium recovered ketone and no carbinol were obtained. Thus, it appears that a fairly basic nitrogen atom as part of a relatively unstrained quasi five- or six-membered ring (Structure VI or XII) is necessary for carbinol formation to occur.

4. *Molar Ratio of Reactants.* The mechanism for the acylation of alkylpyridines as originally formulated[4] and as revised in the present paper accounts for the facts that higher yields of products (i.e., only ketone or a mixture of ketone and carbinol) are obtained from the reactions of esters with metallic derivatives of alkylpyridines, which carry at least two lateral α-hydrogen atoms, when a 2:2:1 molar ratio of alkylpyridine:condensing agent:ester is used than when a 1:1:1 molar ratio of reactants is employed. Thus, the 80% yield of 2-phenacylpyridine which was obtained using a 2:2:1 molar ratio of 2-picoline:phenyllithium:ethyl benzoate dropped to 61% when a 1:1:1 molar ratio of reactants was employed.[4,18] The first mole of alkylpyridine anion is used to make one mole of the adduct VI.[15] Then, a second mole of the alkylpyridine anion is required for (1) participating in the substitution reaction with VI to give the metalated derivative of the carbinol, VIIb, and/or (2) producing the anion, VIIa, of the free ketone, III, which is formed by eliminating ethanol from VI.

5 *Effect of Solvents on the K/C Ratio.* We have also found that changes in basicity of the solvent have marked effects on the ketone/carbinol (K/C) ratio. If one considers the two solvents, ethyl ether and benzene, the use of ether rather than benzene as the solvent should emphasize the nucleophilic character of the alkylpyridine anion which is involved in the reaction in question. The effect should be more pronounced when the lithium derivative of an alkylpyridine is employed than when the analogous sodium compound is used, as the lithium ion tends to coordinate with ether to a greater extent than does the sodium ion.[19] It might be anticipated that a higher K/C ratio should be obtained when the lithium derivative of a tar base is acylated with an ester in benzene as the solvent than when this derivative is acylated in ether as the solvent. The use of either benzene or ether as the solvent in the acylation of the sodium derivative of a tar base would be expected to result in only a slight change in the K/C ratio, as the sodium ion has a very slight tendency

(14) C. Osuch and R. Levine, *J. Org. Chem.*, **22**, 939 (1957).

(15) J. D. Behun and R. Levine, *J. Am. Chem. Soc.*, **81**, 5157 (1959).

(16) These were methyl furoate, methyl 2-thenoate, and three isomeric methyl pyridinecarboxylates.

(17) The *p*Ka values of pyridine and pyrazine are 5.23 and 0.6 respectively, (A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948)).

(18) In connection with this discussion the reader is referred to a paper by Raynolds and Levine (see ref. 1) on the acylation of 1-(2-pyridyl)-3-dimethylaminopropane (which has two lateral alpha-hydrogen atoms) and 1-(2-pyridyl)-1-phenyl-3-dimethylaminopropane (which has only one lateral alpha-hydrogen atom).

(19) See pages 191–194 of the reference in footnote 11.

to coordinate with either ether or benzene. In support of these ideas it has been found that the acylation of 2-picolyllithium with ethyl propionate gave a K/C ratio of 5.2 using ether as the reaction solvent (Table I, Run 4) and a value of 16.0 (Table I, Run 6) using benzene as the solvent. In similar experiments involving the propionylation of the lithium derivative of 2-benzylpyridine, the K/C ratio in ether was 0.37 (Table I, Run 11) and ∞ in benzene (Table I, Run 15). Furthermore, the propionylation of 2-picolylsodium in ether (Table I, Run 7) and in benzene (Table I, Run 2) gave essentially the same K/C ratios, *viz.*, 1.4 and 1.7, respectively. Similar results were obtained in the propionylation of the sodium derivative of 2-benzylpyridine in ether (Table I, Run 16) and benzene (Table I, Run 13).

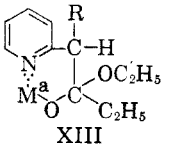
The acylations of 2-picoline and 2-benzylpyridine with ethyl propionate using both lithium diisopropylamide and sodium diisopropylamide as condensing agents were also studied to see what effects the diisopropylamine which is formed by the metalation of the pyridine derivative has on the course of these reactions.

$$2\text{-}C_5H_4NCH_2R + MN(i\text{-}C_3H_7)_2 \longrightarrow 2\text{-}C_5H_4NCHRM + HN(i\text{-}C_3H_7)_2$$

R = H and C_6H_5; M = Li and Na

A comparison of Runs 4 and 5 with Runs 2 and 3 (Table I) reveals that the presence of diisopropylamine has a more pronounced effect on the K/C ratio when 2-picolyllithium is propionylated than in the analogous reaction involving 2-picolylsodium. Similar results were obtained (compare Runs 11 and 14 with Runs 12 and 13 in Table I) in the acylation of 2-benzylpyridine with ethyl propionate.

The intermediate XIII is believed to be involved in these reactions.

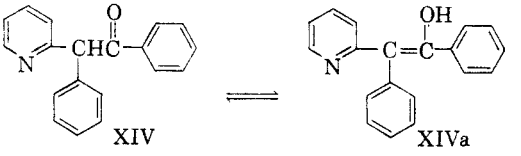


XIII

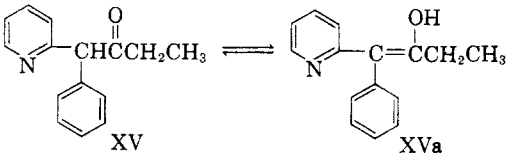
The greater the extent to which M^a is coordinated with diisopropylamine, the less stable chelate XIII should be; therefore, the elimination reaction should occur more readily and the K/C ratio should increase. The solvation effects should be very pronounced when lithium is the metal which is used in these reactions (compare Runs 4 and 5 with Runs 11 and 14 in Table I). Furthermore, when the sodium derivative of 2-picoline was propionylated (Runs 2 and 3 in Table I) and the sodium derivative of 2-benzylpyridine was propionylated (Runs 12 and 13 in Table I) and benzoylated (Runs 19 and 20 in Table I), the presence of diisopropylamine had only a slight effect on the K/C ratio in the case of 2-picoline and no effect was noticed with 2-benzylpyridine, as it would be expected that the sodium ion would be solvated only slightly with diisopropylamine.

The results of the propionylation of 2-benzylpyridine are especially striking as the acylation of its sodium derivative in the absence (Run 12, Table I) or the presence (Run 13, Table I) of diisopropylamine gives a high yield of only ketone while the acylation of the lithium derivative gives mixtures of ketones and carbinol in which the carbinol is the major product in the absence of diisopropylamine (Run 11, Table I) and the ketone is the major product in the presence of diisopropylamine (Run 14, Table I).

6. *Effects of Changing R' in the Acylating Ester,* $R'CO_2C_2H_5$, *from Alkyl to Phenyl.* When an ether solution of 2-picolyllithium is acylated with ethyl propionate and ethyl benzoate, the K/C ratio increases from 5.2 (Run 4, Table I) to ∞ (Run 9, Table I) respectively. Similar results were obtained when an ether solution of the lithium derivative of 2-benzylpyridine was acylated with ethyl propionate (Run 11, Table I, K/C = 0.37) and ethyl benzoate (Run 18, Table I, K/C = 3.75). That the K/C ratio of 3.75 which was observed in the benzoylation of the lithium derivative of 2-benzylpyridine in ether is so much larger than that (0.37) which was observed in its propionylation may be understood from a consideration of the structures of the ketones XIV and XV which are formed.



XIV XIVa



XV XVa

Structures XIVa and XVa are resonance stabilized, as both have an enolic double bond in conjugation with the benzene and pyridine rings which are located on the same carbon atom. In addition XIV and XIVa are further resonance stabilized in the following ways: (a) the carbonyl group in XIV is conjugated with the benzene ring to which it is bonded and (b) the enolic double bond of XIVa is conjugated with two benzene rings as well as the pyridine ring. Such added stabilization is not possible in structures XV and XVa. Thus, it appears that the considerably greater K/C ratio which was observed in the benzoylation of the lithium derivative of 2-benzylpyridine than was observed in its propionylation is due to the formation of the highly resonance stabilized ketone, XIV–XIVa, which is subsequently converted to its anion by another mole of the anion of 2-benzylpyridine.

A similar explanation can be used to account for the results which were observed in the propionylation and benzoylation of 2-picolyllithium. As the

ketones which are derived from the acylation of 2-picoline with aliphatic esters are not resonance stabilized to the same extent as is 2-phenacylpyridine, it is not unreasonable that the already relatively high K/C ratios which are obtained when 2-picoline is acylated with aliphatic esters[20] are further increased so that K/C = ∞ when the acylating ester is ethyl benzoate.

7. The Effects of Changing the Metal and R from Hydrogen to Phenyl in the Pyridine Derivatives, $2 - C_5H_4NCH_2R$. The data in Table I indicate that higher yields of carbinols, *i.e.*, lower K/C ratios, are observed when 2-picolylsodium is propionylated (Table I, Runs 2 and 7) than when 2-picolyllithium is propionylated (Table I, Runs 4 and 6). It might be expected that when M = lithium the chelated adduct VI (R = hydrogen, and R′ = ethyl) would be formed very readily and be more stable than the analogous adduct when M = sodium. Therefore, it is not surprising that a higher K/C ratio is obtained when M = lithium than when M = sodium.

If a stable chelate ring is indeed formed from the reaction of ethyl propionate and 2-picolyllithium, it might seem unreasonable that any carbinol is formed in this reaction, as such a ring would interfere with the backside attack of the 2-picolyllithium on C* of VI, the route by which carbinol is formed. However, it should be emphasized that 2-picolyllithium is a relatively strong base and it might be expected to rupture the chelate ring to some extent and thus form some carbinol. Also, in spite of the fact that 2-picolyllithium is a strong base, the predominant reaction of the chelate which is formed between 2-picolyllithium and ethyl propionate is one of elimination to give the ketone, 1-(2-pyridyl)-butanone-2, as the major product.

A very different situation prevails when 2-benzylpyridine is acylated with ethyl propionate. The data discussed above in factor 2 suggest that when M is lithium, the chelate VI (R is phenyl and R′ is ethyl) is probably less stable than the analogous chelate which is formed in the propionylation of 2-picolyllithium. As the 2-benzylpyridine anion is undoubtedly a considerably weaker base than the anion of 2-picoline, the substitution reaction by which the carbinol is formed from VI and the weakly basic 2-benzylpyridine anion would be expected to be much slower than the corresponding reaction between ethyl propionate and the more strongly basic 2-picoline anion. However, although the lithium derivative of 2-benzylpyridine is a weaker base than 2-picolyllithium, the propionylation of these lithium reagents gives a lower K/C ratio in the 2-benzylpyridine acylation (Table I, Run 11, K/C = 0.37) than in the 2-picoline acylation (Table I, Run 4, K/C = 5.2). This is due to the probability that the chelate VI, where R = phenyl, R′ = ethyl, and M = lithium, is less stable than the analogous chelate which is formed from 2-picolyllithium and ethyl propionate (VI, where R = hydrogen, R′ = ethyl and M = lithium), with the result that it undergoes substitution very extensively and gives a high yield of carbinol even with the weakly basic lithium derivative of 2-benzylpyridine.

A consideration of the adducts of type VI which are formed from ethyl propionate and the lithium and sodium derivatives of 2-benzylpyridine suggests that more carbinol should be formed from the adduct which is more stable and less likely to undergo a rapid elimination reaction to form the ketone. The lithium adduct would be expected to be more stable than the sodium adduct, as lithium forms bonds which are more covalent than those which are formed by sodium. Therefore, as the data in Table I (Runs 11, 13, 15 and 16) indicate. Higher yields of ketone are obtained when M is sodium than when it is lithium regardless of the solvent which is used.

As the 2-benzylpyridine anion is a weak base, its ability to initiate a nucleophilic attack on the initially-formed adduct between the 2-benzylpyridine anion and ethyl propionate should be increased by the use of a solvent such as ether, which would emphasize the nucleophilic character of the 2-benzylpyridine anion by solvating the metal with which it is associated. A solvent such as benzene would make the lithium derivative of 2-benzylpyridine appear to be a weaker base than it is in ether, as the benzene would not aid in its ionization. Therefore, the benzene solvent would not aid the attack of the lithium derivative of 2-benzylpyridine on the initially-formed adduct between the organolithium compound and ethyl propionate. Thus, one would expect the lowest K/C ratio, *i.e.*, the highest yield of carbinol (Table I, Run 11) from the reaction of the lithium derivative of 2-benzylpyridine with ethyl propionate in ether.

Thus, the following three conditions must be fulfilled in order to form carbinol from the acylation of a 2-alkylpyridine with an ester:

(a) The attacking tar base anion must be nucleophilic enough to overcome the energy barrier to substitution. In the case of weakly basic anions, the nucleophilicity may be emphasized by the use of appropriate solvents.

(b) The elimination reaction, by which ketone is formed, must be slow enough to allow the substitution reaction to compete successfully with it, especially when a weakly basic anion is involved.

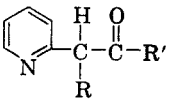
(c) The chelate ring of the initially-formed adduct between the metallic derivative of the tar base and the acylating ester must not be so stable that it interferes with the backside attack of the metallic derivative of the tar base on the acetal-like carbon atom (C* in VI) of the adduct, the route by which carbinol is formed.

In the acylation of 2-benzylpyridine with ethyl propionate these conditions are best met when the metal is lithium and the solvent is ethyl ether. Car-

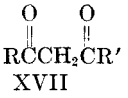
(20) See ref. 4 and the discussion of factor 2 above.

binol is not formed when the lithium derivative of 2-benzylpyridine is acylated with ethyl propionate in benzene as the solvent, as condition (a) is violated. The adduct formed by the reaction of the sodium derivative of 2-benzylpyridine with ethyl propionate in both ether and benzene would be expected to undergo elimination so rapidly that the already slow substitution reaction (because of the weakly basic nature of the 2-benzylpyridine anion) cannot compete with it and therefore only ketone is formed. The data (Table I, Runs 18 and 19) on the benzoylation of the lithium and sodium derivatives of 2-benzylpyridine are also consistent with the above arguments.

Finally, it is of interest to note that ketones, XVI, which are formed by the lateral acylation of 2-picoline and 2-benzylpyridine are structurally analogous to β-diketones, XVII.



R = H and C_6H_5
R′ = alkyl and C_6H_5
XVI



XVII

Although ketones, XVI differs from the β-diketones, XVII, in that the azomethine linkage which is present in XVI is replaced by a carbonyl group in XVII, both of these classes of compounds chelate with cupric ion. Furthermore, Hauser *et al.*[21] have recently obtained evidence in support of the postulate that an adduct, which is structurally analogous to VI, is formed as an intermediate in the base-catalyzed acylation of the lithium and sodium derivatives of ketones with esters to give β-diketones.

(21) D. G. Hill, J. Burkus, and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 602 (1959).

EXPERIMENTAL[22]

In this section three typical experiments are described.

(a) *Reaction of the lithium derivative of 2-benzylpyridine with 1-phenyl-1-(2-pyridyl)-2-butanone,* X. The previously described[4] procedure for acylating 2-picolyllithium was followed except that the ester was replaced by ketone, X. Thus, from an ether solution of phenyllithium (0.1 mole), 2-benzylpyridine (0.1 mole, 17.0 g.), and 1-phenyl-1-(2-pyridyl)-2-butanone (0.05 mole, 11.3 g.), there was isolated 0.8 g. (3%) of 1,3-diphenyl-2-ethylpropanol-2, m.p. 146–147° alone and when mixed with an authentic sample. There were also recovered 16.4 g. of 2-benzylpyridine, b.p. 95–98° at 0.22 mm., and 10.6 g. of X, b.p. 128–130° at 0.28 mm.

(b) *Reaction of 2-benzylpyridine, sodium diisopropylamide and ethyl benzoate.* Sodium diisopropylamide (0.1 mole) was prepared by the reaction of a suspension phenylsodium (0.1 mole) in benzene with diisopropylamine (0.1 mole, 10.1 g.) using the previously described procedure.[23] Then, 2-benzylpyridine (0.1 mole, 17.0 g.) and ethyl benzoate (0.05 mole, 7.5 g.) were added and the reaction was conducted and processed using the procedure which has been described[23] for similar reactions. In this way, there were obtained 11.1 g. (82%) of α-phenyl-α-(2-pyridyl) acetophenone, b.p. 180–185° at 0.25 mm., and 9.2 g. of recovered 2-benzylpyridine, b.p. 95–98° at 0.22 mm.

The reactions involving the use of lithium diisopropylamide as the metalating agent were effected as described previously.[23]

(c) *Reaction of 2-benzylpyridine, phenylsodium and ethyl propionate in ethyl ether.* 2-Benzylpyridine (0.1 mole, 17.0 g.), dissolved in an equal volume of anhydrous benzene, was added to a suspension of phenylsodium (0.1 mole) in benzene and the mixture was stirred for 1 hr. at 30°. Nitrogen was allowed to enter the flask slowly while the benzene was removed by distillation at reduced pressure (100 mm.) using a warm water bath to heat the reaction vessel. After removing as much benzene as possible, approximately 200 ml. of anhydrous ethyl ether was added and the mixture was refluxed for 15 min. Ethyl propionate (0.05 mole, 5.1 g.), dissolved in an equal volume of anhydrous ether, was added and the mixture was refluxed for 1 hr. After the usual processing there were isolated 7.6 g. (68%) of 1-phenyl-1-(2-pyridyl)-2-butanone, b.p. 128–132° at 0.28 mm., and 8.0 g. (48%) of recovered 2-benzylpyridine, b.p. 95–98° at 0.22 mm.

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(22) The 2-picoline and 2-benzylpyridine were supplied through the courtesy of Dr. F. E. Cislak, Reilly Tar and Chemical Corp.

(23) S. Raynolds and R. Levine, *J. Am. Chem. Soc.*, **82**, 472 (1960).