of the reaction studied to change in basicity of the attacking group, as indicated by the Brönsted catalytic constant α. In the case of imidazole the values of α[1] and the heat of ionization[19] are appreciable and thus useful information concerning the mechanism of imidazole-catalyzed ester hydrolysis may not be obtained from calculated energy terms. However, the heats of ionization for carboxylic acids are quite small and allow mechanistic deductions from activation terms for the hydrolysis of esters of salicylic acid.[13a,14]

Although the present results indicate that the *o*-imidazolyl group is an effective assisting group for the solvolysis of phenyl acetate and exceeds, in efficiency, the *o*-carboxyl anion, the maximum rate of solvolysis of I does not approach that of the enzymatic hydrolysis. Clearly factors other than intramolecular reactions play an important role in the mechanism of action of hydrolytic enzymes, and it is possible that the devising of a more efficient model of enzymatic hydrolysis may be more successful if appropriate spatial orientation of "substrate" bond to catalytic site is taken into account.[20]

Acknowledgments.—This work was supported by a grant from the Institute of Arthritis and Metabolic Diseases, National Institutes of Health.

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NEW HAVEN, CONN.

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Condensation of Aldehydes and Ketones with Reissert Compounds

BY LEE R. WALTERS, N. THANUKRISHNA IYER[1] AND WILLIAM E. McEWEN

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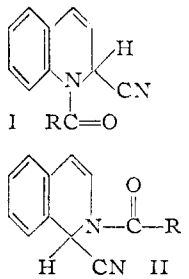
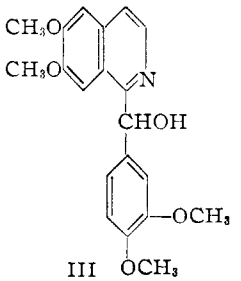
The lithium salts of Reissert compounds undergo reaction with aldehydes to form lithium cyanide and esters of secondary alcohols containing the 2-quinolyl or 1-isoquinolyl group bonded to the carbinol carbon atom. There is an analogous reaction with ketones leading to the formation of esters of tertiary alcohols, but this reaction has only limited applicability. Some aspects of the mechanism of the reactions are discussed.

Although Reissert compounds, 1-acyl-1,2-dihydroquinaldonitriles (I) and 2-acyl-1,2-dihydroisoquinaldonitriles (II), are mainly noted for their ability to form aldehydes as a result of acid-catalyzed hydrolysis, increased attention in recent years has been directed toward the use of such compounds in the synthesis of diverse quinoline and isoquinoline derivatives.[2] The present communication describes a potentially valuable extension of the latter area of work, one leading to the production, frequently in high yields, of esters of alcohols having the 2-quinolyl or 1-isoquinolyl group bonded to the carbinol carbon atom. Subsequent to some of the findings reported in this manuscript, it was possible to devise from appropriate Reissert compounds convenient syntheses of papaverinol (III)[3] and some apparently attractive intermediates for eventual conversion to the ipecac alkaloids.[4]



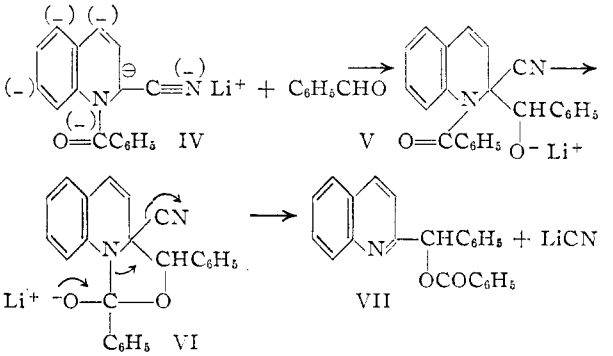
I

II



III

The condensation of the lithium salt IV of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) with benzaldehyde to give phenyl-2-quinolylcarbinyl benzoate (VII) plus lithium cyanide may be taken as the prototype of all of the reactions carried out in this particular study. There can be little doubt that the mechanism of the reaction involves an initial nucleophilic addition of the anion of the Reissert compound to the carbonyl carbon atom of benzaldehyde to form V, which then gives the cyclic derivative VI. Elimination of lithium cyanide (see curved arrows) affords VII, and, in common with other similar reactions of Reissert compounds,[2,5,6] the gain in resonance energy accompanying the elimination–rearrangement step provides an important driving force for the reaction.



IV V VI VII

Inasmuch as the negative charge of the anion of IV is shared by the nitrogen atom of the cyano group and several carbon atoms of the quinoline ring (see the negative charges in parentheses in

(1) Fulbright Scholar 1956–1957; University of Travancore, Trivandrum, India.

(2) W. E. McEwen and R. L. Cobb, *Chem. Revs.*, **55**, 511 (1955).

(3) F. D. Popp and W. E. McEwen, THIS JOURNAL, **79**, 3773 (1957).

(4) F. D. Popp and W. E. McEwen, *ibid.*, **80**, 1181 (1958).

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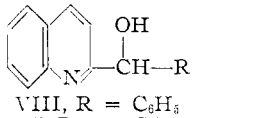
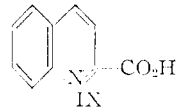
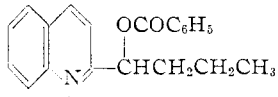
structure IV), and owing to the fact that alkylation of the anion has been observed to occur at both the 2- and 4-positions of the quinoline ring,[7] it was deemed imperative to establish beyond question the structure of the product in this and at least several other cases. In the present instance this was accomplished readily, since saponification of the product gave benzoic acid and phenyl-2-quinolylcarbinol (VIII), the same product obtained by decarboxylation of quinaldic acid (IX) in the presence of benzaldehyde.[8] That the condensation product resulting from the reaction of IV with *n*-butyraldehyde was *n*-propyl-2-quinolylcarbinyl benzoate (X), was established by saponification of the product to benzoic acid and *n*-propyl-2-quinolylcarbinol (XI), followed by reduction of the latter compound to 2-*n*-butylquinoline, a known compound,[9] by the method of Buck, *et al.*[10] The reaction of IV with acetophenone gave, after saponification of the initially formed ester, methylphenyl-2-quinolylcarbinol (XII), the product also obtained by decarboxylation of quinaldic acid (IX) in the presence of acetophenone,[8] or by reaction of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) with methylmagnesium bromide.[11]



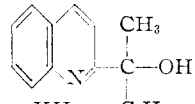
VIII, R = C_6H_5
XI, R = *n*-C_3H_7



IX

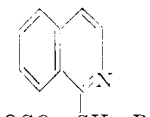


X

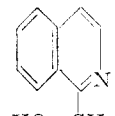


XII

Although it seemed overwhelmingly probable that condensation of the lithium salts of isoquinoline Reissert compounds with aldehydes or ketones would take place at the 1-position of the isoquinoline ring, nevertheless the point was established by experimentation. For example, the product obtained by reaction of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) with *n*-butyraldehyde was saponified and the alcohol component of the hydrolysis mixture reduced by the method of Buck, *et al.*[10] As anticipated, the reduction product proved to be 1-*n*-butylisoquinoline, a known compound.[7] Therefore the initial condensation product must have been *n*-propyl-1-isoquinolylcarbinyl benzoate (XIII), and the saponification products were benzoic acid and *n*-propyl-1-isoquinolylcarbinol (XIV). Analyses and infrared spectra were in accord with these conclusions. Phenyl-1-isoquinolylcarbinyl benzoate (XV) and phenyl-1-isoquinolylcarbinol (XVI) are both known compounds.[8] Although the ester obtained by reaction of the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) with benzaldehyde had a m.p. of 166.6–167.6°, as compared with a reported value of 158–159° for XV,[8] the physical constants of the alcohol obtained by saponification of the initially-formed ester were in complete agreement with those reported for XVI. Finally, as mentioned earlier, papaverinol (III), a known 1-substituted isoquinoline derivative, was obtained by saponification of the initially formed condensation product of the lithium salt of 2-benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile and veratraldehyde.[3]



XIII, R = *n*-C_3H_7
XV, R = C_6H_5



XIV, R = *n*-C_3H_7
XVI, R = C_6H_5

All of the data presently available on the condensation of the lithium salts of Reissert compounds with aldehydes and ketones are given in Tables I and II. It is apparent that, with regard to yields of the condensation products, both steric and electronic factors are of importance. First of all, it is noteworthy that steric effects show up more strongly with 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) than with 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5). Only the latter compound gives the expected condensation product with acetophenone. Also, whereas the quinoline Reissert compound gives the condensation products with *n*-butyraldehyde and 2,6-dichlorobenzaldehyde in 89 and 82% yields, respectively, the isoquinoline Reissert compound gives the products in only 75 and 54% yields, respectively. With each Reissert compound the yield of condensation product is decidedly better with *n*-butyraldehyde than with isobutyraldehyde. The electronic effects show up most clearly in the series of reactions between the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) and various *p*-substituted benzaldehydes. The presence of a relatively weakly electron-donating group in the *p*-position (CH_3, OCH_3) causes a slight lowering in the yield of condensation product, but the presence of the strongly electron-donating dimethylamino group causes the yield to drop to zero. The operation of unfavorable effects, both steric and electronic, must be responsible for the failure of propiophenone and benzophenone to undergo the condensation reaction with either Reissert compound.

All of the condensation reactions were carried out in ether–dioxane solution. The lithium salt of the Reissert compound was first prepared by a metalation reaction with phenyllithium. Following this, the aldehyde or ketone was added to the organometallic reagent. The lithium salt of each Reissert compound possesses a deep red color in ether–dioxane solution, and this color disappears as the condensation reaction with the aldehyde or ketone progresses. In the reactions of benzaldehyde with the lithium salts of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) and 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5), attempts were made to determine whether the rearrangement–elimination or the initial condensation steps were rate determining. After addition

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(10) J. S. Buck, W. H. Perkin, Jr., and T. S. Stevens, *ibid.*, **127**, 1471 (1925).
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TABLE I

CONDENSATION OF REISSERT COMPOUNDS WITH ALDEHYDES AND KETONES

Aldehyde or ketone	Product	M.p., °C.	Yield, %	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
	1-Benzoyl-1,2-dihydroquinaldonitrile									
Acetophenone	Methylphenyl-2-quinolylcarbinol[a]	101–101.5[b]	31							
Benzaldehyde	Phenyl-2-quinolylcarbinyl benzoate	108–109	89	$C_{23}H_{17}NO_2$	81.39	81.50	5.05	4.86	4.13	4.18
Benzophenone			80							
n-Butyraldehyde	Picrate of *n*-propyl-2-quinolyl-carbinyl benzoate	156–158	89[c]	$C_{26}H_{22}N_4O_9$	58.45	58.58	4.15	4.13	10.49	10.46
2,6-Dichlorobenzaldehyde	2,6-Dichlorophenyl-2-quinolyl-carbinyl benzoate	136–137	82	$C_{23}H_{15}NO_2Cl_2$[d]	67.75	67.89	3.70	3.70	3.43	3.41
Isobutyraldehyde	Picrate of isopropyl-2-quinolyl-carbinyl benzoate	161–163	55[c]	$C_{26}H_{22}N_4O_9$	58.45	58.64	4.15	4.33	10.47	10.63
Propiophenone			0							
	2-Benzoyl-1,2-dihydroisoquinaldonitrile									
Acetophenone			0							
Anisaldehyde	*p*-Anisyl-1-isoquinolylcarbinyl benzoate	140.5–141.5	62[c]	$C_{24}H_{19}NO_3$	78.05	78.02	5.15	5.18	3.79	3.79
Benzaldehyde	Phenyl-1-isoquinolylcarbinyl benzoate	166.6–167.6[e]	88	$C_{23}H_{17}NO_2$	81.39	81.13	5.05	4.93	4.13	4.23
Benzophenone			0							
n-Butyraldehyde	Picrate of *n*-propyl-1-isoquinolyl-carbinyl benzoate	163.5–165.8	75[c]	$C_{26}H_{22}N_4O_9$	58.45	58.56	4.15	4.08	10.49	10.49
p-Chlorobenzaldehyde	*p*-Chlorophenyl-1-isoquinolyl-carbinyl benzoate	161.5–162.5	72	$C_{23}H_{16}NO_2Cl$[f]	73.89	74.00	4.28	4.51	3.74	3.64
2,6-Dichlorobenzaldehyde	2,6-Dichlorophenyl-1-isoquinolyl-carbinyl benzoate	162–164	54[c]	$C_{23}H_{15}NO_2Cl_2$[g]	67.75	67.90	3.70	3.85	3.43	3.48
p-Dimethylaminobenzaldehyde			0							
Isobutyraldehyde	Picrate of isopropyl-1-isoquinolyl-carbinyl benzoate	170–172	58[c]	$C_{26}H_{22}N_4O_9$	58.45	58.67	4.15	4.38	10.49	10.54
Propiophenone			0							
Pyridine-4-carboxaldehyde	4-Pyridyl-1-isoquinolylcarbinyl benzoate	149.5–150.0	50	$C_{22}H_{16}N_2O_2$	77.69	77.75	4.72	4.59	8.23	8.27
p-Tolualdehyde	*p*-Tolyl-1-isoquinolylcarbinyl benzoate	167.5–169.0	66	$C_{24}H_{19}NO_2$	81.58	81.64	5.38	5.55	3.96	3.94
Veratraldehyde	3,4-Dimethoxyphenyl-1-isoquinolylcarbinyl benzoate	134–135	86[h]							
	2-Anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile									
Veratraldehyde	Papaverinol[a]	137–138	67[h]							
3-Ethylpyridine-4-carboxaldehyde	1-(6,7-Dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinyl *p*-methoxybenzoate	198.4–199.0	50[i]							
2-Methyl-5-ethylpyridine-4-carboxaldehyde	1-(6,7-Dimethoxyisoquinolyl)-4-(2-methyl-5-ethylpyridyl)-carbinol[a]	174–175	31[i]							
	2-Cinnamoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile									
Veratraldehyde	Papaverinol[a]	137–138	67[h]							
	2-Benzoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile									
Veratraldehyde	Papaverinol[a]	137–138	67[h]							

[a] Isolated after saponification of the ester initially formed. [b] Reported m.p. 102.2–102.8° (ref. 8). [c] This is actually the yield of the carbinol obtained by saponification of the ester. [d] *Anal.* Calcd. for $C_{23}H_{15}NO_2Cl_2$: Cl, 17.37. Found: Cl, 17.46. [e] Reported[8] m.p. 158–159°. [f] *Anal.* Calcd. for $C_{23}H_{16}NO_2Cl$: Cl, 9.50. Found: Cl, 9.28. [g] *Anal.* Calcd. for $C_{23}H_{15}NO_2Cl_2$: Cl, 17.37. Found: Cl, 17.16. [h] See ref. 3. [i] See ref. 4.

of benzaldehyde, the reactions were quenched by addition of water just as soon as the characteristic red color of the lithium salts of the Reissert compounds had been discharged. In each case, only the final condensation–rearrangement product VII or XV, respectively, was isolated in high yield, and no starting material was recovered. Therefore it can be concluded that the rearrangement–elimination step, *e.g.*, the conversion of VI to VII, takes place as fast or faster than the initial condensation step, *e.g.*, the one leading to the formation of V.

Whenever, owing to the operation of an unfavorable steric or electronic effect, the rate of the initial condensation step is relatively slow, the yield of the

TABLE II

QUINOLYL- AND ISOQUINOLYLCARBINOYLS BY SAPONIFICATION OF ESTERS

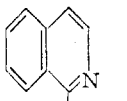
Carbinol	M.p. or b.p. (mm.) °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Phenyl-2-quinolyl-	69.5–71.0[a]							
n-Propyl-2-quinolyl-	75–77	$C_{13}H_{15}NO$	77.62	7.52	6.96	77.73	7.59	6.88
2,6-Dichlorophenyl-2-quinolyl-	113.0–115.5	$C_{16}H_{11}NOCl_2$[b]	63.20	3.65	4.61	63.27	3.65	4.90
Isopropyl-2-quinolyl-	127–128.5 (1)[c]	$C_{13}H_{15}NO$	77.61	7.51	6.96	77.84	7.70	7.16
p-Anisyl-1-isoquinolyl-	97–98	$C_{17}H_{15}NO_2$	76.98	5.66	5.28	76.90	5.63	5.29
Phenyl-1-isoquinolyl-	108.5–109.5[d]							
n-Propyl-1-isoquinolyl-	115–117 (0.6)[e]	$C_{13}H_{15}NO$	77.61	7.51	6.96	77.87	7.70	6.64
Picrate of *n*-propyl-1-isoquinolyl-	169.5–172.6	$C_{19}H_{18}N_4O_8$	53.04	4.21	13.02	53.19	4.24	13.26
p-Chlorophenyl-1-isoquinolyl-	110.5–111.5	$C_{16}H_{12}ONCl$[f]	71.24	4.45	5.19	71.50	4.45	5.34
2,6-Dichlorophenyl-1-isoquinolyl-	139.8–142.5 d.	$C_{16}H_{11}NOCl_2$[g]	63.20	3.65	4.61	63.41	3.62	4.90
Isopropyl-1-isoquinolyl-	128–130 (1.1)[h]	$C_{13}H_{15}NO$	77.61	7.51	6.96	77.83	7.55	7.02
4-Pyridyl-1-isoquinolyl-	142.5–143.5	$C_{15}H_{12}N_2O$	76.27	5.08	11.86	76.52	5.21	11.75
p-Tolyl-1-isoquinolyl-	113–114	$C_{17}H_{15}NO$	81.92	6.02	5.62	82.00	6.05	5.90

[a] Reported[8] m.p. 69°. The picrate was found to have a m.p. of 137–139.5°, reported 138° (H. de Diesbach, A. Pugin, F. Morard, W. Nowaczinski and J. Dessibourg, *Helv. Chim. Acta*, **35**, 2322 (1952)). [b] *Anal.* Calcd. for $C_{16}H_{11}NOCl_2$: Cl, 23.32. Found: Cl, 23.62. [c] $n^{20}D$ 1.5869. [d] Reported[8] m.p. 106°. [e] $n^{20}D$ 1.5847. [f] *Anal.* Calcd. for $C_{16}H_{12}ONCl$: Cl, 13.20. Found: Cl, 13.38. [g] *Anal.* Calcd. for $C_{16}H_{11}NOCl_2$: Cl, 23.32. Found: Cl, 23.11. [h] $n^{20}D$ 1.5851.

desired final product is lowered because of the incursion of side reactions.[12] In only one case, that of the reaction between the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) and acetophenone, was any Reissert compound recovered. In all of the other cases investigated, only intractable materials could be obtained in addition to the desired ester. It is noteworthy that in all of the cases in which the electrophilic reactivity of the carbonyl compound was high, as evidenced by theoretical considerations, rapid discharge of the red color of the anion of the Reissert compound and isolation of a high yield of the ester, the final reaction mixture, before the hydrolysis step, was nearly colorless. In all of the other cases, the reaction mixture became dark brown in color.

Although the data are limited, there is sufficient evidence available to show that the condensation of ketones with the lithium salts of Reissert compounds is a relatively unsatisfactory reaction. However, it should be pointed out that the same tertiary alcohols, those theoretically obtainable by hydrolysis of the esters initially formed in the ketone reactions, can be obtained, frequently in high yields, by the reaction of Grignard reagents with Reissert compounds in ether–dioxane solution.[6,11,13]

Incidental to the main area of research, a few attempts were made to condense the lithium salts of Reissert compound with epoxides. Only in the case of the reaction between the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) and ethylene oxide was there any evidence for the formation of a new product. In this case there was obtained in 50% yield a compound, $C_{18}H_{15}O_2N$, m.p. 79–80°, presumably 2-(1-isoquinolyl)-ethyl benzoate (XVII).



XVII $CH_2CH_2OCOC_6H_5$

Acknowledgment.—This investigation was supported by a research grant, H-2155, from the National Institutes of Health, Public Health Service.

Experimental[14]

Condensation of the Lithium Salts of Reissert Compounds with Aldehydes or Ketones.—To a solution of 0.04 mole of the Reissert compound in 150 cc. of anhydrous ether and 75 cc. of anhydrous dioxane maintained at −10° in an atmosphere of pure nitrogen was added with mechanical stirring an ether solution of 0.04 mole of freshly prepared phenyllithium. To the resultant red solution was added dropwise with stirring a solution of 0.04 mole of the aldehyde or ketone in 25 cc. of anhydrous ether. The mixture was stirred for an hour at −10°, then warmed to room temperature and stirred for an additional 12 hours. Sufficient ether was added to increase the total volume of the mixture to 500 cc., and the mixture was then extracted with 12 cc. of water, 12 cc. of 0.5 *N* hydrochloric acid, and, once again, 12 cc. of water. The solvents were distilled from the ether–dioxane layer, the latter portion *in vacuo*, and the distillation residue, if a solid, was recrystallized from either ethanol or dioxane. The esters obtained from the reactions with *n*-butyraldehyde or isobutyraldehyde were liquids and were converted to picrates by treatment with ethanolic picric acid. The ester obtained from the reaction of IV with acetophenone was an intractable oil and was saponified without purification. In some of the runs a small amount of carbinol resulting from partial hydrolysis of the ester was isolated on neutralization of the 12 cc. of hydrochloric acid extract. The yields of esters reported in Table I include a correction for this material.

Saponification of the Esters.—A solution of about 5 g. of the ester in 50 cc. of 95% ethanol was mixed with a solution of 3 g. of potassium hydroxide in 25 cc. of water, and the resulting mixture was refluxed for 5–24 hr. Some of the ethanol was removed by distillation *in vacuo*, and the residue was mixed with a small amount of water. The alcohol component of the hydrolysis mixture was obtained by ether ex-

(12) These side reactions might include rearrangement of the anion of the Reissert compound to the α-acyl derivative,[7,11] disproportionation of the anion to give, as one of the products, quinaldonitrile or isoquinaldonitrile,[4] decomposition of the anion to form, as one of the products, quinoline or isoquinoline,[3] or condensation reactions occurring either at the carbonyl carbon atom of the acyl group of the Reissert compound or at the carbon atom of the cyano group.[6,13]

(13) N. C. Rose and W. E. McEwen, *J. Org. Chem.*, in press.

(14) All m.p.'s are corrected and all b.p.'s are uncorrected. Analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

traction. All of the carbinols were purified by recrystallization from ethanol except the following: phenyl-2-quinolylcarbinol was recrystallized from low boiling petroleum ether; *n*-propyl-2-quinolylcarbinol was recrystallized from water–acetone; isopropyl-2-quinolylcarbinol, *n*-propyl-1-isoquinolylcarbinol and isopropyl-1-isoquinolylcarbinol were purified by distillation *in vacuo*.

Conversion of *n*-Propyl-2-quinolylcarbinol (XI) to 2-*n*-Butylquinoline.—A solution of 2.00 g. of *n*-propyl-2-quinolylcarbinol in 20 cc. of glacial acetic acid was chilled in an ice-bath, and then anhydrous hydrogen bromide was passed into the solution for a period of an hour. The solution was allowed to stand at 0° for 12 hours, and then it was warmed to room temperature. Over a period of 45 minutes and with mechanical stirring, a total of 1.29 g. (20-fold excess) of zinc dust was added. The resulting clear solution was made alkaline by addition of ammonium hydroxide solution and extracted with ether. After removal of the ether there remained a brown liquid. Distillation gave about 1.5 cc. of 2-*n*-butylquinoline, b.p. 103–108° (0.9–1.0 mm.), reported[9] b.p. 94–98° (0.7 mm.) and 153° (14 mm.). A portion of this material was converted to the picrate by treatment with an ethanol solution of picric acid. After recrystallization from ethanol, the m.p. was 161.5–164.0°, reported[9] m.p. 162°.

Conversion of *n*-Propyl-1-isoquinolylcarbinol (XIV) to 1-*n*-Butylisoquinoline.—The reduction was carried out as described above. The picrate had a m.p. of 183–186° after recrystallization from ethanol; reported[7] for 1-*n*-butylisoquinoline picrate, m.p. 183–185°.

Qualitative Rate Studies.—The condensation reaction between the lithium salt of 1-benzoyl-1,2-dihydroquinaldonitrile (I, R = C_6H_5) and benzaldehyde was carried out exactly as described in the general procedure, but with the exception that the reaction was quenched by addition of 25 cc. of water just as soon as the red color had been discharged. The total time of reaction at −10° from the start of the addition of benzaldehyde to the quenching operation was six minutes. Phenyl-2-quinolylcarbinyl benzoate (VII) was obtained in 97% yield. Phenyl-1-isoquinolylcarbinyl benzoate (XV) was obtained in 88% yield in an identical experiment with the lithium salt of 2-benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) and benzaldehyde. In the reaction between the lithium salt of II (R = C_6H_5) and anisaldehyde, however, the red color was not completely discharged even after several hours. Hydrolysis of the reaction mixture at any time during this interval led to the isolation of both *p*-anisyl-1-isoquinolylcarbinyl benzoate and unreacted 2-benzoyl-1,2-dihydroisoquinaldonitrile.

Reaction of the Lithium Salt of 2-Benzoyl-1,2-dihydroisoquinaldonitrile (II, R = C_6H_5) with Ethylene Oxide.—The reaction was carried out in the same manner as described above for the condensation of the lithium salts of Reissert compounds with aldehydes or ketones. In the work-up of the reaction mixture, the organic layer was extracted with three 50-cc. portions of 10% hydrochloric acid, rather than with 12 cc. of 0.5 *N* hydrochloric acid, as described for the aldehyde reactions. Only an intractable material was obtained after removal of the solvents from the organic layer. However, after the hydrochloric acid extract had been made alkaline by addition of sodium hydroxide solution, ether extraction provided a colorless solid, m.p. 79–80°, after recrystallization from ethanol.

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.98; H, 5.42; N, 5.05. Found: C, 77.95; H, 5.60; N, 4.84.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF KANSAS]

Approaches to the Synthesis of Emetine from Reissert Compounds[1]

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Reasonably convenient syntheses of 3-ethylpyridine-4-carboxaldehyde (III) and 2-methyl-5-ethylpyridine-4-carboxaldehyde (IV) have been developed. Condensation of these aldehydes with the lithium salt of 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II), followed by alkaline hydrolysis of the initially formed anisate esters, gave 1-(6,7-dimethoxyisoquinolyl)-4-(3-ethylpyridyl)-carbinol (XIII) and 1-(6,7-dimethoxyisoquinolyl)-4-(2-methyl-5-ethylpyridyl)-carbinol (XV), respectively. 1-(3,4-Dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-pyridinium bromide (XIX) has been prepared, and oxidation of this compound with alkaline potassium ferricyanide solution gave either 1-(3,4-dimethoxyphenethyl)-3-ethyl-4-(carboxaldehyde diethylacetal)-2-pyridone (XXII) or 1-(3,4-dimethoxyphenethyl)-4-carboxaldehyde diethylacetal)-5-ethyl-2-pyridone (XXIII). Compounds XIII, XV and XXIII are considered to be attractive intermediates for the synthesis of ipecac alkaloids.

Although syntheses of emetine (I)[2] and its dehydrogenation product the rubremetinium cation[3] have been reported, it was of interest to us to attempt the synthesis of the alkaloid or one of its diastereoisomers from 2-anisoyl-6,7-dimethoxy-1,2-dihydroisoquinaldonitrile (II), a compound previously used in the synthesis of papaverine,[4] as a starting material. It was thought that the condensation of the lithium salt of II with an appropriate aldehyde, a recently discovered reaction of Reissert compounds,[5] would serve as a key step in the proposed synthesis. The stereochemistry of emetine, shown in structure I, recently has been determined.[6]

Efforts were first directed toward the development of convenient syntheses of 3-ethylpyridine-4-carboxaldehyde (III) and 2-methyl-5-ethylpyridine-4-carboxaldehyde (IV), the aldehydes which were to be used in the condensation reaction with the lithium salt of II. Inasmuch as Ginsburg and Wilson[7] were able to convert 2,3-dimethylpyridine to 3-methylpyridine-2-carboxaldehyde by a suitable adaptation of a reaction discovered by Boekelheide and Linn,[8] it was thought that the

(1) Abstracted from a portion of the dissertation submitted by Frank D. Popp in partial fulfillment of the requirements for the Ph.D. degree, Kansas University, 1957.

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(3) A. R. Battersby and H. T. Openshaw, *Experientia*, **6**, 378 (1950); A. R. Battersby, H. T. Openshaw and H. C. S. Wood, *J. Chem. Soc.*, 2463 (1953); Y. Ban, *Pharm. Bull. (Japan)*, **3**, 53 (1955); *C. A.*, **50**, 1854 (1956).

(4) F. D. Popp and W. E. McEwen, THIS JOURNAL, **79**, 3773 (1957).

(5) L. R. Walters, T. Iyer and W. E. McEwen, *ibid.*, **80**, 1177 (1958).

(6) A. R. Battersby R. Binks, D. Davidson, G. C. Davidson and T. P. Edwards, *Chemistry & Industry*, 982 (1957). See also E. E. van Tamelen, P. E. Aldrich and J. B. Hester, Jr., THIS JOURNAL, **79**, 4817 (1957).

(7) S. Ginsburg and I. B. Wilson, *ibid.*, **79**, 481 (1957).

(8) V. Boekelheide and W. J. Linn, *ibid.*, **76**, 1286 (1954).