

Action of Amines and Carbonyl Reagents on 3,5-Diphenyl-4-pyrone and Its Thio Analogue

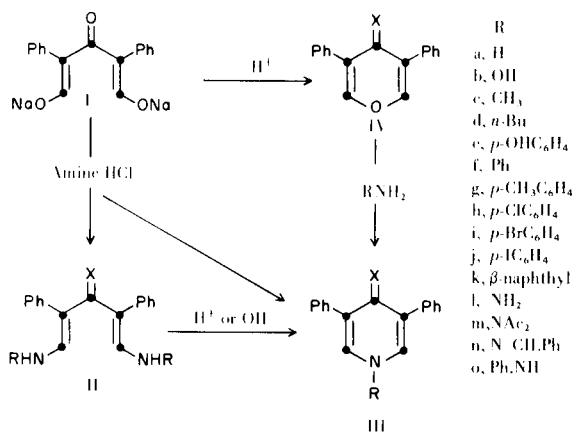
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Several *N*-substituted 3,5-diphenyl-4-pyridones and 4-thiopyridones were obtained by the action of amines on 3,5-diphenyl-4-pyrone and its thio analogue. With hydrazine hydrate, the products were 1-amino-3,5-diphenyl-4-pyridone and the corresponding thione. The spectral characteristics of these pyridones were studied.

In a recent publication (1), we showed that treatment of the sodium salt I with several amine hydrochlorides led to the formation of either pyridones (IIIa-c; X = O) or 1,5-diarylamino-2,4-diphenylpenta-1,4-dien-3-ones (IIb-k; X = S) which could be cyclized to the pyridones (IIIb-k; X = O). Here we wish to report that the pyridones (IIIb-k; X = O) could also be obtained by the action of the respective amines on 3,5-diphenyl-4-pyrone (IV; X = O) (2,3). The ir spectra of these pyridones are characterized by the presence of a strong carbonyl absorption at 1620-1640 cm^{-1} (*cf.* Table II).



A comparison of the reactions of 3,5-diphenyl-4-pyrone (IV; X = O) with 2,6-diphenyl-4-pyrone shows that the attack on the carbonyl group of the former is sterically hindered by the presence of the two bulky phenyl groups around it. Thus, the reaction of 2,6-diphenyl-4-pyrone with hydroxylamine was previously shown (4) to give a mixture of 1-hydroxy-2,6-diphenyl-4-pyridone, 4-hydroxylamino-2,6-diphenylpyridine *N*-oxide, and 2,6-diphenyl-4-pyrone oxime. However, 3,5-diphenyl-4-pyrone gave only

1-hydroxy-3,5-diphenyl-4-pyridone (IIIb; X = O) on similar treatment.

Unlike 2,6-diphenyl-4-pyrone which afforded with hydrazine hydrate, 5-phenacyl-3-phenylpyrazole hydrazone (4,5), 3,5-diphenyl-4-pyrone (IV; X = O) gave 1-amino-3,5-diphenyl-4-pyridone (III; X = O), together with 3,5-diphenyl-4-pyridone (IIIa; X = O). The ir spectrum of (III; X = O) showed two absorption bands at 3300 and 3160 cm^{-1} (NH₂) (6) and a strong carbonyl absorption at 1642 cm^{-1} (4-pyridone) (1). Its nmr spectrum exhibited a singlet of two proton intensity at τ 6.6 (NNH₂; exchangeable) and a multiplet at τ 2.7-2.5 (2 CH and 2 Ph).

The 1-amino-4-pyridone (III; X = O) underwent deamination by nitrous acid to the 4-pyridone (IIIa; X = O). It gave on acetylation the diacetate (IIIm; X = O) which, while it resisted the action of alkalis, readily underwent acid hydrolysis to the parent aminopyridone. Moreover, 1-benzylideneamino-3,5-diphenyl-4-pyridone (IIIn; X = O) was obtained by condensation of the aminopyridone (III; X = O) with benzaldehyde. The ir spectrum of (IIIn; X = O) is devoid of the NH stretching in the 3 μ region and is characterized by a strong absorption at 1638 cm^{-1} (4-pyridone carbonyl) (1) and 1600 cm^{-1} (C = N). This benzylidene while it gave the free amine (III; X = O) on alkaline hydrolysis, resisted acid hydrolysis except in presence of 2,4-dinitrophenylhydrazine.

The pyrone (IV; X = O) was converted by the action of phosphorus pentasulphide into 3,5-diphenyl-4-thiopyrone (IV; X = S); characterized by a band of medium intensity at 1100 cm^{-1} (C = S) (4). This thione was converted into the corresponding oxygen analogue by means of hydrogen peroxide, but failed to give a dipyrrole derivative (7) probably due to steric factors.

TABLE I
Electronic Spectra of Pyridones and Thiopyridones (III)

	Solvent		λ max/nm (ϵ)	
a, X = O	Ethanol (a)	237	285	305
	0.1N HCl	220 (13190)	245 (18750)	
c, X = O	Ethanol	237 (26130)	290 (12690)	308 (12690)
	0.1N HCl	225 (17180)	247 (24620)	
	Cyclohexane (a)	230, 248 sh	290	323
l, X = O	Ethanol	238 (23040)	290 (11240)	311 (11240)
	Cyclohexane (a)	225	315	335
a, X = S	Ethanol	234 (22040)	254 sh (15460) 315 (7443)	350 sh (4868)
	0.1N HCl	229 (18880)	266 (13170)	325 (5707)
c, X = S	Ethanol	237 (24770)	266 (12120)	367 (25330)
	0.1N HCl	232 (21150)	270 (15660)	330 (16705)
	Cyclohexane (a)	235	305	396
f, X = S	Ethanol	240 (26810)	266 (11210)	382 (31360)
	Cyclohexane (a)	238	277	394
o, X = S	Ethanol	233 (37940)	275 sh (13290)	372 (24820)
	Cyclohexane (a)	230	275 sh	325 sh
l, X = S	Ethanol	234 (31550)	265 (11420)	366 (27040)

(a) For saturated solutions.

The thiopyrone (IV; X = S) reacted with hydrazine hydrate giving 1-amino-3,5-diphenyl-4-thiopyridone (IIIi; X = S) and not the alternative pyrazole derivative (4). The aminothiopyridone was characterized by absorption bands at $3260\text{-}3160\text{ cm}^{-1}$ (NH_2) and 1120 cm^{-1} ($\text{C}=\text{S}$). It gave a benzylidene derivative (IIIj; X = S) which was readily hydrolyzed to the parent amino compound (IIIi; X = S) by acid or alkali.

Moreover, 3,5-diphenyl-4-thiopyrone gave the 4-thiopyridone (IIIa; X = S), the 1-methyl-4-thiopyridone (IIIc; X = S) and the 1-phenylamino-4-thiopyridone (IIIo; X = S) when treated with ammonium acetate, methylamine and phenylhydrazine, respectively. 1,3,5-Triphenyl-4-thiopyridone (III f; X = S) was obtained by the action of phosphorus pentasulphide on the respective pyridone (III f; X = O). It could also be obtained, besides, 1,5-dianilino-2,4-diphenylpenta-1,4-diene-3-thione (III f; X = S) by the action of aniline on 3,5-diphenyl-4-thiopyrone (IV; X = S). The thione (III f; X = S) was characterized by a weak broad NH absorption at $3500\text{-}3400\text{ cm}^{-1}$ and a medium thiocarbonyl band at 1077 cm^{-1} .

The electronic spectra of the pyridones and thiopyridones are recorded in Table I. The band of longer wavelength suffers a red shift in non-polar solvents and disappears or its intensity decreases appreciably in presence of 0.1N hydrochloric acid. Thus, this band is most probably attributed to $n \rightarrow \pi^*$ transition of the carbonyl or the thiocarbonyl groups inspite of its relatively high

intensity (8). This also indicates that in acid solution, protonation occurs on the carbonyl oxygen or thiocarbonyl sulphur, represented as follows:

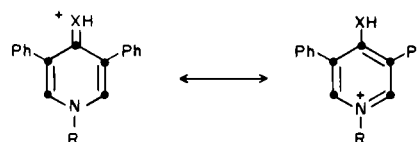


TABLE II
3,5-Diphenyl-4-pyridones (III; X = O)

	Reagent	Medium	Yield (%)	ν CO Pyridone (cm^{-1})
b	$\text{NH}_2\text{OH}\cdot\text{HCl}$	Py	65	1620
c	$\text{CH}_3\text{NH}_2\cdot\text{HCl}$	Py	60	1640
d	<i>n</i> -Butylamine	Ac	40	1638
e	<i>p</i> - $\text{OHC}_6\text{H}_4\text{NH}_2$	Ac	40	1628
f	$\text{C}_6\text{H}_5\text{NH}_2$	Ac	80	1635
g	<i>p</i> - $\text{CH}_3\text{C}_6\text{H}_4\text{NH}_2$	Ac	65	1640
h	<i>p</i> - $\text{ClC}_6\text{H}_4\text{NH}_2$	Ac	25	1640
i	<i>p</i> - $\text{BrC}_6\text{H}_4\text{NH}_2$	Ac	25	1635
j	<i>p</i> - $\text{IC}_6\text{H}_4\text{NH}_2$	Ac	15	1627
k	β -Naphthylamine	Ac	65	1626

Py = Pyridine; Ac = Acetic acid.

EXPERIMENTAL

Analyses were performed by Microanalysis Unit, Faculty of Science, Cairo University, Cairo. Ir spectra were measured with a Unicam SP 200 spectrophotometer in potassium bromide pellets or in nujol, uv and visible spectra with a Unicam SP 800 spectrophotometer and nmr spectra with a Varian A-60D instrument using solutions in carbon tetrachloride with TMS as internal standard.

3,5-Diphenyl-4-pyridones (III; X = O) (Table II).

They were prepared by refluxing 3,5-diphenyl-4-pyrone (1 mole) with the suitable primary amine (2.5 moles) in acetic acid or with the amine hydrochloride (2.5 moles) in pyridine for 5 hours.

1-Amino-3,5-diphenyl-4-pyridone (IIIa; X = O).

A solution of the pyrone (IV; X = O) (0.7 g.) in methanol (15 ml.) was refluxed with 98% hydrazine hydrate (3 ml.) for 3 hours. On cooling, the aminopyridone (0.4 g.) which separated was crystallized from methanol in needles, m.p. 204°.

Anal. Calcd. for C₁₇H₁₄N₂O: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.66; H, 5.32; N, 10.79.

On slow evaporation of the methanol mother liquor, 3,5-diphenyl-4-pyridone (IIIa; X = O) (0.35 g.), m.p. and mixed m.p. 396° (1) separated out.

Action of Nitrous Acid on 1-Amino-3,5-diphenyl-4-pyridone.

A solution of the pyridone (IIIa; X = O) (0.4 g.) in acetic acid (10 ml.) was gradually treated with an aqueous solution of sodium nitrite (2 g.). On dilution with water, 3,5-diphenyl-4-pyridone (0.35 g.), m.p. and mixed m.p. 396° was obtained.

1-Diacetylamino-3,5-diphenyl-4-pyridone (IIIb; X = O).

It was obtained (85% yield) by the action of acetic anhydride in pyridine on the aminopyridone (IIIa; X = O). It crystallized from methanol in white prisms, m.p. 232°.

Anal. Calcd. for C₂₁H₁₈N₂O₃: C, 72.80; H, 5.24; N, 8.09. Found: C, 72.48; H, 5.40; N, 8.50.

When a solution of this diacetate in ethanol was refluxed with hydrochloric acid for 30 minutes, (IIIb; X = O), m.p. and mixed m.p. 204°, separated out. However, it was recovered unchanged when refluxed with 20% ethanolic potassium hydroxide for 2 hours.

1-Benzylideneamino-3,5-diphenyl-4-pyridone (IIIc; X = O).

This compound was prepared (90% yield) by heating the aminopyridone (IIIa; X = O) (0.4 g.) and benzaldehyde (0.5 ml.) for 2 hours. It crystallized from benzene-methanol in prisms, m.p. 232°.

Anal. Calcd. for C₂₄H₁₈N₂O: C, 82.26; H, 5.18; N, 8.00. Found: C, 82.00; H, 5.08; N, 7.71.

The benzylidene (IIIc; X = O) was hydrolyzed to the aminopyridone (IIIa; X = O), m.p. and mixed m.p. 204°, when refluxed with 20% ethanolic potassium hydroxide for 1 hour. However, it was recovered unchanged when its solution in 80% ethanol was refluxed with hydrochloric acid for 3 hours.

Hydrolysis of the Benzylidene Derivative (IIIc; X = O) with Acid in the Presence of 2,4-Dinitrophenylhydrazine.

A mixture of the benzylidene derivative (IIIc; X = O) (0.3 g.) and 2,4-dinitrophenylhydrazine (0.3 g.) in ethanol (40 ml.) was refluxed with concentrated hydrochloric acid (1 ml.) and water (3 ml.) for 1 hour. An orange solid separated which was filtered

and identified as benzaldehyde 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 237°. The ethanol mother liquor gave after concentration and cooling 1-amino-3,5-diphenyl-4-pyridone (IIIa; X = O) (0.2 g.), m.p. and mixed m.p. 204°.

3,5-Diphenyl-4-thiopyrone (IV; X = S).

It was prepared (80% yield) by refluxing the pyrone (IV; X = O) (1 g.) in toluene (50 ml.) with phosphorus pentasulphide (3 g.) for 1.5 hours. It crystallized from benzene in dark red prisms, m.p. 131°.

Anal. Calcd. for C₁₇H₁₂OS: C, 77.26; H, 4.58; S, 12.13. Found: C, 77.50; H, 4.48; S, 11.80.

This thiopyrone was recovered unchanged when heated at 220-230° for 10 minutes, but was changed to the pyrone (IV; X = O) when its solution in dry xylene was refluxed with copper powder for 1 hour.

Action of Hydrogen Peroxide on the Thiopyrone (IV; X = S).

When a warm solution of the thiopyrone (0.5 g.) in glacial acetic acid (10 ml.) was treated with 1 ml. of hydrogen peroxide (100 vol.), the initial dark red color suddenly changed to pale yellow and on dilution, the corresponding pyrone (IV; X = O) (0.4 g.) which separated was crystallized from benzene in plates, m.p. and mixed m.p. 184°.

3,5-Diphenyl-4-thiopyridone (IIIa; X = S).

This compound was quantitatively prepared by refluxing the thiopyrone (IV; X = S) in glacial acetic acid with ammonium acetate for 2 hours. It crystallized from benzene-methanol in lemon-yellow prisms, m.p. 218°, ν max: 1090 (C = S), and 3160 (NH) cm⁻¹.

Anal. Calcd. for C₁₇H₁₃NS: C, 77.55; H, 4.97; N, 5.35; S, 12.17. Found: C, 77.78; H, 4.73; N, 5.32; S, 12.40.

1-Amino-3,5-diphenyl-4-thiopyridone (IIIb; X = S).

This compound was prepared (60% yield) by refluxing the thiopyrone (IV; X = S) (0.4 g.) and 98% hydrazine hydrate (2 ml.) in methanol (15 ml.) for 2 hours. It crystallized from ethanol in yellow flakes, m.p. 230° dec.

Anal. Calcd. for C₁₇H₁₄N₂S: C, 73.35; H, 5.07; N, 10.07; S, 11.52. Found: C, 73.23; H, 5.05; N, 10.11; S, 11.80.

1-Benzylideneamino-3,5-diphenyl-4-thiopyridone (IIIc; X = S).

This compound was obtained from (IIIb; X = S) and benzaldehyde, and crystallized from benzene in red-violet needles, m.p. 231° dec., ν max: 1615 (C = N) and 1093 (C = S) cm⁻¹.

Anal. Calcd. for C₂₄H₁₈N₂S: C, 78.63; H, 4.95; N, 7.65; S, 8.75. Found: C, 78.60; H, 4.94; N, 7.87; S, 8.90.

Hydrolysis of 1-Benzylideneamino-3,5-diphenyl-4-thiopyridone (IIIc; X = S).

(a) By Acid.

A suspension of the benzylidene derivative (0.3 g.) in ethanol (15 ml.) was refluxed with concentrated hydrochloric acid (1 ml.) for 30 minutes. On dilution with water, 1-amino-3,5-diphenyl-4-thiopyridone (IIIb; X = S) (0.2 g.), m.p. and mixed m.p. 230°, separated out.

(b) By Alkali.

A suspension of the benzylidene (0.3 g.) in ethanol (15 ml.) was refluxed with 20% aqueous sodium hydroxide (1 ml.) for 30 minutes. On dilution with water, 1-amino-3,5-diphenyl-4-thiopyridone (0.2 g.), m.p. and mixed m.p. 230°, separated out.

1-Phenylamino-3,5-diphenyl-4-thiopyridone (IIIo; X = S).

This compound was prepared (70% yield) by refluxing the thiopyrone (IV; X = S) (0.7 g.) in ethanol (15 ml.) with phenylhydrazine (1 ml.) for 1 hour. It crystallized from benzene-methanol in yellow prisms, m.p. 206°, ν max: 1088 (C = S) and 3400 (NH) cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{18}\text{N}_2\text{S}$: C, 77.93; H, 5.12; N, 7.90; S, 9.04. Found: C, 77.64; H, 5.16; N, 7.47; S, 9.20.

1-Methyl-3,5-diphenyl-4-thiopyridone (IIIc; X = S).

This compound was prepared (95% yield) by refluxing the thiopyrone (IV; X = S) (0.4 g.) in ethanol (10 ml.) with a solution of methylamine hydrochloride (0.3 g.) and sodium acetate (0.3 g.) in water (1 ml.) for 2 hours. It crystallized from methanol in yellow needles, m.p. 166°, ν max: 1115 (C = S) cm^{-1} .

Anal. Calcd. for $\text{C}_{18}\text{H}_{15}\text{NS}$: C, 77.95; H, 5.45; N, 5.05; S, 11.56. Found: C, 77.90; H, 5.40; N, 5.13; S, 11.80.

1,3,5-Triphenyl-4-thiopyridone (IIIf; X = S).

This compound was prepared (50% yield) by refluxing a solution of the pyridone (IIIf; X = O) (0.4 g.) in dry toluene (25 ml.) with phosphorus pentasulphide (2 g.) for 4 hours. It crystallized from methanol in orange flakes, m.p. 223°, ν max: 1090 (C = S) cm^{-1} .

Anal. Calcd. for $\text{C}_{23}\text{H}_{17}\text{NS}$: C, 81.37; H, 5.05; N, 4.13; S, 9.45. Found: C, 81.01; H, 5.20; N, 4.35; S, 9.70.

1,5-Dianilino-2,4-diphenylpenta-1,4-diene-3-thione (IIIg; X = S).

A solution of the thiopyrone (IV; X = S) (1 g.) in methanol (25 ml.) was refluxed with aniline (1 ml.) for 3 hours. After cooling, the thione (0.5 g.) was collected and crystallized from benzene in red needles, m.p. 260°.

Anal. Calcd. for $\text{C}_{29}\text{H}_{24}\text{N}_2\text{S}$: C, 80.52; H, 5.59; N, 6.48; S, 7.41. Found: C, 80.68; H, 5.48; N, 6.92; S, 7.80.

The methanol mother liquor, on further cooling, afforded 1,3,5-triphenyl-4-thiopyridone (0.5 g.), m.p. and mixed m.p. 223°.

The thione (IIIg; X = S) was also prepared by adding phosphorus pentasulphide (2 g.) to a warm solution of 1,5-dianilino-2,4-diphenylpenta-1,4-dien-3-one (IIIg; X = O) (0.6 g.) in dry benzene (15 ml.). The orange solution which changed immediately into deep red was filtered while hot and the residue washed with benzene. The benzene solution was washed with ammonium sulphide, water, and then dried (sodium sulphate). The residue after evaporation of the solvent afforded on treatment with methanol, the thione (0.1 g.) m.p. and mixed m.p. 260°. On slow evaporation of the methanol mother liquor, 1,3,5-triphenyl-4-pyridone (0.4 g.), m.p. and mixed m.p. 200° (1) separated out.

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