3-Arylcarbamyl-2,6-dimethyl-4-pyrones Formed by the Action of Polyphosphoric Acid on o-Haloacetoacetanilides

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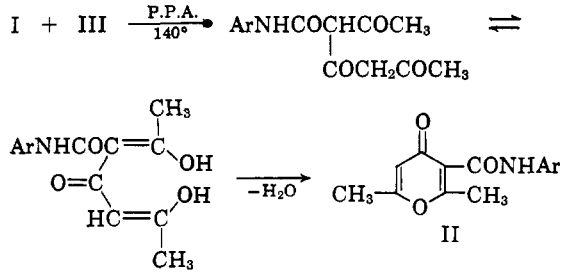
The treatment of *o*-haloacetoacetanilides with polyphosphoric acid gave a new series of substituted pyrones (3-arylcarbamyl-2,6-dimethyl-4-pyrones). The structures of these compounds were established by degradation studies and their characteristic infrared absorptions. Acid hydrolysis using 70% sulfuric acid caused the 4-pyrone ring to rupture at the ether bond.

On heating the *o*-haloacetoacetanilides I with polyphosphoric acid at 140° the corresponding 4-hydroxyquinaldines and 3-arylcarbamyl-2,6-dimethyl-4-pyrones II were formed.[2] The formation of 4-hydroxyquinaldines from acetoacetanilides in the presence of polyphosphoric acid has been shown to occur through anil–anilide intermediates, the formation of which depends upon heterolytic fission of the anilides at the amide group to give the arylamines.[2,3] The formation of 3-arylcarbamyl-2,6-dimethyl-4-pyrones II is also dependent upon heterolytic fission of the anilides. Thus while acetoacet-2-toluidide, which undergoes negligible fission to the arylamine in polyphosphoric acid,[2] did not form a pyrone of the type II, the anilides I, which undergo heterolytic fission in polyphosphoric acid, gave rise to the pyrones II. The initial formation of a carbonium ion III from the anilides I in polyphosphoric acid is consistent with the proposal of Duffy and Leisten.[4]

$$\underset{\text{I}}{\text{ArNHCOCH}_2\text{COCH}_3} \xrightarrow[140°]{\text{P.P.A.}} \text{ArNH}_2 + \underset{\text{III}}{\text{CH}_3\text{COCH}_2\text{CO}^+}$$

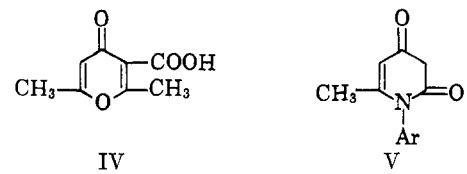
Ar = 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,5-$Cl_2C_6H_3$, and 2-BrC_6H_4

The carbonium ion III can react with the acetoacetanilides I to give the 3-arylcarbamyl-2,6-dimethyl-4-pyrones II. The intermediates were not isolated.

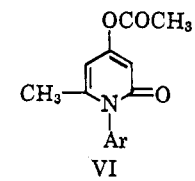


Acid hydrolysis of the 3-arylcarbamyl-2,6-dimethyl-4-pyrones II using 70% sulfuric acid gave the previously known[5] 2,6-dimethyl-4-pyrone-3-carboxylic acid (IV), the corresponding arylamine ($ArNH_2$ where Ar = 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,5-$Cl_2C_6H_3$, and 2-BrC_6H_4), and in addition the corresponding 1-aryl-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridines Va.

The pyridones Va were very soluble in cold dilute alkali, cold concentrated acids, and hot dilute acids, and, as no effervescence occurred with hot aqueous sodium carbonate, the acidic character was attributed to an enolic group. This was substantiated on treatment with an aqueous–alcoholic ferric chloride solution, when an orange color developed on standing for about 1 hr.[6] The basic properties of these compounds were attributed to a tertiary nitrogen atom as no primary amino group was present as shown by the failure of these compounds to diazotize and no NH-stretching bands were visible in the infrared spectra. On warming with acetic anhydride O-acylation occurred to give the 4-acetoxy-1-aryl-2-keto-6-methyl-1,2-dihydropyridines VI.

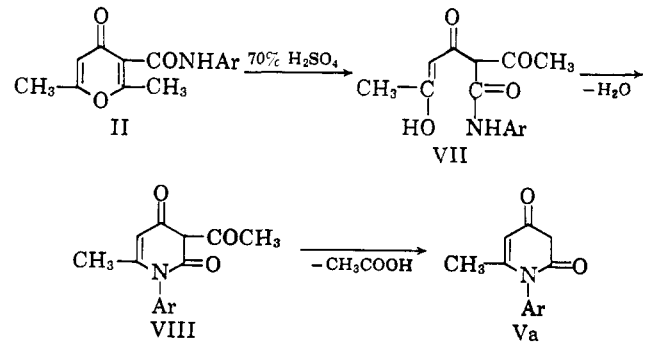


a, Ar = 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,5-$Cl_2C_6H_3$, and 2-BrC_6H_4
b, Ar = C_6H_5



Ar = 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,5-$Cl_2C_6H_3$, and 2-BrC_6H_4

The structures of the pyridones Va were established by a known synthesis.[7] The formation of the pyridones Va during the acid hydrolysis of the 3-arylcarbamyl-2,6-dimethyl-4-pyrones II must involve a rupture of the 4-pyrone ring at the ether bond with subsequent cyclization of the intermediates VII to give the 3-acetylpyridones VIII. The latter, in the presence of 70% sulfuric acid, were hydrolyzed to the corresponding pyridones Va. The intermediates VII and VIII were not isolated.



(1) Department of Chemistry, Queen Mary College, University of London.

(2) A. K. Mallams and S. S. Israelstam, *J. Org. Chem.*, **29**, 3548 (1964).

(3) B. Staskun, *ibid.*, **29**, 1153 (1964).

(4) J. A. Duffy and J. A. Leisten, *Nature*, **178**, 1242 (1956).

(5) J. N. Collie and T. P. Hilditch, *J. Chem. Soc.*, 787 (1907).

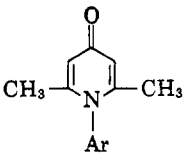
(6) N. Zonew and P. Petrenko-Kritschenko, *J. Russ. Phys. Chem. Soc.*, **45**, 173.

(7) F. Arndt, B. Eistert, H. Scholz, and E. Aron, *Ber.*, **69B**, 2373 (1936).

Rupture of the 4-pyrone ring does not occur in polyphosphoric acid since the pyrones II were recovered unchanged after heating with polyphosphoric acid for 1 hr. at 140°.

The effect of 70% sulfuric acid on the acetylpyridones VIII has not been reported in the literature.[8] 3-Acetyl-2,4-diketo-6-methyl-1-phenyl-1,2,3,4-tetrahydropyridine (VIII, Ar = C_6H_5), prepared by the method of von Pechmann and Neger,[9,10] on refluxing with 70% sulfuric acid gave 1-phenyl-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine (Vb) in quantitative yield. This lends support to the proposed mechanism for the formation of the pyridones Va during the acid hydrolysis of the 3-arylcarbamyl-2,6-dimethyl-4-pyrones II.

The attempted synthesis of the acid chloride of 2,6-dimethyl-4-pyrone-3-carboxylic acid (IV) resulted in extensive decomposition,[11] even in an inert solvent such as benzene. The thermal condensation of the acid IV with the haloarylamines gave the corresponding 1-aryl-2,6-dimethyl-4(1H)-pyridones IX, which have previously been prepared from the arylamine and 2,5-heptadiyne-4-one.[12]



IX

Ar = 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,5-$Cl_2C_6H_3$, and 2-BrC_6H_4

The direct condensation of the acid IV with the haloarylamines using dicyclohexylcarbodiimide,[13] or polyphosphoric acid,[14] failed to give the desired amides II. Alternative methods for the preparation of the amides II are being investigated.

Experimental[15]

3-Arylcarbamyl-2,6-dimethyl-4-pyrones II (Table I).—*o*-Haloacetoacetanilides I on heating with polyphosphoric acid at 140° for 1 hr. gave mixtures of the corresponding 4-hydroxyquinaldines and 3-arylcarbamyl-2,6-dimethyl-4-pyrones II.[2] In general the pyrones II were insoluble in water, mineral acids, alkalis, ether, and benzene, but soluble in hot glacial acetic acid and hot methanol.

Acid Hydrolysis of 3-Arylcarbamyl-2,6-dimethyl-4-pyrones (Table II).—The 3-arylcarbamyl-2,6-dimethyl-4-pyrone and 70% sulfuric acid were refluxed for 1 hr. and diluted; the 2,6-dimethyl-4-pyrone-3-carboxylic acid was extracted with ether. Dilute sodium hydroxide was added to the acid solution until the 1-aryl-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine was precipitated (the solution was still strongly acidic, pH *ca.* 1). The mixture was cooled and filtered. The partially neutralized acid filtrate on being made alkaline gave the arylamine which was ether extracted and acetylated.

(8) Zonew and Petrenko-Kritschenko[6] have converted 3-acetyl-2,4-diketo-6-methyl-1-phenyl-1,2,3,4-tetrahydropyridine (VIII, Ar = C_6H_5) to 1-phenyl-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine (Vb) by heating with concentrated hydrochloric acid in a sealed tube.

(9) H. von Pechmann and F. Neger, *Ann.*, **273**, 183 (1893).

(10) Attempted preparation of the acetylpyridones VIII (Ar = 2-ClC_6H_4, 2,4-$Cl_2C_6H_3$, 2,5-$Cl_2C_6H_3$, and 2-BrC_6H_4) by this method gave only the unreacted starting materials.

(11) The instability of 4-pyronecarboxylic acids to chlorinating agents is well known [L. F. Cavalieri, *Chem. Rev.*, **41**, 525 (1947)].

(12) J. Chauvelier, *Bull. soc. chim. France*, 734 (1954).

(13) A. Buzas, C. Egnell, and P. Fréon, *Compt. rend.*, **252**, 896 (1961).

(14) H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **76**, 3039 (1954).

(15) All melting points were determined on a Kofler block and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137 spectrophotometer in the solid state using a potassium bromide disk.

TABLE I

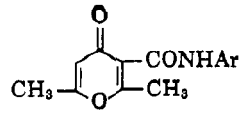
3-ARYLCARBAMYL-2,6-DIMETHYL-4-PYRONES

Ar	Formula	M.p., °C.	Mol. wt. Calcd.	Mol. wt. Found	Calcd., % C	Calcd., % H	Calcd., % N	Calcd., % X[c]	Found, % C	Found, % H	Found, % N	Found, % X[c]	Infrared absorption bands, cm.$^{-1}$[a,b] Amide I C=O	Amide II	Amide III	4-Pyrone C=O	Aromatic substitution
2-ClC_6H_4	$C_{14}H_{12}O_3NCl$	201–204	277.5	286	60.53	4.32	5.04	12.79	60.59	4.27	5.07	12.97	1700 (s)	1580 (s)	1290 (m)	1650 (s)	1520 (s), 758 (s)
2,4-$Cl_2C_6H_3$	$C_{14}H_{11}O_3NCl_2$	232–235	312	308	53.84	3.53	4.49	22.76	54.12	3.70	4.52	22.51	1690 (s)	1560 (s)	1280 (m)	1650 (s)	1520 (s), 848 (s)
2,5-$Cl_2C_6H_3$	$C_{14}H_{11}O_3NCl_2$	179–181	312	320	53.84	3.53	4.49	22.76	54.08	3.74	4.51	22.91	1690 (s)	1560 (s)	1270 (m)	1650 (s)	1520 (s)
2-BrC_6H_4	$C_{14}H_{12}O_3NBr$	195–196.5	321.9	330	52.19	3.73	4.35	24.82	52.40	3.85	4.32	25.00	1690 (s)	1560 (s)	1280 (m)	1650 (s)	1520 (s), 755 (s)

[a] L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., Methuen and Co., Ltd., London, 1958. [b] s = strong; m = medium. [c] X = Cl, or Br, respectively.

TABLE II

ACID HYDROLYSIS OF THE 3-ARYLCARBAMYL-2,6-DIMETHYL-4-PYRONES



	Hydrolysis products										
	2,6-Dimethyl-4-pyrone-3-carboxylic acid,[a]	1-Aryl-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine							Arylamine (acetyl derivative)		
					Calcd., %		Found, %				
Ar	yield, %	Yield, %	M.p., °C.[b]	Formula	N	X[c]	N	X[c]	Yield, %	M.p., °C.[d]	Lit.[e] m.p. °C.
2-ClC_6H_4	30	21	263–5	$C_{12}H_{10}O_2NCl$	5.94	15.08	5.92	15.19	41	89–91	88
2,4-$Cl_2C_6H_3$	31	17	280–3	$C_{12}H_9O_2NCl_2$	5.18	26.29	5.29	26.00	38	145–146	146
2,5-$Cl_2C_6H_3$	29	19	237–9	$C_{12}H_9O_2NCl_2$	5.18	26.29	5.27	26.45	33	131–132	132
2-BrC_6H_4	33	20	278–80.5	$C_{12}H_{10}O_2NBr$	5.00	28.54	5.07	28.78	39	98–99	99

[a] Crystallized from water, m.p. 98–100°. *Anal.* Calcd. for $C_8H_8O_4$: C, 57.15; H, 4.76; equiv. wt., 168. Found: C, 57.43; H, 4.90; equiv. wt., 168.7. A mixture melting point with 2,6-dimethyl-4-pyrone-3-carboxylic acid (m.p. 99°) prepared by the method of Collie and Hilditch[5] showed no depression. The infrared spectra were also identical. [b] Crystallized from dilute acetic acid. [c] X = Cl or Br. [d] Crystallized from dilute ethanol. A mixture melting point with an authentic sample showed no depression. [e] A. I. Vogel, "Practical Organic Chemistry," 3rd Ed., Longmans, Green and Co., Ltd., London, 1957, p. 656.

4-Acetoxy-1-aryl-2-keto-6-methyl-1,2-dihydropyridines VI.—1-(2-chlorophenyl)-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine was acetylated using the method of Zonew and co-author[6] to give 4-acetoxy-1-(2-chlorophenyl)-2-keto-6-methyl-1,2-dihydropyridine in 85% yield. The product was crystallized from dilute acetic acid, m.p. 140–141°.

Anal. Calcd. for $C_{14}H_{12}ClNO_3$: N, 5.04. Found: N, 5.12.

The following compounds were prepared in a similar manner.

4-Acetoxy-1-(2,4-dichlorophenyl)-2-keto-6-methyl-1,2-dihydropyridine (88%) had m.p. 143–144°.

Anal. Calcd. for $C_{14}H_{11}Cl_2NO_3$: N, 4.49. Found: N, 4.57.

4-Acetoxy-1-(2,5-dichlorophenyl)-2-keto-6-methyl-1,2-dihydropyridine (83%) had m.p. 135–137°.

Anal. Calcd. for $C_{14}H_{11}Cl_2NO_3$: N, 4.49. Found: N, 4.60.

4-Acetoxy-1-(2-bromophenyl)-2-keto-6-methyl-1,2-dihydropyridine (81%) had m.p. 133–134°.

Anal. Calcd. for $C_{14}H_{12}BrNO_3$: N, 4.35. Found: N, 4.41.

1-Aryl-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridines.—The following pyridines were prepared from triacetic lactone by the method of Arndt, *et. al.*[7]

1-(2-Chlorophenyl)-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine (3%) had m.p. 263–265°.

1-(2,4-Dichlorophenyl)-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine (1%) had m.p. 280–283°.

1-(2,5-Dichlorophenyl)-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine (2%) had m.p. 237–239°.

1-(2-Bromophenyl)-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine (2%) had m.p. 278–280.5°.

In all cases a mixture melting point with the corresponding 1-aryl-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine, obtained from the acid hydrolysis of the 3-arylcarbamyl-2,6-dimethyl-4-pyrone, showed no depression.

5-Arylcarbamyldehydroacetic Acid.—The following 5-arylcarbamyldehydroacetic acids were prepared using the method described by Wiley, *et al.*[16]

5-Phenylcarbamyldehydroacetic acid (96%) had m.p. 187–189°.

5-(2-Chlorophenylcarbamyl)dehydroacetic acid (83%) had m.p. 147–149°.

Anal. Calcd. for $C_{15}H_{12}ClNO_5$: N, 4.35. Found: N, 4.43.

5-(2,4-Dichlorophenylcarbamyl)dehydroacetic acid (92%) had m.p. 202–204°.

Anal. Calcd. for $C_{15}H_{11}Cl_2NO_5$: N, 3.93. Found: N, 4.05.

5-(2,5-Dichlorophenylcarbamyl)dehydroacetic acid (90%) had m.p. 183–184°.

Anal. Calcd. for $C_{15}H_{11}Cl_2NO_5$: N, 3.93. Found: N, 4.13.

5-(2-Bromophenylcarbamyl)dehydroacetic acid (84%) had m.p. 158–160°.

Anal. Calcd. for $C_{15}H_{12}BrNO_5$: N, 3.83. Found: N, 3.90.

Only 5-phenylcarbamyldehydroacetic acid reacted on vacuum distillation according to the method of von Pechmann, and Neger[8] to give 3-acetyl-2,4-diketo-6-methyl-1-phenyl-1,2,3,4-tetrahydropyridine (17%), m.p. 220–222°, lit.[9] m.p. 217–218°.

2,4-Diketo-6-methyl-1-phenyl-1,2,3,4-tetrahydropyridine.—3-Acetyl-2,4-diketo-6-methyl-1-phenyl-1,2,3,4-tetrahydropyridine (125 mg.) was refluxed with 5 ml. of 70% sulfuric acid for 1 hr. and the reaction mixture was neutralized to give 2,4-diketo-6-methyl-1-phenyl-1,2,3,4-tetrhydropyridine, 100 mg. (97%); crystallized from dilute ethanol, m.p. 270–271°. A mixture melting point with the corresponding compound prepared by the method of Zonew and co-author[6] showed no depression. It gave an orange coloration with aqueous–alcoholic ferric chloride on standing for 1 hr.[17]

1-Aryl-2,6-dimethyl-4(1H)-pyridones.—2,6-Dimethyl-4-pyrone-3-carboxylic acid[5] (0.5 g.) and 0.38 g. of 2-chloroaniline were heated in a sealed tube at 140–160° for 8 hr. and the reaction mixture was triturated with ether to give 1-(2-chlorophenyl)-2,6-dimethyl-4(1H)-pyridone 0.35 g. (53%), which was crystallized from dilute ethanol, m.p. 144–146°, lit.[12] m.p. 147°.

The following pyridones were prepared in a similar manner.

1-(2,4-Dichlorophenyl)-2,6-dimethyl-4(1H)-pyridone (48%) had m.p. 206–208°, lit.[12] m.p. 209°.

1-(2,5-Dichlorophenyl)-2,6-dimethyl-4(1H)-pyridone (50%) had m.p. 201–203°, lit.[12] m.p. 203°.

1-(2-Bromophenyl)-2,6-dimethyl-4(1H)-pyridone (50%) had m.p. 194–196°, lit.[12] m.p. 196°.

Lower yields of the pyridones were obtained when the reactants were heated at 140° for 6 hr. at atmospheric pressure.

Acknowledgment.—The author wishes to express his gratitude to the Sir Ernest Oppenheimer Memorial Trust for the award of a fellowship and also to Professor S. S. Israelstam for his sustained interest in the investigation.

(16) R. H. Wiley, C. H. Jarboe, H. G. Ellert, H. Kraus, E. J. Hittinger, C. L. de Silva, and S. C. Slaymaker, *J. Org. Chem.*, **21**, 686 (1956).

(17) Zonew and co-author[6] reported that 1-phenyl-2,4-diketo-6-methyl-1,2,3,4-tetrahydropyridine (Vb) gave a weak alcoholic ferric chloride test on warming.