1-Ethyl-1,4-dihydro-4-oxo-7-(pyridinyl)-3-quinolinecarboxylic Acids. I. Synthesis of 3- and 4-(3-Aminophenyl)pyridine Intermediates

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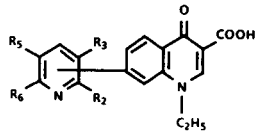
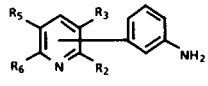
A series of substituted 3- and 4-(3-aminophenyl)pyridines has been prepared as intermediates for the synthesis of some 1-alkyl-1,4-dihydro-4-oxo-7-pyridinyl-3-quinolinecarboxylic acids. The Hantzsch, Hauser and other pyridine syntheses were used. 4-(3-Aminophenyl)pyridine was prepared *via* 3-(4-pyridinyl)-2-cyclohexen-1-one using the Semmler-Wolff reaction.

J. Heterocyclic Chem., **21**, 1849 (1984).

A synthetic program aimed at the title compounds **1** required the preparation of a number of substituted 3- and 4-pyridinylanilines of the general structure **2**. This paper covers the preparation of these intermediates **2**, while Part II, which follows, describes the preparation of the pyridinyl quinolones **1** which have significant antibacterial activity.



1



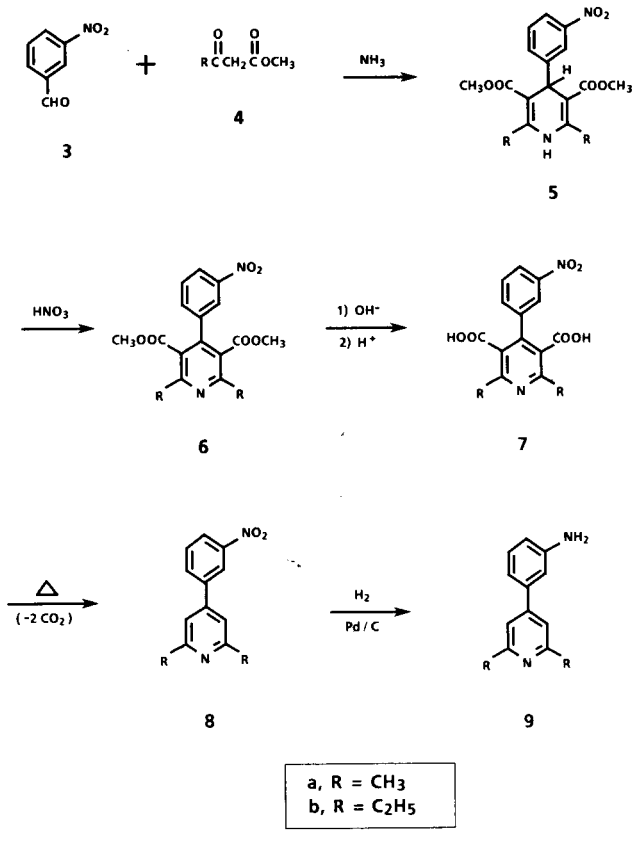
2

A variety of methods was used in the preparation of these anilinopyridines **2**.

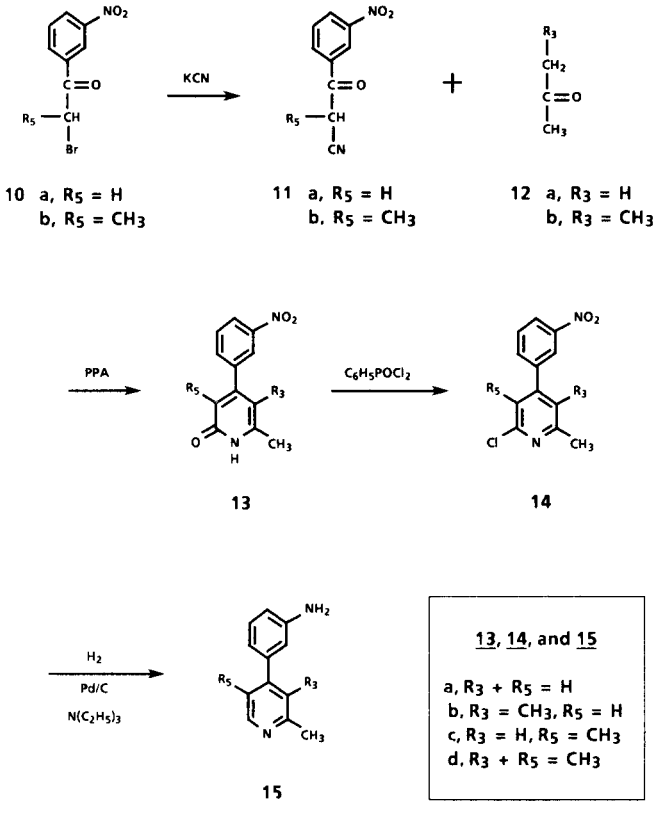
I. The Hantzsch synthesis [1] (Scheme 1) was very useful in preparing 2,6-dialkylpyridines. The methyl, rather than ethyl esters, **6** were used because they greatly improved the yields and quality of the diacids **7** obtained in the hydrolysis step. It was found that decarboxylation of these diacids **7** could be conveniently carried out, even on a large scale, in boiling Dowtherm A® . The anilines **9** were prepared by catalytic reduction of the corresponding nitro compounds **8** with palladium-on-carbon in dimethylformamide. The β-ketoester **4b**, needed for the preparation of **9b**, was prepared on a large scale by a process that was reported earlier [2].

II. The procedure of Hauser and Eby [3] was adopted to prepare other methylpyridine derivatives **15** as shown in Scheme 2. Treatment of the bromoketones **10** with excess potassium cyanide in ethanol-water readily gave the nitriles **11** [4] which are then condensed with an excess of the ketones **12** in polyphosphoric acid to give, in fair yields, the pyridones **13**. Phenylphosphonic dichloride [5] (bp 258°) was used to convert the pyridones to the 2-chloropyridines **14** in excellent yield. This reagent gave better yields than phosphorus oxychloride (bp 106°) probably because of its higher boiling point. In the last step, a facile one pot procedure was developed for reduction of the nitro group and removal of the chlorine. This involved the reduction of the nitro group followed by addition of triethylamine and then further hydrogenolysis of the chloro group to give the pyridinylanilines **15**.

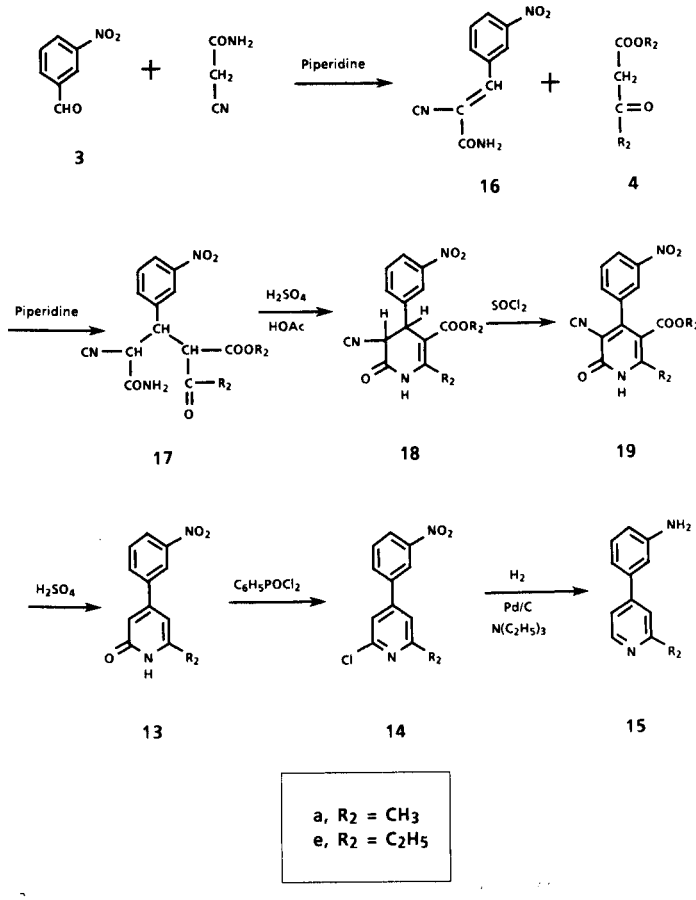
SCHEME 1



SCHEME 2



SCHEME 3

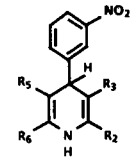


III. A little used procedure described by Hoffer [6] (Scheme 3) was adopted to prepare **15a** and **15e**. This sequence involved a combination of a Knoevenagel condensation to give **16** followed by a Michael reaction to give **17**. Cyclization of **17** in sulfuric acid gave **18** which was aromatized to **19** in boiling thionyl chloride [6]. Hot sulfuric acid hydrolyzed and decarboxylated **19a** and **19e** to give **13a** and **13e** in good yield. Chlorination, followed by reduction, as described earlier in II, resulted in **15a** and **15e**.

IV. The 2-methylpyridine **15a** was also made in an exploratory sequence shown in Scheme 4. Particularly noteworthy is the ready decarbonylation of the pyridinylcarboxaldehyde **23** to **24** by the method of Hawthorne and Wilt [7].

Table 1

1,4-Dihydro-4-(3-nitrophenyl)pyridines



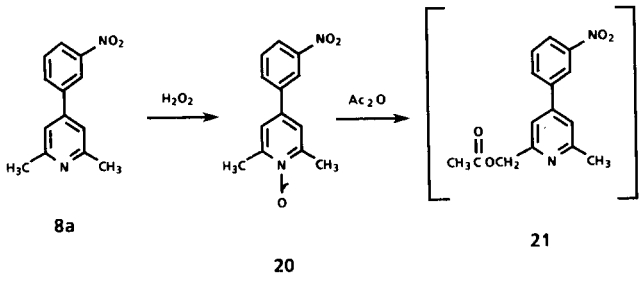
Compound No.	R_2	R_3	R_5	R_6	Mp (°C)	Yield (%)	Procedure
5b	CH_3	$COOCH_3$	$COOCH_3$	CH_3	202-205 [a]	80	A
5b	C_2H_5	$COOCH_3$	$COOCH_3$	C_2H_5	158-160	59	A
18a	CH_3	$COOCH_3$	CN	OH	211-213	95	I
18b	C_2H_5	$COOC_2H_5$	CN	OH	175-176	95	I

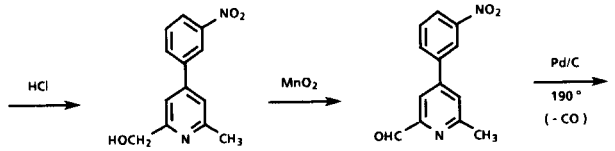
[a] Lit mp 209-210° [11].

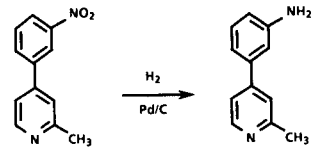
Table 1a

Compound No.	Formula	Analysis % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
5a	$C_{17}H_{18}N_2O_6$	58.96	59.04	5.25	5.28	8.09	7.93
5b	$C_{19}H_{22}N_2O_6$	60.95	60.65	5.92	5.91	7.43	7.43
18a	$C_{15}H_{13}N_3O_5$	57.14	57.03	4.16	4.14	13.33	13.40
18b	$C_{17}H_{17}N_3O_5$	59.47	59.71	4.99	4.94	12.24	12.43

SCHEME 4

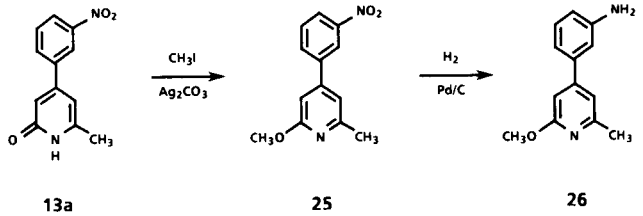


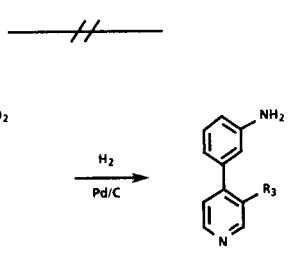




V. Methoxypyridine **26** was prepared in good yield by methylation of pyridone **13a** with methyl iodide-silver carbonate followed by catalytic reduction of the nitro group in **25** as outlined in Scheme 5.

SCHEME 5

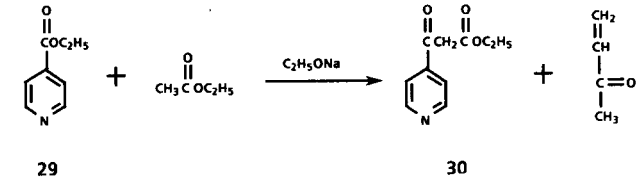


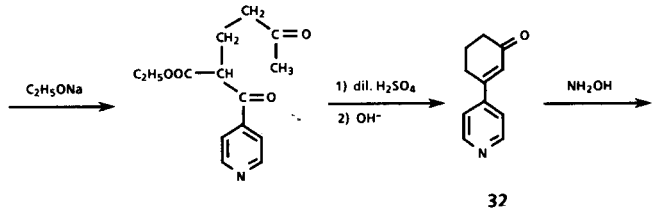


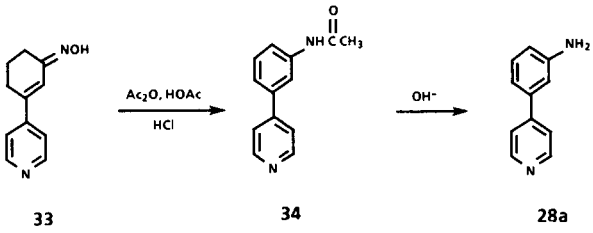
a, R_3 = H
b, R_3 = CH_3

VI. Nitration of 4-phenylpyridine gave a mixture of predominantly the 3-nitro- and 4-nitrophenyl isomers [8]. The 3-nitro derivative **27a** was isolated and reduced to **28a**. 4-(3-Nitrophenyl)pyridine (**27a**) was also prepared, as was its 3-methyl derivative **27b**, by a major variation of the Hantzsch reaction described earlier [9] and then reduced to the corresponding anilines **28** (Scheme 5).

SCHEME 6

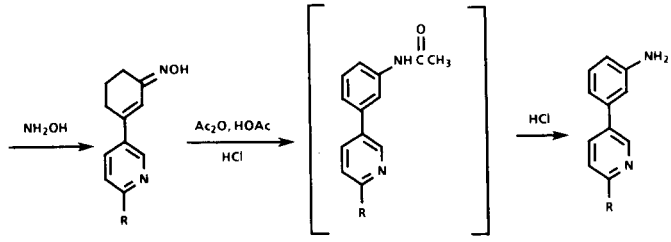




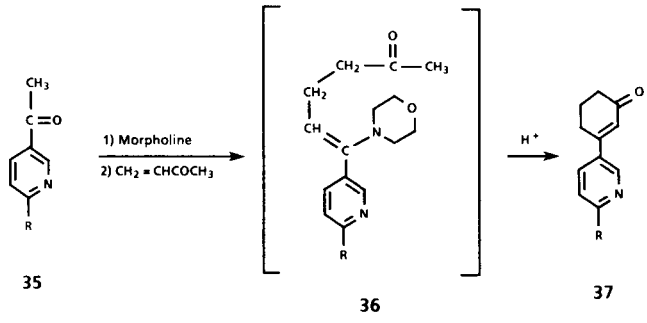


VII. During the course of this work large quantities of **28a** became necessary and a better method of synthesis was sought. The method developed (Scheme 6) has been used to make multikilogram quantities of this compound.

The Michael addition of pyridinyl β-ketoester **30** to methyl vinyl ketone gave the oily ketone **31** in quantitative yield which was used without purification. Hydrolysis and then decarboxylation of **31** in dilute sulfuric acid followed by alkaline cyclization gave a good yield of the pyridinylcyclohexenone **32**. This was converted to the oxime **33** which was then converted to the acetanilide **34** *via* the Semmler-Wolff reaction [10]. Hydrolysis of **34** gave the desired **28a** in good yield.



SCHEME 7

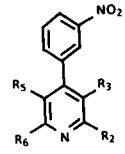


a, R = H
b, R = CH_3

VIII. The 3-pyridinylanilines **40a** and **40b** were prepared in a fashion similar to that of **28a** as outlined in Scheme 7.

Table 2

4-(3-Nitrophenyl)pyridines



Compound No.	R_2	R_3	R_5	R_6	Mp (°C)	Yield (%)	Procedure
6a	CH_3	$COOCH_3$	$COOCH_3$	CH_3	122-125	96	B
6b	C_2H_5	$COOCH_3$	$COOCH_3$	C_2H_5	[a]	90	B
7a	CH_3	COOH	COOH	CH_3	275-276.5 [b]	82	C
7b	C_2H_5	COOH	COOH	C_2H_5	[a]	—	C
8a	CH_3	H	H	CH_3	121-123.5 [c]	99	D
8b	C_2H_5	H	H	C_2H_5	222-225 [a]	80	D
13a	CH_3	H	H	OH	285-286	45	F
					284-286 [b]	83	K
13b	CH_3	CH_3	H	OH	270-271	41	F
13c	CH_3	H	CH_3	OH	284-286	55	F
13d	CH_3	CH_3	CH_3	OH	266-267	43	F
13e	C_2H_5	H	H	OH	223-224	86	K
14a	CH_3	H	H	Cl	168.5-171	96	G
14b	CH_3	CH_3	H	Cl	166-168	75	G
14c	CH_3	H	CH_3	Cl	138-140	94	G
14d	CH_3	CH_3	CH_3	Cl	207-208	67	G
14e	C_2H_5	H	H	Cl	111-113	95	G
19a	CH_3	$COOCH_3$	CN	OH	231-235	75	J
19e	C_2H_5	$COOC_2H_5$	CN	OH	185-190	55	J
20	CH_3	H	H	CH_3 [d]	236-238	100	—
22	CH_3	H	H	CH_2OH	149-151	80	—
23	CH_3	H	H	CHO	193-195	76	—
24	CH_3	H	H	H	154-155 [e]	95	—
25	CH_3	H	H	OCH_3	115-116	66	—

[a] Impure, used as such. [b] Not analyzed. [c] Lit mp 122-123 [12] reported for an isomeric 4-(anilino)-2,6-lutidine which was shown not to be the *p*-anilino isomer. The *o*- and *m*-anilino derivatives were the other possibilities. Our melting point suggests that they had the *m*-anilino isomer. [d] As *N*-(py)-oxide. [e] Lit mp 155-156° [16].

Table 2a

Compound No.	Formula	Analysis % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
6a	$C_{17}H_{16}N_2O_4$	59.30	59.33	4.68	4.70	8.14	8.08
8a	$C_{13}H_{12}N_2O_2$	68.41	68.36	5.30	5.30	12.27	12.27
8b	$C_{15}H_{16}N_2O_2 \cdot HCl$	61.53	61.80	5.81	5.92	9.57	9.59
13a	$C_{12}H_{10}N_2O_3$	62.61	62.62	4.38	4.35	12.17	12.16
13b	$C_{13}H_{12}N_2O_3$	63.93	63.98	4.95	4.90	11.47	11.43
13c	$C_{13}H_{12}N_2O_3$	63.93	64.27	4.95	4.99	11.47	11.50
13d	$C_{14}H_{14}N_2O_3$	65.10	64.88	5.46	5.47	10.85	10.90
13e	$C_{13}H_{12}N_2O_3$	63.93	64.12	4.95	4.90	11.47	11.64
14a	$C_{12}H_9ClN_2O_2$		(Cl,	14.26	14.07)	11.27	11.18
14b	$C_{13}H_{11}ClN_2O_2$	59.44	59.23	4.22	4.15	10.66	10.63
14c	$C_{13}H_{11}ClN_2O_2$	59.44	59.31	4.22	4.21	10.66	10.94
14d	$C_{14}H_{13}ClN_2O_2$	60.77	61.03	4.74	4.53	10.13	10.05
14e	$C_{13}H_{11}ClN_2O_2$	59.44	49.10	4.22	4.13	10.66	10.62
19a	$C_{15}H_{11}N_3O_5$	57.14	57.03	4.16	4.14	13.33	13.40
19e	$C_{17}H_{15}N_3O_5$	59.82	59.63	4.43	4.35	12.31	12.48
20	$C_{13}H_{12}N_2O_3$	63.93	63.97	4.95	4.94	11.47	11.45
22	$C_{13}H_{12}N_2O_3$	63.93	63.95	4.95	5.01	11.47	11.42
23	$C_{13}H_{10}N_2O_3$	64.56	64.35	4.16	4.18	11.56	11.61
24	$C_{12}H_{10}N_2O_2$	67.28	67.25	4.71	4.69	13.08	13.06
25	$C_{13}H_{12}N_2O_3$	63.93	64.05	4.95	4.90	11.47	11.52

EXPERIMENTAL

Melting points are uncorrected. All new compounds have compatible ir, ms and/or nmr spectra.

Procedure A. Dimethyl 1,4-Dihydro-2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinecarboxylate (**5a**).

A mixture of 3-nitrobenzaldehyde (**3**) (151 g, 1.0 mole), methyl acetoacetate (**4a**) (256 g, 2.2 moles), concentrated ammonium hydroxide (80 ml) and methanol (600 ml) was refluxed for four hours then cooled. The resulting yellow solid was filtered, washed with methanol, dried and recrystallized from isobutyl methyl ketone to afford 275.8 g (80%) of **5a**, mp 202-205°, lit mp 209-210° [11].

Procedure B. Dimethyl 2,6-Dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**6a**).

Nitric acid (4*N*) (4.2 ℓ) was heated on a steam bath with stirring. The dihydropyridine **5a** (260 g, 0.75 mole) was added slowly and heating continued for one hour. After cooling, the solution was basified with solid potassium carbonate. The product was extracted with methylene dichloride. This was dried (magnesium sulfate), treated with charcoal and evaporated to give 248 g (96%) of **6a**, mp 122-125°.

Procedure C. 2,6-Dimethyl-4-(3-nitrophenyl)-3,5-pyridinecarboxylic Acid (**7a**).

A solution of sodium hydroxide (650 g, 6.3 moles) in water (6 ℓ) and 95% ethanol (2 ℓ) was prepared. Dimethyl 2,6-dimethyl-4-(3-nitrophenyl)-3,5-pyridinedicarboxylate (**6a**) (1.384 g, 4.02 moles) was added with vigorous stirring and the mixture was heated on a steam bath for two hours, and then allowed to stand overnight. The ethanol was distilled and the aqueous solution was acidified to *p*H 2 with concentrated hydrochloric acid. The mixture was stirred while it cooled to room temperature. The resulting solid was collected and slurried with boiling 2-propanol (6 ℓ). This was cooled and the solid was collected and dried to give 1.408 g (82%) of **7a**, mp 275-276.5°.

Procedure D. 2,6-Dimethyl-4-(3-nitrophenyl)pyridine (**8a**).

A mixture of **7a** (110 g, 0.348 mole) and Dowtherm® (1 ℓ) was refluxed 1.5 hours. The dark solution was cooled, extracted with 6*N* hydrochloric acid (2 × 2 ℓ) and the extract was basified with ammonium hydroxide with stirring. The resulting product **8a**, was collected and dried (78 g, 99%), mp 118-124°. Recrystallization from ethanol-water (9:1) raised the mp to 121-123.5°, lit mp 122-123° [12].

Procedure E. 4-(3-Aminophenyl)-2,6-dimethylpyridine (**9a**).

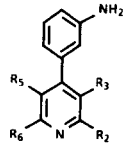
A solution of **8a** (12.0 g, 0.053 mole) in dimethylformamide (100 ml) was hydrogenated (palladium/charcoal) in a Parr apparatus. After hydrogenation was complete the catalyst was filtered and the filtrate concentrated to an oil which crystallized. Recrystallization from carbon tetrachloride-cyclohexane gave 8.6 g (82%) of **9a**, mp 114-117°, lit mp 117° [13].

(3-Nitrobenzoyl)acetonitrile (**11a**).

To a solution of potassium cyanide (109 g, 1.67 moles) in water (325

Table 3

4-(3-Aminophenyl)pyridines



Compound No.	R_2	R_3	R_5	R_6	Mp (°C)	Yield (%)	Procedure
9a	CH_3	H	H	CH_3	114-117 [a]	82	E
9b	C_2H_5	H	H	C_2H_5	>300 [b]	77	E
15a	CH_3	H	H	H	110-112.5	96	H
15b	CH_3	CH_3	H	H	143-144.5	87	H
15c	CH_3	H	CH_3	H	90-92	84	H
15d	CH_3	CH_3	CH_3	H	147-149	67	H
15e	C_2H_5	H	H	H	61-62	87	H
26	CH_3	H	H	OCH_3	[c]	92	E
28a	H	H	H	H	167-169 [d]	77	E
28b	H	CH_3	H	H	128-130	92	E

[a] Lit mp 177° [13]. [b] As dihydrochloride salt, not analyzed. [c] Bp 166-169°/0.2 mm. [d] Lit mp 165-166° [18].

Table 3a

Compound No.	Formula	Analysis % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
9a	$C_{13}H_{14}N_2$	78.75	78.43	7.12	7.26	14.13	13.91
15a	$C_{12}H_{12}N_2$	78.23	77.86	6.57	6.70	15.21	14.85
15b	$C_{13}H_{14}N_2$	78.75	78.78	7.12	6.48	14.13	14.13
15c	$C_{13}H_{14}N_2$	78.75	78.46	7.12	7.13	14.13	14.16
15d	$C_{14}H_{16}N_2$	79.20	79.16	7.60	7.56	13.20	13.02
15e	$C_{13}H_{14}N_2$	78.75	78.44	7.12	7.53	14.13	14.00
26	$C_{13}H_{14}N_2O$	72.87	72.75	6.59	6.56	13.08	12.95
28a	$C_{11}H_{10}N_2$	77.62	77.56	5.92	5.83	16.46	16.47
28b	$C_{12}H_{12}N_2$	78.23	77.91	6.57	6.54	15.21	15.09

ml) was added dimethylformamide (325 ml). The solution was cooled to 25° and a solution of 3-nitrophenacyl bromide (**10a**) (162 g, 1.51 moles) in dimethylformamide (240 ml) was added during 80 minutes with stirring and occasional cooling to maintain the temperature near 25°. Stirring was continued for 45 minutes longer without cooling. After dilution with cold water (2.75 ℓ), the solution was acidified (Hood!) with 6*N* hydrochloric acid (300 ml). The resulting solid was collected, washed with water and air dried. It was then dissolved in hot acetonitrile (150 ml) and ether (150 ml) with stirring. After chilling, **11a** was collected (97.6 g, 77%) mp 150-153.5°, lit mp 150-153° [4].

2-(3-Nitrobenzoyl)propanenitrile (**11b**).

Dimethyl sulfoxide (400 ml) was added to a stirred solution of potassium cyanide (80.4 g, 1.2 moles) in water (160 ml). The temperature rose to 40°. After cooling in ice, 3-nitro-α-bromopropiophenone (**10b**) (103.2 g, 0.4 mole) was added slowly enough to keep the temperature below 35°. Stirring was continued overnight. The solution was poured into a mixture of ice-water (2 ℓ) and concentrated hydrochloric acid (100 ml). The product was collected, taken up in ethyl acetate and then washed with water and brine. After drying (magnesium sulfate), the solvent was evaporated, the residue dissolved in hot benzene and this was treated with charcoal and filtered. The filtrate was diluted with hexane and chilled. The tan **11b** was collected and dried, (64 g, 78%), mp 71-73°.

Procedure F. 5,6-Dimethyl-4-(3-nitrophenyl)-2(1*H*)-pyridinone (**13b**).

A solution of (3-nitrobenzoyl)acetonitrile (**11a**) (19.0 g, 0.1 mole) in 2-butanone (**12b**) (60 ml) was added with stirring to polyphosphoric acid (140 g) preheated to 70°. The mixture was heated on the steam bath for one hour, then heated at 125° for 15 minutes and then poured into water with stirring. The aqueous suspension was extracted twice with chloroform, the chloroform was filtered, dried (potassium carbonate) and evaporated to a partly crystalline gum. Trituration of the gum with ethanol gave a tan solid. A further quantity was obtained by evaporation of the ethanol filtrate and crystallization of this gum from acetonitrile. The combined solids were recrystallized from dimethylformamide. There was obtained 10.1 g (41%) of **13b**, mp 270-271°.

Procedure G. 2-Chloro-5,6-dimethyl-4-(3-nitrophenyl)pyridine (**14b**).

A mixture of 5,6-dimethyl-4-(3-nitrophenyl)-2(1*H*)-pyridinone (**13b**) (27.0 g, 0.11 mole) and phenylphosphonic dichloride (40 ml) was heated to 165-175° for one hour. The clear dark solution was cooled to 80° and poured into water. Treatment with ammonium hydroxide gave a white solid which was collected, washed with water, dried and recrystallized from isopropyl acetate. There was obtained 21.7 g (75%) of **14b**, mp 166-168°.

Procedure H. 4-(3-Aminophenyl)-2,3-dimethylpyridine (**15b**).

A solution of 2-chloro-5,6-dimethyl-4-(3-nitrophenyl)pyridine (**14b**). (21.7 g, 0.083 mole) in dimethylformamide (270 ml) was hydrogenated in a Parr shaker (palladium/charcoal). After the absorption of three equivalents of hydrogen the hydrogenation was stopped. Triethylamine (30 ml) and more palladium/charcoal was added and hydrogenation continued. Another equivalent of hydrogen was absorbed. The catalyst was collected and the filtrate evaporated. The residue was suspended in dilute sodium hydroxide and extracted three times with methylene dichloride. The extract was dried (magnesium sulfate) and concentrated to a yellow solid which was crystallized from isopropyl acetate to give 14.2 g (87%) of **15b**, mp 143-144.5°.

2-Cyano-3-(3-nitrophenyl)-2-propenamide (**16**).

Piperidine (10 ml) was added to a stirred mixture of 3-nitrobenzaldehyde (**3**) (151.1 g, 1.0 mole), cyanoacetamide (84.0 g, 1.0 mole) and 95% ethanol (1 ℓ). A clear orange solution resulted which was filtered to remove a small amount of insoluble material. The solution was allowed to stand overnight. A solid formed, which was collected, washed with 95% ethanol and dried to give 183.5 g (84%) of **16**, mp 158-160°, lit mp 163° [14].

Methyl 2-Acetyl-5-amino-4-cyano-3-(3-nitrophenyl)-5-oxopentanoate (**17a**).

To a vigorously stirred solution of 2-cyano-3-(3-nitrophenyl)-2-propenamide (**16**) (180.4 g, 0.83 mole) and methyl acetoacetate (**4a**) (120.4 g, 1.04 moles) in methanol (750 ml) was added piperidine (15 ml). The solution became red, then rapidly changed to a thick slurry. After standing for one hour, the product **17a** was collected, washed with methanol and dried, (245.3 g, 88%). An analytical sample (acetonitrile) had a mp of 197-199°.

Anal. Calcd. for $C_{15}H_{15}N_3O_6$: C, 54.05; H, 4.54; N, 12.61. Found: C, 53.97; H, 4.47; N, 12.92.

Ethyl 5-Amino-4-cyano-3-(3-nitrophenyl)-5-oxo-2-(1-oxopropyl)pentanoate (**17b**).

This compound was prepared in the same fashion as **17a** (above), using ethyl propionylacetate (**4b**) [2]. The product **17b** was obtained in 72% yield, mp 212-213°.

Anal. Calcd. for $C_{17}H_{19}N_3O_6$: C, 56.50; H, 5.30; N, 11.63. Found: C, 56.25; H, 5.26; N, 11.79.

Procedure I. Methyl 5-Cyano-1,4,5,6-tetrahydro-2-methyl-4-(3-nitrophenyl)-6-oxo-3-pyridinecarboxylate (**18a**).

To a stirred suspension of methyl 2-acetyl-5-amino-4-cyano-3-(3-nitrophenyl)-5-oxopentanoate (**17a**) (245.3 g, 0.736 mole) in acetic acid (1.3 ℓ) was added concentrated sulfuric acid (150 ml). A clear solution resulted in five minutes. The product began to crystallize in about ten minutes. After standing one hour, the solid was collected and washed with water. There was obtained 221.8 g (95%) of **18a**. An analytical sample (acetonitrile) had a mp of 211-213°.

Procedure J. Methyl 5-Cyano-1,6-dihydro-2-methyl-4-(3-nitrophenyl)-6-oxo-3-pyridinecarboxylate (**19a**).

A solution of methyl 5-cyano-1,4,5,6-tetrahydro-2-methyl-4-(3-nitrophenyl)-6-oxo-3-pyridinecarboxylate (**18a**) (55.0 g, 0.164 mole) in thionyl chloride (150 ml) was refluxed for one hour. A vigorous evolution of hydrogen chloride occurred. The clear brown solution was evaporated to a solid which was recrystallized from acetonitrile to give 32.8 g (75%) of **19a**, mp 231-235°.

Procedure K. 6-Methyl-4-(3-nitrophenyl)-2(1*H*)-pyridinone (**13a**).

A mixture of sulfuric acid (500 ml) and water (500 ml) and methyl 5-cyano-1,6-dihydro-2-methyl-4-(3-nitrophenyl)-6-oxo-3-pyridinecarboxylate (**19a**) (74.1 g, 0.239 mole) was refluxed for two hours. There was a vigorous gas evolution and a clear solution resulted. The solution was poured onto ice and the resulting white solid was collected and washed with water and then ethanol. The solid was recrystallized from dimethylformamide, washed with acetonitrile and dried. The product **13a** (45.8 g, 83%), melting at 284-286°, was shown to be identical with material made by the Hauser method (Procedure F) by mixed mp and identical ir spectra.

2,6-Dimethyl-4-(3-nitrophenyl)pyridine *N*(py)-Oxide (**20**).

To a solution of 2,6-dimethyl-4-(3-nitrophenyl)pyridine (**8a**) (34.0 g, 0.152 mole) in acetic acid (150 ml) was added 30% hydrogen peroxide (45 ml). The solution was heated on the steam bath for three hours and then allowed to cool. After dilution with water (500 ml) the resulting yellow crystalline product was collected, washed with water and dried. There was obtained 38.0 g (100%) of **20**, mp 235-238° dec. An analytical sample (acetonitrile) melted at 236-238°.

6-Methyl-4-(3-nitrophenyl)-2-pyridinemethanol (**22**).

Acetic anhydride (41 ml) was heated to reflux, the heat removed and 2,6-dimethyl-4-(3-nitrophenyl)pyridine *N*(py)-oxide (**20**) (10.0 g, 0.04 mole) was added in portions with stirring. After the exotherm had subsided, the solution was refluxed for 30 minutes, cooled, diluted with ethanol (to destroy excess acetic anhydride) and evaporated to an oil. The oil was dissolved in concentrated hydrochloric acid (50 ml), refluxed for one hour and this was evaporated. The resulting residue was dissolved in water and then made basic with ammonium hydroxide. The precipitated solid was collected, washed with water and recrystallized from methanol-water (1:1) (charcoal). The yellow product **22** (3.0 g, 80%) melted at 149-151°.

6-Methyl-4-(3-nitrophenyl)-2-pyridinecarboxaldehyde (**23**).

A mixture of the alcohol **22** (21.0 g, 0.086 mole), activated manganese dioxide [15] (42 g) and chloroform (520 ml) was refluxed with stirring under a Dean-Stark trap. The theoretical amount of water was collected in six hours. The mixture was filtered hot, the filter cake washed with hot chloroform (2 × 400 ml) and the combined filtrate and washes were evaporated. The resulting solid was recrystallized from acetone (charcoal) to give 13.2 g of **23**. Evaporation of the acetone filtrate yielded starting material which was treated again with manganese dioxide to give, after recrystallization from acetone, a further 1.74 g of **23**. Both samples melted at 193-195° (total yield 14.9 g, 76%).

2-Methyl-4-(3-nitrophenyl)pyridine (**24**).

A mixture of the aldehyde **23** (5.1 g, 0.021 mole), 10% palladium on charcoal (0.51 g) and Dowtherm® (40 ml) was flushed with nitrogen and heated with stirring to 190° during one hour. The effluent gas was passed through water to observe the reaction rate. Gas evolution began at 95° and was rapid above 150°. After cooling, the mixture was diluted with three volumes of benzene and filtered. The filtrate was extracted three times with 3*N* hydrochloric acid. The hydrochloric acid extract was washed with benzene, treated with charcoal and then made basic with ammonium hydroxide. The resulting white solid was taken up in methylene dichloride. This solution was dried (magnesium sulfate) and evaporated to give 4.3 g (95%) of **24**. An analytical sample (methanol) melted at 154-155°, lit mp 155-156° [16].

2-Methoxy-6-methyl-4-(3-nitrophenyl)pyridine (**25**).

A mixture of 6-methyl-4-(3-nitrophenyl)-2(1*H*)-pyridinone (**13a**) (37.3 g, 0.162 mole), silver carbonate (86.0 g, 0.324 mole), methyl iodide (46 g, 0.325 mole) and tetrahydrofuran (1.5 ℓ) was refluxed for nine hours. The mixture was filtered and the solid was extracted with tetrahydrofuran. The extract was concentrated to a tan solid. This solid dissolved in chloroform was stirred with 50 g of Florisil® , filtered and the filtrate evaporated. The residue crystallized from ethanol to give **25** (26.3 g, 66%), melting at 115-116°.

Ethyl β-Oxo-4-pyridinepropanoate (**30**).

A 57% dispersion of sodium hydride (206 g, 4.9 moles) was washed free of mineral oil by repeated decantation with dry ether. Absolute ether (1.3 ℓ) was added and the suspension stirred vigorously while absolute ethanol (230 g, 5.0 moles) was added at a rate causing reflux. A thick white slurry that was difficult to stir resulted. A mixture of dry ethyl acetate (570 g, 6.5 mole) and freshly distilled ethyl 4-pyridinecarboxylate (**29**) (489.2 g, 3.24 moles) was added all at once with stirring. Some foaming occurred. The ether was distilled on the steam bath and the resulting solution was then refluxed for 17 hours with stirring. A yellow-brown solid crystallized after the first 30 minutes. After cooling, the solution was diluted with water (4 ℓ), stirred to dissolve the sodium salt and this was washed twice with ether. The aqueous layer was acidified with acetic acid and the resulting upper layer of orange-red oil was separated. The lower layer was extracted twice with methylene dichloride and the extracts combined with the oil layer. After drying (magnesium sulfate), the solvent was evaporated to an orange oil that crystallized. The solid was slurried with cold cyclohexane to give 528 g of **30**, mp 56-58°. The cyclohexane filtrate was evaporated to a red oil that crystallized on standing. Recrystallization of this second crop from isobutyl methyl ketone gave 33.8 g of **30**, mp 55-57°, lit mp 53-55° [17]. The total yield was 561.8 g (90%).

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.95; H, 6.11; N, 7.65.

Ethyl β-Oxo-α-(3-oxobutyl)-4-pyridinepropanoate (**31**).

A solution of ethyl β-oxo-4-pyridinepropanoate (**30**) (77.0 g, 0.4 mole) in benzene (600 ml) and absolute methanol (200 ml) was flushed with nitrogen and sodium methoxide (0.2 g) was added with stirring. A solution of freshly distilled methyl vinyl ketone (30.8 g, 0.44 mole) in benzene (120 ml) and methanol (40 ml) was added with stirring during 40 minutes so that the temperature was maintained at 26-30°. After the reaction was complete (five hours, tlc) the mixture was washed with saturated sodium chloride solution (300 ml), that was backwashed with benzene. The combined organic layers were dried (magnesium sulfate), treated with charcoal and evaporated to give an oil **31** (104.5 g, 100%), which was used without purification in the next step.

3-(4-Pyridinyl)-2-cyclohexen-1-one (**32**).

Ethyl β-oxo-α-(3-oxobutyl)-4-pyridinepropanoate (**31**) (116 g, 0.44 mole) was dissolved in a cold solution of concentrated sulfuric acid (220 ml) and water (660 ml). The solution was heated at 95° for 15 hours. Evolution of carbon dioxide began at about 50°. After 35 minutes at 95°, carbon dioxide evolution had ceased. The reaction was cooled to 25° and made basic by the slow addition of 35% sodium hydroxide solution (*ca.* 600 ml) while maintaining the temperature at 25-30° during the addition and for one hour further. The mixture was extracted four times with chloroform. It was necessary to filter the initial chloroform layer to break up an emulsion. The organic extract was dried (magnesium sulfate), treated with charcoal and evaporated to give an oil that was then taken up in 2-propanol (750 ml). Methanesulfonic acid (42 g, 0.44 mole) was added and the resulting solution cooled. The solid product that formed was collected, washed with 2-propanol and then with ether. The methanesulfonic acid salt of **32** was recrystallized (ethanol) and dried, 94.0 g (80%), mp 178-181°.

Anal. Calcd. for $C_{11}H_{11}NO{\cdot}CH_4O_3S$: C, 53.52; H, 5.61; N, 5.20. Found: C, 53.25; H, 5.57; N, 5.10.

The free base **32** was obtained by dissolving the methanesulfonate salt in water, making this basic with ammonium hydroxide, extracting with methylene dichloride and then evaporating the extract. It melted at 61-67°.

3-(4-Pyridinyl)-2-cyclohexen-1-one Oxime (**33**).

To a solution of hydroxylamine hydrochloride (280 g, 4.0 moles) in pyridine (2.2 ℓ) was added 3-(4-pyridinyl)-2-cyclohexen-1-one (**32**) (327 g, 1.0 mole). This mixture was heated on the steam bath for 2.5 hours. The pyridine was evaporated, cold water added to the residue, and this was made basic with ammonium hydroxide. The solid **33** was collected, washed with water and dried (335 g, 93%), mp 183-185°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.48. Found: C, 69.93; H, 6.39; N, 14.84.

4-(3-Aminophenyl)pyridine (**28a**).

Hydrogen chloride was passed through a mixture of 3-(4-pyridinyl)-2-cyclohexen-1-one oxime (**33**) (168 g, 0.89 mole), acetic acid (1.1 ℓ) and acetic anhydride (170 ml) in a rapid stream until the solution began to reflux. External heat was applied to maintain reflux while continuing a

slow hydrogen chloride flow for six hours. A precipitate had started to form after two hours. The solvent was removed, the resulting residue was dissolved in water (500 ml) and was made basic with 35% sodium hydroxide. Ethanol was added to this until a solution was obtained. This was then refluxed with stirring overnight. The resulting mixture was cooled and the product that formed was collected and washed with cold 50% ethanol. There was obtained 116 g (77%) of **28a**, mp 167-169°, lit mp 165-166° [18].

3-(2-Methyl-5-pyridinyl)-2-cyclohexen-1-one (**37b**).

A mixture of 5-acetyl-2-methylpyridine (**35b**) [19] (49.1 g, 0.634 mole), morpholine (32.0 g, 0.37 mole), toluene (250 ml) and *p*-toluenesulfonic acid (6.5 g) was refluxed for 19 hours with a Dean-Stark water trap, during which time 6.0 ml of water (theory, 6.5 ml) was collected. The solution was evaporated to an oil that was taken up in dry benzene (125 ml). This solution was warmed to 40° and methyl vinyl ketone (25.5 g, 0.634 mole) was added all at once. This solution was refluxed for seven hours and then evaporated to give an oil **36b**. A solution of sodium acetate trihydrate (3.0 g) in water (60 ml) and acetic acid (60 ml) was added to this crude enamine **36b** and the mixture refluxed for 35 hours and then evaporated to a semi-solid. This was taken up in water (200 ml) and the solution made basic with 35% sodium hydroxide and extracted six times with chloroform. After drying (magnesium sulfate), the chloroform was evaporated and the resulting oil distilled. Starting ketone **35b** (29.0 g), (bp 53-60°/-0.11 mm) was recovered and the product **37b** (bp 125-150°/0.11 m.n) crystallized after distillation. There was obtained 17.4 g (62% based on unrecovered ketone) of product **37b** which was used without further purification.

3-(2-Methyl-5-pyridinyl)-2-cyclohexen-1-one Oxime (**38b**).

A mixture of the crude ketone **37b** (17.4 g, 0.093 mole), hydroxylamine hydrochloride (12.5 g, 0.18 mole) and pyridine (50 ml) was heated on the steam bath for 2.5 hours and evaporated to a thick oil which was shaken with 10% potassium carbonate solution. This mixture was extracted three times with methylene dichloride and the combined extracts washed with water, dried (magnesium sulfate) and evaporated to give an oil which crystallized on standing. Recrystallization of this product from acetonitrile, then from methanol, gave 12.0 g (63%) of **38b**, mp 167-161°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.12; H, 6.98; N, 13.93.

5-(3-Aminophenyl)-2-methylpyridine (**40b**).

The oxime **38b** (11.6 g, 0.576 mole) was combined with acetic acid (16 ml) and acetic anhydride (16 ml). The temperature rose to 45°. Dry hydrogen chloride gas was passed into the mixture until the temperature rose to 90° at which point heat was applied and the hydrogen chloride treatment continued for one hour at 110°. The mixture was allowed to stand for one hour, then evaporated to dryness. The solid residue, 5-(3-acetamidophenyl)-2-methylpyridine (**39b**), was dissolved in water (40 ml) and concentrated hydrochloric acid (12 ml) and refluxed for 20 hours. The resulting solution was evaporated to a solid which was taken up in water and then made basic with 35% sodium hydroxide. The mixture was extracted three times with ether, the combined extracts were dried (magnesium sulfate) and evaporated to a solid which was recrystallized from isopropyl acetate (charcoal). There was obtained 8.6 g (81%) of **40b**, mp 113-116°. An analytical sample (isopropyl acetate) melted at 114-116°.

Anal. Calcd. for $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21. Found: C, 77.83; H, 6.59; N, 14.95.

3-(3-Pyridinyl)-2-cyclohexen-1-one (**37a**).

This compound was prepared from 3-acetylpyridine (**35a**) in a fashion similar to that of 2-methyl-5-pyridinyl ketone **37b** in 33% yield, (bp 135-141°/0.15 mm). It crystallized during distillation, mp 70-73°. This was used without further purification.

3-(3-Pyridinyl)-2-cyclohexen-1-one Oxime (**38a**).

This compound was prepared in a fashion similar to that of 2-methyl-5-pyridinyl analog **38b** in 76.5% yield, mp 163-165°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.19; H, 6.43; N, 14.95.

3-(3-Aminophenyl)pyridine (**40a**).

This compound was prepared in a fashion similar to that of 5-(3-aminophenyl)-2-methylpyridine (**40b**), 68%, mp 72-74°, lit mp 77-78° [18].

Anal. Calcd. for $C_{11}H_{10}N_2$: C, 77.60; H, 5.92; N, 16.45. Found: C, 77.29; H, 5.86; N, 16.77.

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