

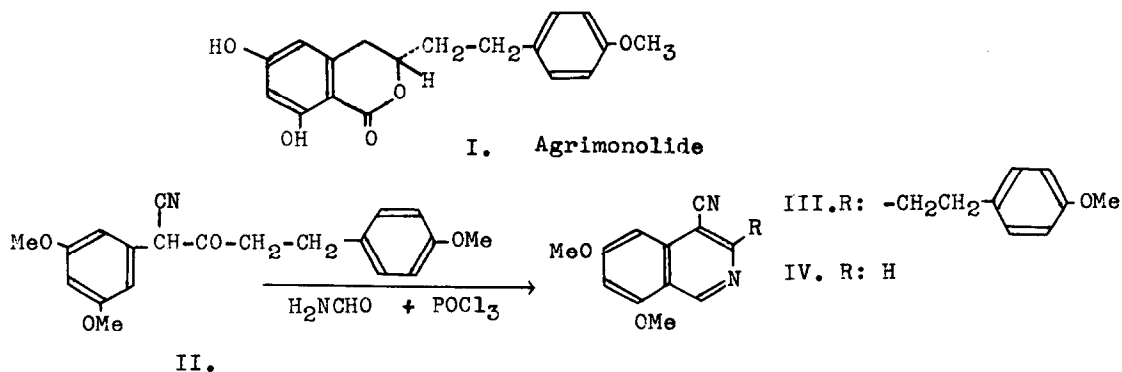
REACTIONS OF BENZYL CARBONYL COMPOUNDS WITH FORMAMIDE I.

A NOVEL SYNTHESIS OF ISOQUINOLINES.

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In an attempt to synthesize N-analogue of agrimonolide(1), isoquinolines, III** and IV, were obtained from II in the ratio of ca. 3:1 by treating II with hot H_2NCHO and $POCl_3$.



The structures of the isoquinolines (III and IV) have been supported by the following data.

4-Cyano-6,8-dimethoxy-3-p-methoxyphenethylisoquinoline (III).

$C_{21}H_{20}N_2O_3$, colorless needles (from MeOH), m.p.150-151.5°; ν_{\max} (KBr): 2243(C=N), 1625 cm^{-1} (C=N), λ_{\max} (in EtOH): 256,340m μ (log ϵ 4.63, 3.72); τ ($CDCl_3$): multiplet centered at 6.85 (4H, $-\text{CH}_2-\text{CH}_2-$), 6.35, 6.16, 6.14(each 3H, s., $3\text{CH}_3\text{O}-$), 3.70,

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** Satisfactory analytical data have been secured for all the compounds reported here.

3.37(each 1H, d., J: 2cps, aromatic proton), 3.43, 3.05(each 2H, d., J: 9cps, aromatic protons), 0.87(1H, s., C₁-H).

4-Cyano-6,8-dimethoxyisoquinoline (IV).

C₁₂H₁₀N₂O₂, colorless needles (from MeOH:H₂O=4:1), m.p.201-202.5^o, ν_{\max} (KBr): 2259(C=N), 1623cm⁻¹(C-N), λ_{\max} (in EtOH); 217,254m μ (log ϵ 4.63, 4.51), τ (CDCl₃): 5.96, 5.94(each 3H, s., 2CH₃O-), 3.34, 3.03(each 1H,d., J: 2cps, aromatic proton), 1.10(1H, br. s., C₃-H), 0.38 (1H, br. s., C₁-H).

A related observation was already reported by Peláez et al (2) describing the synthesis of 3,4-dihydroisoquinolines by treating O-methylisoeugenol or isosafrol with hot H₂NCHO and POCl₃, but their products must be dehydrogenated to obtain isoquinolines.

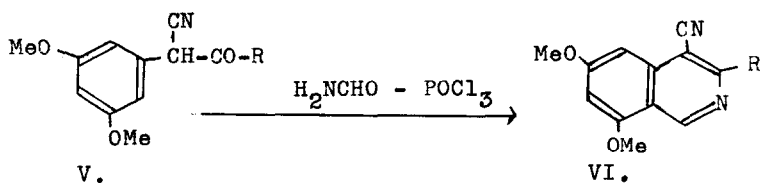
Concerning direct isoquinoline syntheses from benzyl ketones or benzyl cyanide, G.H. Birchall et al (3) obtained 3-alkyl-6,8-dihydroxyisoquinolines by the Gatterman reaction of 3,5-dihydroxybenzyl ketones, and J.D. White et al (4) yielded 3-halo-6,8-dimethoxyisoquinolines by the analogous reaction of 3,5-dimethoxyphenylacetonitrile.

Our starting material, II, is either a substituted benzyl ketone or a cyanide, but in our present study, not the cyano but the carbonyl function is involved in the reaction, therefore 4-cyanoisoquinolines are formed under the Vielsmeier reaction conditions only modified by using H₂NCHO for (CH₃)₂NCHO.

We are particularly interested in the formation of IV from II, but because we have not captured p-methoxyphenethyl moiety in the pure form, the reaction mechanism of this unusual cleavage will be reported after the elucidation of this part.

To generalize this new isoquinoline synthesis, we further treated V as described before, and obtained corresponding isoquinolines VI. These are summarized

in Table 1.



a, R: H

a, R: H (identified as IV)

b, R: CH₃b, R: CH₃c, R: CH₂CH₃c, R: CH₂CH₃d, R: C₆H₅d, R: C₆H₅

TABLE I.

Starting Material	Product No.	Mol. Formula	Crystalline Form (from Solvent)	m.p. °C	Yield, %
II	III	C ₂₁ H ₂₀ N ₂ O ₃	Colorless Needles (MeOH)	150-151.5	24
	IV	C ₁₂ H ₁₀ N ₂ O ₂	Colorless Needles (MeOH: H ₂ O 4:1)	201-202.5	8
Va	VIa or IV	"	"	"	28
Vb	VIb	C ₁₃ H ₁₂ N ₂ O ₂	Colorless Needles (MeOH)	216-217	35
Vc	VIc	C ₁₄ H ₁₄ N ₂ O ₂	Colorless Needles (MeOH)	177	30
Vd	VI d	C ₁₈ H ₁₄ N ₂ O ₂	Colorless Needles (MeOH)	193.5-194.5	26

The IR, UV, and NMR data of VI are as follows.

4-Cyano-6,8-dimethoxy-3-methylisoquinoline (VIb).

ν_{\max} (KBr): 2254 (C≡N), 1624 cm⁻¹ (C=N); λ_{\max} (EtOH): 216.255 μm, (log ε 4.45, 4.53);

τ (CDCl₃): 7.13 (3H, s., CH₃-), 6.01, 5.99 (each 3H, s., 2 CH₃O-), 3.49, 3.18 (each 1H, d., J: 2.5 cps) 0.57 (1H, s., C₁-H).

4-Cyano-3-ethyl-6,8-dimethoxyisoquinoline (VIc).

ν_{\max} (KBr): 2245 (C≡N), 1623 cm⁻¹ (C=N); λ_{\max} (EtOH): 218, 256 μm (log ε 4.43, 4.54);

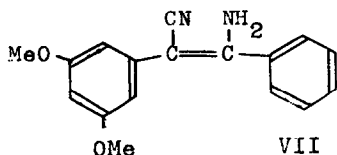
τ (HCOOH): 8.56 (3H, t., J: 7 cps, CH₃-CH₂-), 6.90 (2H, q., J: 7 cps, CH₃-CH₂-), 6.16, 6.06,

(each 3H, s., 2 CH_3O -), 2.93, 2.75 (each 1H, d., J: 2cps, aromatic proton), 0.54 ? (1H, s., $\text{C}_1\text{-H}$).

4-Cyano-6,8-dimethoxy-3-phenylisoquinoline (VIId).

ν_{max} (KBr): 2243 (C=N), 1630 cm^{-1} (C=N); λ_{max} (EtOH): 278, 326 m μ (log ϵ 4.67, 3.71); τ (CDCl_3): 6.05 (6H, s., 2 CH_3O -), 3.52, 3.09 (each 1H, d., J: 2.5cps, aromatic proton), multiplet centered at 2.55 (3H, phenyl protons), multiplet centered at 2.20 (2H, phenyl protons), 0.58 (1H, s., $\text{C}_1\text{-H}$).

In the reaction of Vd, light yellow needles (m.p. 124.5 $^\circ$, from benzene-cyclohexane) were obtained as a by-product (in ca. 2% yield). The structure of this compound is assigned as VII based on the IR, NMR data.



Further studies are in progress and more complete details will be reported later.

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