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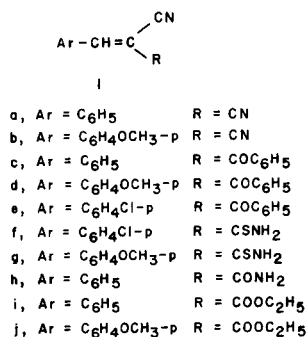
Whereas acetoacetanilide (II) reacted with α -cyano- and α -benzoylcinnamonitrile derivatives Ia-e to give hexa-substituted pyridines III and V, it reacted with α -carboxamido- and α -thiocarboxamidocinnamonitrile derivatives If-h to afford penta-substituted pyridines VI. One mole of acetonedicarboxylic acid dianilide (VII) reacted with two moles of each of α -cyano- and α -thiocarboxamidocinnamonitriles Ia,b,f,g to yield the dipyrindyl ketones VIII and IX, respectively. On the other hand, α -benzoyl- and α -ethoxycarbonylcinnamonitriles Ic,d,i,j reacted with VII in equimolecular ratio to give the pyran derivatives X and XI, respectively. Several schemes were proposed to illustrate reactions steps. The structures of the synthesized compounds were proved by chemical and spectral methods.

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The reaction of β -keto acid anilides with nitriles is one of the most efficient and useful methods for the synthesis of pyridine derivatives [1-3].

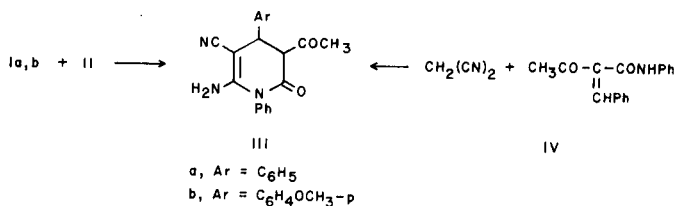
In continuation to our interest in the chemistry of α -substituted cinnamonitriles [4-6], we would like to report here a simple method for the synthesis of penta- and hexa-substituted pyridines by the reaction of α -substituted cinnamonitrile derivatives Ia-j with acetoacetanilide (II). The reaction of I with acetonedicarboxylic acid dianilide is also reported.

When each of the α -cyanocinnamonitrile derivatives Ia,b was refluxed in ethanol with II in presence of a catalytic amount of piperidine, there were obtained 3-acetyl-6-amino-4-aryl-5-cyano-1-phenyl-1,2,3,4-tetrahydropyridin-2-ones IIIa,b.

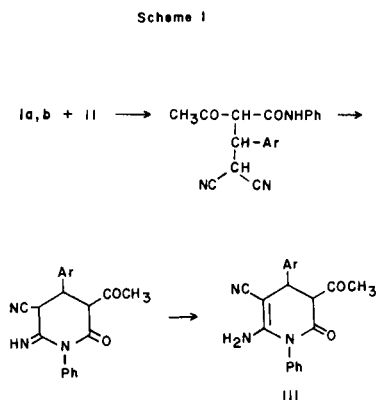


The assignment of structure III to the reaction products was based on the facts that, (a) the ir spectrum of IIIa showed bands at 1723 cm⁻¹ (CO), 2180 (C≡N) and 3350, 3480 (NH₂), (b) the pmr spectrum (DMSO-d₆) of IIIa showed signals at δ 2.3 ppm (s, 3H, CH₃), 4.3 (s, 1H, pyridine 4-H), 5.9 (broad s, 1H, pyridine 3-H), 7.55 (m, 12H, Ar-H and NH₂). Addition of deuterium oxide led to disappearance of the pyridine 3-H and decreasing of the signal at δ 7.55 ppm by two protons (NH₂), (c) compounds III give deep violet color with ferric chloride solution, and (d) com-

pound IIIa could also be synthesized by the reaction of benzalacetoacetanilide (IV) [7] with malononitrile.

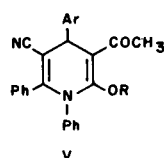


The formation of III may be proceeded as in Scheme I.



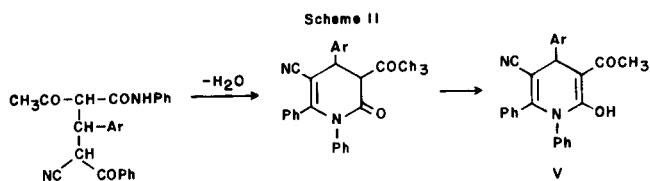
Compounds Ic-e reacted with II under the same experimental conditions to give the 3-acetyl-4-aryl-5-cyano-2-hydroxy-1,6-diphenyl-1,4-dihydropyridines Va-c whose structures were based on analytical and spectral data (cf. Tables I and II).

Acetylation of Vb,c with a mixture of acetic anhydride and acetic acid yielded the *O*-acetyl derivatives Vd,e, respectively. They gave no color with ferric chloride solution and their ir spectra showed no absorption at the OH region (cf. Table II).



- V
- a, Ar = C₆H₅ R = H
 b, Ar = C₆H₄OCH₃-p R = H
 c, Ar = C₆H₄Cl-p R = H
 d, Ar = C₆H₄OCH₃-p R = COCH₃
 e, Ar = C₆H₄Cl-p R = COCH₃

Compounds V seemed to be formed *via* cyclization of the adduct of Ic-e and II by loss of elements of water (Scheme II).



When If-h were reacted with II under the same experimental conditions, the 4-aryl-3-cyano-2-mercapto-6-methyl-4,5-dihydropyridine-5-carboxanilides VIa,b and the oxygen analogue 2-hydroxy derivative VIc were obtained. Formulation of structures was based on elemental and spectral data. Thus the pmr spectrum of VIa, as an example, showed a singlet at δ 10.7 ppm attributed to the presence of the anilide proton, while its ir spectrum displayed characteristic absorption bands (*cf.* Table II). Further confirmation of the structure of VIa was obtained from identity with an authentic sample prepared from thiocyanacetamide and IV.

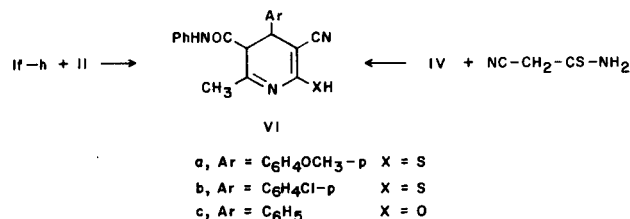


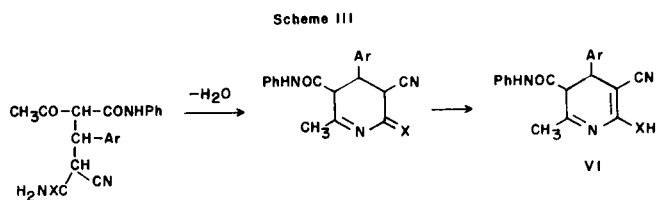
Table I

List of Products of Reaction of I with Acetoacetanilide and Acetonedicarboxylic acid Dianilide

Compound	Mp°C	Solvent of Crystallization	Yield %	Molecular Formula (Molecular Weight)	Analysis %		
					C	H	N
IIIa	215	Dioxan	62	C ₂₀ H ₁₁ N ₃ O ₂ (331.4)	72.48 72.6	5.17 5.0	12.69 12.5
IIIb	220	Dimethylformamide	65	C ₂₁ H ₁₉ N ₃ O ₃ (361.4)	69.79 70.0	5.29 5.4	11.64 11.5
Va	223	Dimethylformamide	57	C ₂₆ H ₂₀ N ₂ O ₂ (392.5)	79.57 79.7	5.14 5.3	7.14 7.0
Vb	232	Dioxan	52	C ₂₇ H ₂₂ N ₂ O ₃ (422.5)	76.76 76.5	5.25 5.3	6.63 6.5
Vc [a]	225	Dioxan	50	C ₂₆ H ₁₉ ClN ₂ O ₂ (426.9)	73.15 73.3	4.49 4.4	6.56 6.5
VIa [b]	270	Dimethylformamide	60	C ₂₇ H ₁₉ N ₃ O ₂ S (377.5)	66.82 66.6	5.07 4.9	11.14 11.0
VIb [c]	273	Dioxan	64	C ₂₆ H ₁₆ ClN ₃ OS (381.9)	62.90 63.1	4.22 4.3	11.00 11.1
VIc	189	Dioxan	63	C ₂₀ H ₁₉ N ₃ O ₃ (349.4)	68.75 68.6	5.48 5.6	12.03 12.1
VIIIa	> 300	Dimethylformamide	78	C ₃₇ H ₂₆ N ₄ O ₅ (606.7)	73.26 73.5	4.32 4.1	9.24 9.4
VIIIb	272	Dimethylformamide	77	C ₃₉ H ₃₀ N ₄ O ₇ (666.8)	70.26 70.0	4.54 4.5	8.40 8.3
IXa [d]	213	Aqueous dimethylformamide	75	C ₃₅ H ₂₆ N ₄ O ₅ S ₂ (732.9)	63.92 64.1	4.95 4.7	11.47 11.4
IXb [e]	240	Dioxan	75	C ₃₇ H ₃₀ Cl ₂ N ₆ O ₃ S ₂ (741.7)	59.92 60.2	4.08 4.0	11.33 11.2
Xa	283	Dioxan	69	C ₃₃ H ₂₅ N ₃ O ₃ (511.6)	77.48 77.3	4.93 4.8	8.21 8.4
Xb	295	Dioxan	73	C ₃₄ H ₂₇ N ₃ O ₄ (541.6)	75.40 75.6	5.03 4.9	7.72 7.9
XIa	256	Aqueous dimethylformamide	71	C ₂₉ H ₂₇ N ₃ O ₅ (497.6)	70.01 70.2	5.47 5.7	8.45 8.4
XIb	293	Aqueous dimethylformamide	72	C ₃₀ H ₂₉ N ₃ O ₆ (527.6)	68.30 68.5	5.54 5.7	7.96 8.1

[a] Calcd.: Cl, 8.30. Found: Cl, 8.2. [b] Calcd.: S, 8.49. Found: S, 8.3. [c] Calcd.: Cl, 9.28; S, 8.40. Found: Cl, 9.4; S, 8.3. [d] Calcd.: S, 8.75. Found: S, 8.6. [e] Calcd.: Cl, 9.55; S, 8.64. Found: Cl, 9.5; S, 8.8.

Compounds VI were probably formed by the loss of a water molecule from the adduct of If-h and II, as shown in Scheme III.

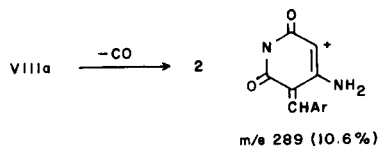


The reactions of I with acetonedicarboxylic acid dianilide (VII) were also investigated.

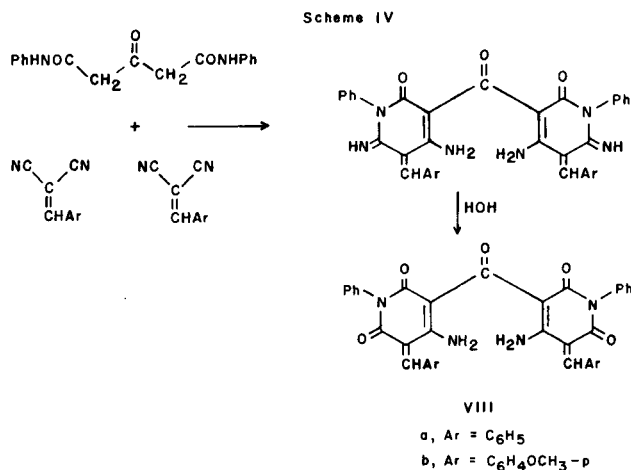
Whereas the reactions of VII with Ia,b,f,g proceeded by addition of two moles of I to one mole of VII to give di-pyridyl ketone derivatives, it occurred by the addition in equimolar ratio of Ic,d,i,j, and VII to yield pyran derivatives.

When Ia,b reacted with VII in refluxing ethanol in presence of piperidine bis(4-amino-5-arylmethylene-2,6-diketo-1-phenyl-1,2,5,6-tetrahydropyrid-3-yl) ketones VIIIa,b were obtained.

The assignment of structure VIII to the reaction products was based on the facts that, (a) the ir spectrum of VIIIa showed absorption bands at 1725 cm^{-1} (CO) and no absorption at the $\text{C}\equiv\text{N}$ region, (b) the mass spectrum of VIIIa was helpful: its fragmentation began with elimination of the acyclic carbonyl group and led to a peak at m/e



289 (10.6%), (c) the pmr of VIIIb (DMSO- d_6) displayed signals at δ 3.7 ppm (s, 6H, 2CH₃) and 7.35 (m, 24H, Ar-H + 2NH₂ + 2 vinyl protons). The latter signal was decreased by four protons (2 NH₂) on addition of deuterium oxide. The formation of VIII may be proceeded as in Scheme IV.



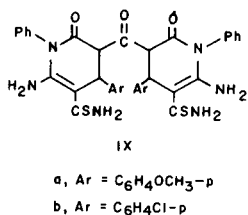
The reaction of VII with If,g proceeded in a similar manner under the same experimental conditions to yield

Table II

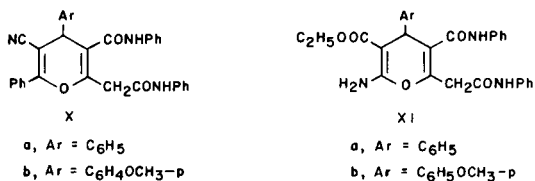
IR and PMR Data of Products in Table I

Compound	IR [cm ⁻¹]	PMR δ ppm
IIIa	3350, 3480 (NH ₂), 2180 (CN), 1723 (CO), 1682 (CO)	2.3 (s, 3H, CH ₃), 4.3 (s, 1H, pyridine 4-H), 5.9 (s, 1H, pyridine 3-H), 7.55 (m, 12H, Ar-H + NH ₂)
IIIb	3350, 3485 (NH ₂), 2220 (CN), 1720 (CO), 1680 (CO)	
Va	3330 (OH), 3040, 2920 (CH), 2220 (CN), 1720 (CO)	2.3 (s, 3H, CH ₃), 4.2 (s, 1H, pyridine 4-H), 7.45 (m, 16H, Ar-H + OH)
Vb	3270 (OH), 2940 (CH), 2220 (CN), 1695 (CO)	
Vc	3300 (OH), 3000 (CH), 2220 (CN), 1700 (CO)	
VIa	3280 (NH), 2600 (SH), 2220 (CN), 1650 (CO)	2.05 (s, 1H, SH), 2.7 (s, 3H, CH ₃), 3.45 (d, 1H, pyridine 4-H), 3.75 (s, 3H, OCH ₃), 4.2 (d, 1H, pyridine 5-H), 7.25 (m, 7H, Ar-H), 8.0 (s, 2H, Ar-H), 10.7 (s, 1H, NH)
VIb	3380, 3200 (NH ₂), 2985 (CH), 2600 (SH), 2220 (CN), 1650 (CO)	
VIc	3460-3150 (OH and NH), 2220 (CN), 1680 (CO)	
VIIIa	3270 (NH), 3080 (CH), 1725 (CO), 1660, 1650 (CO)	3.7 (s, 6H, 2CH ₃), 7.35 (m, 24H, Ar-H + 2NH ₂ + 2 vinyl H)
VIIIb	3250 (NH), 3080 (CH), 1720 (CO), 1670, 1665 (CO)	2.7 (d, 2H, 2 pyridine 5-H), 3.6 (s, 6H 2CH ₃), 4.0 (m, 2H, 2 pyridine 4-H), 5.2 (d, 2H, 2pyridine 3-H), 6.7-7.7 (m, 18H, Ar-H), 7.83 (s, 2H, 2NH), 10.35 (bd. s, 4H, 2NH ₂)
IXa	3380-3140 (NH), 1690 (CO), 1660 (CO)	2.7 (d, 2H, 2 pyridine 5-H), 4.0 (m, 2H, 2 pyridine 4-H), 5.15 (d, 2H, 2 pyridine 3-H), 6.7-7.6 (m, 18H, Ar-H), 7.9 (s, 2H, 2NH), 10.3 (bd. s, 4H, 2NH ₂)
IXb	3400-3150 (NH), 1695 (CO), 1670 (CO)	
Xa	3390 (NH), 2220 (CN), 1655, 1640 (CO)	
Xb	3390 (NH), 2220 (CN), 1655, 1645 (CO)	3.45 (s, 3H, CH ₃), 3.83 (s, 3H, CH ₂ + pyran 4-H), 7.33 (m, 19H, Ar-H), 10.5 (s, 2H, 2NH)
XIa	3330 (NH), 2875 (CH), 1735 (CO), 1660 (CO)	
XIb	3270 (NH), 2900 (CH), 1725 (CO), 1650 (CO)	1.0 (t, 3H, CH ₃), 3.7 (s, 3H, OCH ₃), 3.9 (s, 2H, CH ₂), 4.0 (s, 1H, pyran 4-H), 4.45 (q, 2H, CH ₂), 7.3 (m, 16H, Ar-H + NH ₂), 10.35 (s, 2H, 2NH)

bis(6-amino-4-aryl-5-thiocarboxamido-2-keto-1-phenyl-1,2,3,4-tetrahydropyridin-3-yl) ketones IXa,b. The addition of VII, in this reaction, occurred at the cyano and the ethylene linkage of I. The structure of IX was based on analytical and spectral data (cf. Tables I and II).



In contrast to the behaviour of Ia,b,f,g compounds Ic,d reacted with VII in equimolecular ratio under the same experimental conditions to give 4-aryl-3-carboxanilido-5-cyano-6-phenyl-4H-pyran-2-acetic acid anilides (Xa,b). These structures were based on: (a) analytical and spectral data. Thus the ir spectrum of Xb displayed an absorption band at 2220 cm⁻¹ (C≡N) and its pmr spectrum (DMSO-d₆) showed a singlet at δ 10.5 ppm (s, 2H, 2NH) attributed to the presence of anilide protons, and (b) active methylene compounds are known to react with α-substituted cinnamionitriles to give pyran derivatives [8,9]



The reaction of VII and Ii,j almost proceeded in a way similar to the above reaction. Thus when equimolecular amounts of VII and each of Ii,j were reacted under the same experimental conditions, the 6-amino-4-aryl-5-carboxy-3-carboxanilido-4H-pyran-2-acetic acid anilides XIa,b were obtained. The structure of XI was supported by analytical and spectral data (cf. Tables I and II).

EXPERIMENTAL

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. The ir spectra were recorded (potassium bromide) with a Pye-Unicam SP 1000 spectrophotometer. The pmr spectra were taken with a Varian 90 MHz EM 390 nmr spectrometer using TMS as internal standard.

Reaction of α-Substituted Cinnamionitriles Ia-h with II. Preparation of III, V and VI. General Procedure.

A mixture of 1.77 g (0.01 mole) of II and 0.01 mole of each of Ia-h was refluxed in 50 ml of ethanol containing few drops of piperidine for 5 hours. The mixture was concentrated and left to cool. The solid that separated was filtered off, dried and recrystallized from the proper solvent (cf. Table I).

2-Acetoxy-3-acetyl-4-aryl-5-cyano-1,6-diphenyl-1,4-dihydropyridines Vd,e.

A mixture of 2 g of Vb or Vc, 15 ml of acetic acid and 10 ml of acetic anhydride was refluxed for 3 hours, left to cool and poured into cold water. The solid that separated was collected and dried.

Compound Vd was recrystallized from ethanol, mp 114°, yield 70%; ir: 2900 cm⁻¹ (CH), 2200 (C≡N), 1730 (C=O), 1650 (C=O).

Anal. Calcd. for C₂₅H₂₄N₂O₄: C, 74.98; H, 5.21; N, 6.03. Found: C, 74.8; H, 5.3; N, 5.9.

Compound Ve was recrystallized from dioxan, mp 201°, yield 76%; ir: 2950 (CH), 2220 (C≡N), 1700 (C=O), 1670 (C=O).

Anal. Calcd. for C₂₈H₂₁ClN₂O₃: C, 71.72; H, 4.51; Cl, 7.56; N, 5.97. Found: C, 72.0; H, 4.7; Cl, 7.5; N, 6.0.

Reaction of Acetonedicarboxylic Acid Dianilide (VII) with Ia,b and If,g. Preparation of VIII and IX. General Procedure.

A mixture of 2.96 g (0.01 mole) of VII, 0.02 mole of each of Ia,b,f,g, 70 ml of ethanol and few drops of piperidine was refluxed for 5 hours. The reaction mixture was concentrated and left to cool. The solid that separated was collected, dried and recrystallized from the proper solvent (cf. Table I).

Reaction of VII with Ic,d and Ii,j. Preparation of X and XI. General Procedure.

A mixture of 2.96 g (0.01 mole) of VII, 0.01 mole of each of Ic,d,i,j, 50 ml of ethanol and few drops of piperidine was refluxed for 5 hours, concentrated and left to cool. The solid that separated was filtered off, dried and recrystallized from the proper solvent (cf. Table I).

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