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

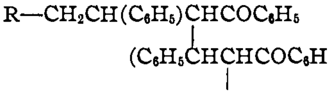
α- or γ-methyl pyridyl compounds such as quinaldine (2-methylquinoline), α-picoline (2-methylpyridine) and lepidine (4-methylquinoline) have previously been condensed with alkyl halides,[3] esters[3,4] and aldehydes.[3] The fourth possible type of carbon–carbon condensation[5] with these active hydrogen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

$$\mathrm{R{-}CH_3} \xrightarrow{\mathrm{NaNH_2}} \mathrm{R{-}CH_2Na} \xrightarrow{\mathrm{C_6H_5CH{=}CHCOC_6H_5}}$$

$$\underset{\text{(I)}}{[\mathrm{R{-}CH_2CH(C_6H_5)CHCOC_6H_5}]^-}\ \mathrm{Na^+} \xrightarrow{\mathrm{HOH}} \underset{\text{(II)}}{\mathrm{R{-}CH_2CH(C_6H_5)CH_2COC_6H_5}}$$

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.

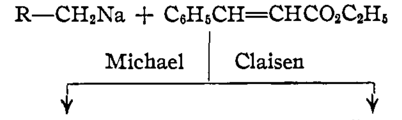


$$\mathrm{R{-}CH_2CH(C_6H_5)CHCOC_6H_5}$$
$$\mathrm{(C_6H_5CHCHCOC_6H_5)_n}$$

(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.



$$\mathrm{R{-}CH_2Na + C_6H_5CH{=}CHCO_2C_2H_5}$$

$$\underset{\text{(IV)}}{\mathrm{R{-}CH_2CH(C_6H_5)CH_2CO_2C_2H_5}} \qquad \underset{\text{(V)}}{\mathrm{R{-}CH_2COCH{=}CHC_6H_5}}$$

---

(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).

Experimental

Quinaldine (b. p. 245–245.5°), lepidine (b. p. 262°) and α-picoline (b. p. 129–130°) were all redistilled Reilly products.

Condensations with Benzalacetophenone.—To a suspension of 0.11 mole of sodium amide[6] in about 300 ml. of liquid ammonia, prepared in a 500-ml. three-necked flask (ground-glass joints) equipped with a mercury sealed stirrer, reflux condenser (Drierite tube) and dropping funnel, was added 0.11 mole of quinaldine, lepidine or α-picoline in an equal volume of anhydrous ether. The reaction flask was placed on the steam-bath and the liquid ammonia was gradually replaced by anhydrous ether. After the ether suspension had been stirred and refluxed for three to four hours (one hour with lepidine), an ether solution of 0.10 mole of benzalacetophenone (m. p. 60–61°) was added at such a rate as to maintain gentle refluxing. The mixture was stirred and refluxed four to five hours (seven hours with lepidine) and water then added.

In the experiment with quinaldine, the heavy yellow precipitate (21.4 g., m. p. 107–110°) was filtered off, washed with water and air dried. Additional crude material (1.5 g.) was obtained by extracting the ether phase of the filtrate with several portions of 6 *N* hydrochloric acid and making the combined acid extracts basic with 7 *N* ammonium hydroxide solution. The combined crude material was recrystallized from ethanol-water yielding 20.3 g. (60%) of β-phenyl-γ-(2-quinolyl)-butyrophenone (II, R = α-quinolyl) melting at 113.5–115°. Additional recrystallizations from ethanol-water gave white crystals melting at 115°.

Anal.[7] Calcd. for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.34; H, 6.04; N, 4.08.

The product was converted[8] in 88% yield to the oxime, m. p. 162–166°; recrystallizations from ethanol-water gave cream colored crystals melting at 167–169°.

Anal.[7] Calcd. for $C_{25}H_{22}N_2O$: C, 81.93; H, 6.05; N, 7.65. Found: C, 81.68; H, 6.07; N, 8.18.

In the experiment with lepidine, the aqueous-ether reaction mixture was separated and the ether shaken with several portions of 6 *N* hydrochloric acid solution. To the acid extracts, containing precipitated hydrochloride salt, was added excess 7 *N* ammonium hydroxide solution. The viscous oil, which became partly crystalline on standing in the refrigerator, was rubbed with 60 ml. of ethanol. The resulting gray solid (11.3 g., m. p. 105–110°) was dissolved in 40 ml. of hot dioxane (Norite) and, after cooling to room temperature, 25 ml. of water was added. Chilling the mixture gave 9.5 g. (27%) of β-phenyl-γ-(4-quinolyl)-butyrophenone (II, R = γ-quinolyl) melting at 109–112°. Recrystallizations from dioxane-water gave white crystals melting at 114–115°.

Anal.[7] Calcd. for $C_{25}H_{21}NO$: C, 85.44; H, 6.02; N, 3.99. Found: C, 85.14; H, 5.79; N, 3.66.

Attempts to form the oxime of this compound were unsuccessful and, although the semicarbazone appeared to be formed, it was not possible to purify it.

In the experiment with α-picoline, the aqueous-ether reaction mixture was treated as described above for lepidine. The semi-solid, obtained from the ammonium hydroxide treatment, was washed with water, followed by 50 ml. of ethanol, and ground with water in a mortar to give a gray solid (13.5 g.) which melted at 90–110°. Recrystallizations of 2 g. of the material gave 1 g. of dimer (III, R = α-pyridyl, $n = 1$) or trimer (III, R = α-pyridyl, $n = 2$) melting at 145–149°. Repeated recrystallizations from dioxane-ethanol and from benzene-Skellysolve B gave white crystals, m. p. 147.5–148.5°.

Anal.[9] Calcd. for $C_{36}H_{31}NO_2$ (dimer): C, 84.84; H, 6.13; N, 2.75; for $C_{51}H_{43}NO_3$ (trimer): C, 85.33; H, 6.04; N, 1.95. Found: C, 84.96, 85.07; H, 6.16, 6.46; N, 1.69, 1.75.

When the reaction of quinaldine and benzalacetophenone was carried out with only 20 mole per cent. of sodium amide, the only substance isolated was apparently the dimer (III, R = α-quinolyl, $n = 1$) or trimer (III, R = α-quinolyl, $n = 2$) which was obtained as white crystals melting at 285–287° after repeated recrystallizations from dioxane-water.

Anal.[7] Calcd. for $C_{39}H_{31}NO_2$ (dimer): C, 85.84; H, 5.73; N, 2.57; for $C_{54}H_{43}NO_3$ (trimer): C, 86.03; H, 5.75; N, 1.86. Found: C, 85.95, 85.58; H, 5.84, 5.49; N, 1.96.

Quinaldine with Ethyl Cinnamate.—The suspension of sodium quinaldyl, obtained from 0.11 mole each of quinaldine and sodium amide, was stirred and refluxed for three hours. After the addition of 0.10 mole of ethyl cinnamate, the reaction mixture was stirred and refluxed for thirteen hours. The reaction was halted by the careful addition of a 3 *N* hydrochloric acid solution. The ether phase was extracted with several portions of 6 *N* hydrochloric acid and the extracts together with the red amorphous salts were combined with the original acid phase. The mixture was cooled in an ice-bath and treated with excess 7 *N* ammonium hydroxide. The resulting mixture was extracted thoroughly with ether. The combined ether extracts were dried over Drierite and the solvent distilled. The residue was distilled ***in vacuo*** in a Claisen distilling flask. After recovering 1.1 g. of quinaldine, the residue was distilled using a mercury vapor high vacuum system yielding 13.2 g. of a dark red oil, b. p. 190–205° at 1–2 mm., which deposited some red-orange crystals on standing.

The product was refluxed for several hours with 10% alcoholic potassium hydroxide solution. The alcohol was evaporated and water added. The alkaline insoluble oil was taken up in ether (see below). The alkaline solution, which was made quite dilute, was added dropwise with stirring to a small excess of a 10% acetic acid solution. The precipitated brown colored acid was filtered off, washed with water and air dried to give a crude product (m. p. about 160° dec.; 29% yield), which was dissolved in a mixture of equal amounts of acetone and isopropyl ether. The solution was treated with Norite and chilled in a Dry Ice-alcohol-bath to give β-phenyl-γ-(2-quinolyl)-butyric acid as a brown powder, m. p. 190–191°, in 10% yield. White crystals, m. p. 192–193°, were obtained after several recrystallizations from a mixture of water and isopropyl alcohol and from benzene-Skellysolve **B**, treating once with Norite.

Anal.[9] Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.26; H, 5.74; N, 5.19.

The solvent was removed from the ether solution of the alkali insoluble material, obtained from the alkaline hydrolysis, and the residue, which was partially solid, was converted to a picrate (m. p. 230–240°), which after one recrystallization from a mixture of dioxane and methyl cellosolve melted at 237–240° and after several recrystallizations melted at 240.5–241.5°. This substance analyzed for the picrate of quinaldyl-(β-styryl)-ketone; the yield of the ketone (V), insolated as the picrate, (m. p. 230–240°) was 14% and (m. p. 237–240°) was 5%.

Anal.[9] Calcd. for $C_{25}H_{18}N_4O_8$: C, 59.76; H, 3.61. Found: C, 60.03; H, 3.62.

Summary

The Michael condensation of quinaldine, lepidine and α-picoline with benzalacetophenone and of quinaldine with ethyl cinnamate has been effected by sodium amide. In certain cases dimers or trimers have been obtained.

DURHAM, NORTH CAROLINA RECEIVED DECEMBER 6, 1948

---

[6] Levine and Hauser, THIS JOURNAL, **66**, 1768 (1944).

[7] Analysis by the University of Pittsburgh Microchemical Laboratory.

[8] The method of Breslow, Yost, Walker and Hauser (THIS JOURNAL, **66**, 1921 (1944)) was employed except that the heating period was extended to eight hours.

[9] Analysis by Clark Microanalytical Laboratory, Urbana, Illinois.