hexen-2-yl-4 mesitoate and *t*-butyl mesitoate with the phenyl Grignard reagent have been studied.

The results favor the ionic mechanism previously proposed for the cleavage reaction.

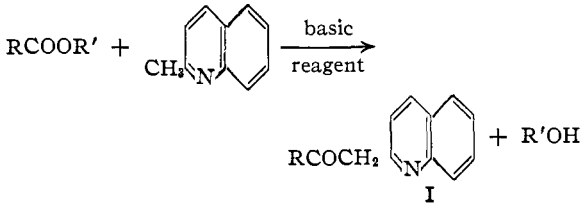
MINNEAPOLIS, MINNESOTA RECEIVED OCTOBER 18, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

The Acylation and Carbethoxylation of Quinaldine, Lepidine and α-Picoline Using Sodium Amide or Potassium Amide[1,2]

BY MARTIN J. WEISS[3] AND CHARLES R. HAUSER

Like methyl ketones, α- and γ-methyl pyridyl systems such as α-picoline, quinaldine and lepidine, which may be regarded as methyl ketones or their vinylogs in the ammonia system of compounds,[4] may undergo the Claisen type of acylation or carbethoxylation. For example, quinaldine may be acylated with esters in the presence of suitable basic reagents to form the corresponding acyl derivative (I).



I

However, the scope of the methods for effecting such reactions has previously been somewhat limited. An alkoxide (potassium ethoxide) has been employed apparently only for the acylation of quinaldine and lepidine with ethyl oxalate,[5] which is a relatively reactive ester. Potassium amide[4] in ether has been used for the aroylation of quinaldine with ethyl benzoate and certain other aromatic esters but the method failed with α-picoline or lepidine and ethyl benzoate and also with quinaldine and ethyl acetate or ethyl oxalate. Potassium amide in liquid ammonia was later used successfully for the benzoylation of lepidine[6] but no details were given. Phenyllithium has been employed for the acylation of α-picoline with ethyl acetate,[7] acetyl chloride,[8] acetic anhydride,[7,8] benzoyl chloride,[8,9] benzoic anhydride[8] and half acid chlorides of certain dibasic acid esters,[10] but most of the yields have been low. In certain cases further condensation products have been reported.[7,8]

In the present investigation the recently developed alkali amide method[11] for the acylation and carbethoxylation of ketones has been adapted to the acylation and carbethoxylation of α-picoline, quinaldine and lepidine. The process consists in first converting the methyl pyridyl compound essentially completely to its sodium or potassium derivative by means of sodium or potassium amide and then reacting the alkali derivative with the acylating or the carbethoxylating agent. With esters and probably also with anhydrides or acid chlorides, the resulting acyl or carbethoxyl derivative is converted in the reaction mixture to its alkali derivative; this acid-base reaction may be effected either by part of the alkali derivative of the methyl pyridyl compound or by excess alkali amide. These three steps may be illustrated by the following equations in which CH_3P represents the methyl pyridyl system.

$$CH_3P + KNH_2 \longrightarrow K(CH_2P) + NH_3 \quad (1)$$

$$RCO_2R' + K(CH_2P) \longrightarrow RCOCH_2P + KOR' \quad (2)$$

$$RCOCH_2P + K(CH_2P) \longrightarrow K(RCOCHP) + CH_3P \quad (3)$$
$$\text{or } KNH_2 \qquad\qquad\qquad\qquad \text{or } NH_3$$

On the basis of this interpretation it has seemed advantageous to employ either two molecular equivalents of alkali amide to one of methyl pyridyl compound and at least one of ester (Method A)[12] or two equivalents each of alkali amide and methyl pyridyl compound to one of ester (Method B). It may be considered that, in Method A, the third step is effected by the extra equivalent of alkali amide whereas, in Method B, the third step is effected by part of the alkali derivative of the methyl pyridyl compound which is formed in the first step. Obviously half of the methyl pyridyl compound would be regenerated in the third step of Method B.

(1) Paper XLIII on Condensations; paper XLII, THIS JOURNAL, **71**, 1350 (1949).

(2) Part of this work was supported by a grant from the Duke University Research Council.

(3) Eli Lilly Fellow, 1947–1948.

(4) Bergstrom and Moffat, THIS JOURNAL, **59**, 1494 (1937).

(5) Wislicenus and Kleisinger, *Ber.*, **42**, 1140 (1909).

(6) Bergstrom, *Chem. Rev.*, **35**, 184 (1944).

(7) Beets, *Chem. Weekblad*, **39**, 187 (1942); *C. A.*, **37**, 5064 (1943).

(8) Kloppenburg and Wibaut, *Rec. trav. chim.*, **65**, 393 (1946).

(9) Bergmann and Rosenthal, *J. prakt. Chem.*, [2] **135**, 267 (1932).

(10) Graef, Fredericksen and Burger, *J. Org. Chem.*, **11**, 257 (1945).

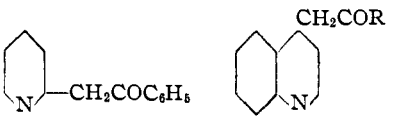
(11) See Adams and Hauser, THIS JOURNAL, **66**, 1220 (1944); Levine and Hauser, *ibid.*, **66**, 1768 (1944).

(12) Bergstrom and Moffat[4] reported that, in the benzoylation of quinaldine with an equivalent of ethyl benzoate in ether, the use of two and one-half equivalents of potassium amide gave a 60% yield of 2-phenacylquinoline whereas the use of two equivalents gave only a 35% yield. However, we have obtained a 62% yield with two equivalents of the base. It should be mentioned also that, in the benzoylation of lepidine in liquid ammonia, the yield of 4-phenacylquinoline was actually greater (37%) with two equivalents of sodium amide than with two and one-half equivalents (28%).

Method B appears to be generally applicable but Method A is not always successful. In certain cases the extra equivalent of the alkali amide employed in Method A, instead of the alkali derivative of the methyl pyridyl compound, reacts with most of the ester. This appears to have occurred when Bergstrom and Moffat[4] attempted to benzoylate α-picoline or lepidine by means of excess potassium amide in ether in which the potassium salts of these methyl pyridyl compounds are relatively insoluble. However, this side reaction was apparently greatly minimized when the reaction was carried out in liquid ammonia.[6] Although Method B was generally effected in ether, it could presumably also be carried out in liquid ammonia. Our results using Methods A and B are summarized in Table I. The yields are not necessarily the optimum obtainable. The percentages in the left-hand column under "Yield" are based on the acylating agent or the carbethoxylating agent or, when Method A is employed, also on the methyl pyridyl compound; the percentages in the right-hand column are based on the amount of methyl pyridyl compound used minus that recovered. In general quinaldine and lepidine are readily recoverable but α-picoline is too water soluble to be recovered easily.

It can be seen from Table I that various derivatives of quinaldine (I, R = alkyl or phenyl[13]) have been prepared although some of the yields have not been very satisfactory. Since Bergstrom and Moffat[4] failed to realize acetylation with ethyl acetate presumably because the α-hydrogen of is ester was attacked, we employed phenyl acetate and acetic anhydride[14] which are more reactive acetylating agents. However, only a slight yield of product has been obtained with acetyl chloride which is a still more reactive acetylating agent. Apparently the acid chloride reacted with ammonia, some of which could have been present in the reaction mixture. Phenyl propionate and propionic anhydride were used for propionylations. However, ethyl isobutyrate was found satisfactory for the isobutyrylation. It can be seen from Table I that the yields are better with phenyl propionate than with phenyl acetate and with ethyl isobutyrate than with ethyl *n*-butyrate. This is presumably because the α-hydrogen of the propionate is less reactive than that of the acetate and because the α-hydrogen of the isobutyrate is less reactive than that of the *n*-butyrate.

Similarly the benzoyl derivative of α-picoline (II) and the benzoyl and ethoxalyl[15] derivatives of lepidine (III, R = C_6H_5 and $CO_2C_2H_5$, respectively) were prepared. It seems likely that various acyl derivatives of these methyl pyridyl compounds may also be prepared by the present methods.



II III

The carbethoxyl derivatives of quinaldine, lepidine and α-picoline in which R in $RCH_2COOC_2H_5$ is α- and γ-quinolyl and α-pyridyl, respectively, have been prepared although the yields for the latter two derivatives have been only low to fair. The α-quinolyl derivative is also represented by I in which R is ethoxide. In agreement with previous reports,[16,17] attempts[18] to carbonate the sodium and potassium derivative of quinaldine were unsuccessful, the quinaldine being recovered quantitatively.

The present direct method for preparing acyl, aroyl or carbethoxyl derivatives of the methyl pyridyl compounds appears to be more convenient than indirect methods[19] described previously. Moreover the direct method could probably be extended to methyl or methoxy substituted aroyl derivatives and to longer chain acyl derivatives.

Finally it should be mentioned that, although 2-phenacylquinoline has been reported[4] to show no ketonic reactions we have been able to prepare the oximes of 2-phenacylpyridine, 4-phenacylquinoline and isopropylquinaldyl ketone (I, R = isopropyl) in good yields.

Experimental

Quinaldine (b. p. 245–245.5°), lepidine (b. p. 262°) and α-picoline (b. p. 129–130°) were redistilled Reilly products. The esters were dried and redistilled. Propionic anhydride was redistilled; acetic anhydride was refluxed over magnesium and then distilled.

Method A in Liquid Ammonia.—In a 500-ml. three-necked flask with ground glass joints and with attached Dry Ice reflux condenser (Drierite tube), mercury-sealed stirrer and dropping funnel was prepared 0.20 mole (or 0.25 mole) of sodium amide[11] or potassium amide[20] in about 300 ml. of liquid ammonia. The methyl pyridyl compound, dissolved in an equal volume of anhydrous ether, was added, followed in a few minutes by the dropwise addition of the ester also dissolved in ether. The ammonia was then allowed to reflux. The reaction was

(13) An unsuccessful attempt was made to prepare 2-phenacylquinoline by refluxing quinaldine with diethylaminomagnesium bromide (see Hauser and Walker, THIS JOURNAL, **69**, 295 (1947)) in ether for ten hours followed by treatment with ethyl benzoate; 88% of the quinaldine was recovered. Apparently diethylaminomagnesium bromide was incapable of converting quinaldine to its magnesium derivative.

(14) Unsuccessful attempts were made to effect the acetylation of quinaldine with acetic anhydride in the presence of boron trifluoride according to the method of acylation of ketones by this reagent (see Hauser and Adams, THIS JOURNAL, **66**, 345 (1944)). The reaction also failed when the boron trifluoride complex, prepared at 0°, was heated at 70° for two hours. In both cases quinaldine was largely recovered.

(15) However, with α-picoline and ethyl oxalate, there has been obtained a substance, melting at 164–165°, which is apparently not the simple ethoxalyl derivative. This product is being further investigated.

(16) Bergstrom, THIS JOURNAL, **53**, 3037 (1931).

(17) Ziegler and Zeiser, *Ann.*, **485**, 182 (1931).

(18) These experiments were carried out by Mr. George A. Reynolds of this Laboratory.

(19) (a) Borsche and Manteuffel, *Ann.*, **526**, 22 (1936); (b) Borsche and Bütschli, *ibid.*, **529**, 266 (1937); (c) Clemo, Morgan and Raper, *J. Chem. Soc.*, 1743 (1935); (d) Fischer and Kuzel, *Ber.*, **16**, 163 (1883); (e) Scheuing and Winterhalder, *Ann.*, **473**, 126 (1929).

(20) Yost and Hauser, THIS JOURNAL, **69**, 2325 (1947).

TABLE I

ACYLATION AND CARBETHOXYLATION OF QUINALDINE, LEPIDINE AND α-PICOLINE BY MEANS OF ALKALI AMIDES

Method	Time, hr.	Product[a]	B. p. °C.	B. p. Mm.	Yield,[b] %		Formula[c]	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
Condensations with Quinaldine													
A(KNH_2)[d]	4	2-Phenacylquinoline	M. p. 114–116[e]		62								
B(KNH_2)	12[f]	Methyl-quinaldyl-ketone[g]	M. p. 75–77[h]		17	35							
B($NaNH_2$)	2	Methyl-quinaldyl-ketone[i]	143–148	4.5[j]	33	36							
B(KNH_2)	12[f]	Ethyl-quinaldyl-ketone[k,l]	172–175	6.5	32	64	$C_{13}H_{13}NO$	78.36	77.92	6.58	6.09		
B($NaNH_2$)	2	Ethyl-quinaldyl-ketone[l,m]	167–168	6	32	38	$C_{19}H_{16}N_4O_8$[n]	53.27	52.91	3.77	3.42	13.08	13.16
A($NaNH_2$)	4	*n*-Propyl-quinaldyl-ketone[l]	156	3	14	37	$C_{14}H_{15}NO$	78.84	78.43	7.09	7.39	6.57	6.97
							$C_{20}H_{18}N_4O_8$[o]					12.67	12.59
A($NaNH_2$)	4	Isopropyl-quinaldyl-ketone[l]	144	2.5[p]	36	65	$C_{14}H_{15}NO$	78.84	79.09	7.09	7.00		
							$C_{14}H_{16}N_2O$[q]	73.65	73.93	7.07	6.73		
B(KNH_2)[r]	12	Ethyl α-quinolyl-acetate[l]	174–178	10[s]	36	43							
Condensations with Lepidine													
B(KNH_2)	12	4-Phenacylquinoline	M. p. 112–114[t]		44		$C_{17}H_{15}NO$	82.57	82.29	5.30	4.90	5.67	5.21
A($NaNH_2$)	5	4-Phenacylquinoline	M. p. 112–115		37[u]	56	$C_{17}H_{14}N_2O$[v]	77.84	77.77	5.38	5.62	10.68	11.12
B(KNH_2)	12[e]	Ethyl γ-quinolyl-pyruvate	M. p. 188–189[w]		60								
B(KNH_2)	20	Ethyl γ-quinolyl-acetate[l]	156	3[x]	14	17							
Condensations with α-Picoline													
A(KNH_2)[y]	5	2-Phenacylpyridine[l]	150–160	4[z]	57								
B(KNH_2)	10	2-Phenacylpyridine[l]	150–160	3[aa]	47		$C_{13}H_{12}N_2O$[bb]	73.56	73.18	5.70	5.39	13.20	13.20
B(KNH_2)	14	Ethyl α-pyridyl-acetate	128–132	21[cc]	25		$C_{15}H_{14}N_4O_8$[dd]	45.69	45.87	3.58	3.67	14.21	14.51

[a] Acylating or carbethoxylating agent was the ethyl ester except as noted. [b] Yields in left-hand column are based on starting materials and those in right-hand column, on the amount of methyl pyridyl compound used minus that recovered. [c] Analyses are by Oakwold Laboratories, Alexandria, Virginia. [d] Refluxing ether was used according to the procedure of Bergstrom and Moffat (ref. 4). [e] After one recrystallization from ethanol–water; reported m. p. 116–117° (ref. 4). [f] Allowed to stand at room temperature an additional 10–12 hours. [g] Acetylating agent was phenyl acetate. [h] After two recrystallizations from isopropyl ether (Norite); reported m. p. 76° (ref. 19 d). [i] Acetylating agent was acetic anhydride. [j] M. p. 72–75°. [k] Acylating agent was phenyl propionate. [l] Some decomposition occurred on standing (see ref. 8, 9). [m] Acylating agent was propionic anhydride. [n] Picrate, m. p. 181–181.5° dec. cor., after several recrystallizations from 95% ethanol. [o] Picrate, m. p. 181° cor., after five recrystallizations from a mixture of ethyl acetate and dioxane. [p] Boiling point of redistilled product. [q] Oxime, m. p. 125–126° after several recrystallizations from ethanol–water, prepared by the procedure of Hauser and co-workers (THIS JOURNAL, **66**, 1921 (1944)) except that the heating period was five hours. [r] A 32% yield was obtained using sodium amide. An 8% yield of product was obtained using Method A in liquid ammonia; a slight yield was obtained using Method A in ether. [s] Reported b. p. 204° at 16 mm. (ref. 19a). The picrate after one recrystallization from 95% ethanol melted at 151–153° cor.; reported m. p. 152° (ref. 19a). [t] After two recrystallizations from ethanol–water. Repeated recrystallizations from isopropyl alcohol and isopropyl ether gave white crystals melting at 115.5–116°. [u] The yield was 28% when two and one-half equivalents of sodium amide were used and 25% when two and one-half equivalents of potassium amide were employed. [v] Oxime, m. p. 165–166° (see note *q*) after several recrystallizations from ethanol–water. [w] After one recrystallization from dioxane–water. Three more recrystallizations raised the melting point to 193–193.5° (much sintering); reported m. p. 194–196° (ref. 5). [x] The picrate after two recrystallizations from 95% ethanol melted at 160.5–161° cor.; reported m. p. 157° (ref. 19b). [y] Two and one-half equivalents of potassium amide were used. [z] M. p. 45–47. [aa] M. p. 48–51. Three recrystallizations raised the melting point to 53–54°; reported m. p. 54° (ref. 8). [bb] Oxime, m. p. 114–116° after several recrystallizations from Skellysolve B and isopropyl ether, obtained in 46% yield (see note *q*). [cc] Reported b. p. 134–135° at 21 mm. (ref. 19c). [dd] Picrate, m. p. 139–139.5° cor. (reported m. p. 136–137°, ref. 19c), after two recrystallizations from isopropyl alcohol.

halted by the careful addition of ordinary ether followed by water. After the ammonia had evaporated and the two phases separated, the ether phase was extracted with several portions of 6*N* hydrochloric acid solution. The acid solution or suspension[21] was saturated with sodium bicarbonate and the resulting mixture thoroughly extracted with ether. After the combined ether extracts had been dried over Drierite or anhydrous sodium sulfate, the solvent was distilled and the residue fractionated through an 11-cm. Vigreux column. Quinaldine was recovered in the forerun. Certain of the reaction mixtures were worked up as described below.

With ethyl benzoate and α-picoline, 2-phenacylquinoline was obtained by distillation through an 11-cm. Vigreux column surmounted by a von Braun head.

With ethyl benzoate and lepidine, the product was formed as an oily solid on saturation of the acid extracts with sodium bicarbonate. The crude product, after filtration, was washed with water and then dissolved in 80 ml. of glacial acetic acid. The acetic acid solution was slowly stirred into 720 ml. of water to give 4-phenacylquinoline as a yellow solid, which was suction-filtered, washed with water and air-dried. Lepidine may be recovered from the acetic acid mother liquor by neutralization.

The results are summarized in Table I.

Method B in Ether.—In the apparatus described above (having an ordinary reflux condenser) was prepared a solution of 0.20 mole of potassium amide or a suspension of 0.20 mole of sodium amide. To this reagent was added 0.20 mole of quinaldine, lepidine or α-picoline, dissolved in an equal volume of ether. The reaction flask was placed on the steam-bath and about 300 ml. of anhydrous ether was added gradually as the ammonia was evaporated. Stirring and refluxing were continued five to ten hours so as to obtain essentially complete conversion to the alkali metal derivative of the methyl pyridyl compound.[22] The steam-bath was removed and 0.10 mole of the ester or anhydride, dissolved in ether, was added at such a rate so as to maintain gentle refluxing. The reaction mixture was

(21) The hydrochloride salts of 2-phenacylpyridine and 4-phenacylquinoline are not very soluble in 6 *N* hydrochloric acid solution.

(22) Potassium and sodium quinaldyl and potassium α-picolyl, which formed red solutions in liquid ammonia, gave crystalline suspensions in ether which varied in color from red to black. Potassium lepidyl, which was also soluble in liquid ammonia, was first precipitated in ether as a black tarry mass which, after continued refluxing, became fairly crystalline.

then stirred and refluxed. Hydrochloric acid solution (6 *N*) was carefully added to the reaction mixture, the layers separated and the ether layer thoroughly extracted with 6 *N* acid. The compounds were then isolated generally as described in Method A.

With ethyl carbonate and quinaldine, lepidine or α-picoline, a cold 3 *N* hydrochloric acid solution was added to the reaction mixture, the reaction flask being immersed in an ice-bath during the addition of the acid.

With ethyl oxalate and lepidine, the reaction mixture was acidified with a cold 3 *N* hydrochloric acid solution while the reaction flask was immersed in an ice-bath. The ether layer was separated from the acid suspension which was then neutralized by the dropwise addition of a chilled 2 *N* ammonium hydroxide solution.

With ethyl benzoate and lepidine, the oily solid, which precipitated on the addition of sodium bicarbonate to the acid extracts, was filtered off and the lepidine removed from it by steam distillation. The remaining solid was dissolved in 3 *N* hydrochloric acid solution and reprecipitated by the addition of sodium carbonate solution. The crude greenish solid was filtered off, washed with water and dried in air. Several recrystallizations from a mixture of ethanol and water followed by repeated recrystallizations from a mixture of isopropyl ether and isopropyl alcohol gave white crystals of 4-phenacylquinoline. This method of isolation is probably inferior to that described under Method A.

The results are summarized in Table I.

Summary

1. The recently developed alkali amide method for the acylation and carbethoxylation of ketones has been adapted to the acylation and carbethoxylation of quinaldine, lepidine and α-picoline.

2. This method appears to be convenient for the preparation of a number of acyl and carbethoxyl derivatives of these methyl pyridyl compounds.

DURHAM, NORTH CAROLINA

RECEIVED NOVEMBER 17, 1948

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

Michael Condensations by Sodium Amide with Quinaldine, α-Picoline or Lepidine as the Active Hydrogen Component[1]

BY MARTIN J. WEISS[2] AND CHARLES R. HAUSER

α- or γ-methyl pyridyl compounds such as quinaldine (2-methylquinoline), α-picoline (2-methylpyridine) and lepidine (4-methylquinoline) have previously been condensed with alkyl halides,[3] esters[3,4] and aldehydes.[3] The fourth possible type of carbon–carbon condensation[5] with these active hydrogen compounds, involving the Michael condensation with α,β-unsaturated ketones or esters, has been realized in the present investigation.

In this condensation, the methyl pyridyl compound was converted by a molecular equivalent of sodium amide to its sodium derivative, which was condensed with the α,β-unsaturated ketone or ester. With quinaldine and benzalacetophenone, compound (II) in which R is α-quinolyl was obtained in good yield. That this product was (II) and not the aldol product which might have been formed by addition of the anion of quinaldine to the carbonyl carbon of benzalacetophenone is shown by its formation of an oxime in high yield.

$$\text{R—CH}_3 \xrightarrow{\text{NaNH}_2} \text{R—CH}_2\text{Na} \xrightarrow{\text{C}_6\text{H}_5\text{CH=CHCOC}_6\text{H}_5}$$

$$[\text{R—CH}_2\text{CH(C}_6\text{H}_5)\text{CHCOC}_6\text{H}_5]^-\ \text{Na}^+ \xrightarrow{\text{HOH}}$$

(I)

$$\text{R—CH}_2\text{CH(C}_6\text{H}_5)\text{CH}_2\text{COC}_6\text{H}_5$$

(II)

With lepidine and benzalacetophenone, compound (II) in which R is γ-quinolyl was apparently formed in fair yield. With α-picoline and benzalacetophenone, a mixture was obtained from which was isolated a product analyzing for compound (III, R = α-pyridyl) in which *n* is 1 (a dimer) or 2 (a trimer). The analogous dimer or trimer (III, R = α-quinolyl) was obtained with quinaldine when the reaction was carried out with only about one-fifth of an equivalent of sodium amide instead of an equivalent as described above. The dimer would result from the Michael type of addition of anion (I) to benzalacetophenone and the trimer, by a further reaction of the same type.

$$\text{R—CH}_2\text{CH(C}_6\text{H}_5)\text{CHCOC}_6\text{H}_5$$
$$|$$
$$(\text{C}_6\text{H}_5\text{CHCHCOC}_6\text{H}_5)_n$$
$$|$$

(III)

With quinaldine and mesityl oxide, the sodium quinaldyl appeared only to convert the ketone to its sodium derivative, thereby regenerating the quinaldine which was largely recovered.

With quinaldine and ethyl cinnamate, the Michael product (IV, R = α-quinolyl), isolated as its acid, was obtained in fair yield. The Claisen acylation product (V, R = α-quinolyl) also was formed.

$$\text{R—CH}_2\text{Na} + \text{C}_6\text{H}_5\text{CH=CHCO}_2\text{C}_2\text{H}_5$$

Michael | Claisen

$$\text{R—CH}_2\text{CH(C}_6\text{H}_5)\text{CH}_2\text{CO}_2\text{C}_2\text{H}_5 \qquad \text{R—CH}_2\text{COCH=CHC}_6\text{H}_5$$

(IV) (V)

(1) Paper XLIV on Condensations; paper XLIII, THIS JOURNAL, **71**, 2023 (1949).

(2) Eli Lilly Fellow, 1947–1948.

(3) See Bergstrom, *Chem. Revs.*, **35**, 77 (1944).

(4) Weiss and Hauser, THIS JOURNAL, **71**, 2023 (1949).

(5) For the four type classification of carbon–carbon condensations with active hydrogen compounds, see Hauser and Breslow, *ibid.*, **62**, 2389 (1940).