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Synthesis of Some New 3-Cyanopyridine Derivatives from 1-Indanone of Expected Biological Activity

E.M.M. Kassem

Chemotherapy Chemistry Department, National Research Centre, Dokki, Cairo, Egypt.

Abstract :

A new series of condensed 3-cyanopyridine derivatives is synthesized by reacting 1-Indanone with malononitrile or ethyl cyanoacetate in the presence of the appropriate aldehyde and ammonium acetate or by reacting 1-indanone with arylidenecyanothio-acetamides in the presence of ammonium acetate.

Some of these compounds were tested for their antimicrobial activity. Structures of the new compounds were confirmed by elemental analysis and spectral data.

Introduction :

1-Indanone derivatives possess chemotherapeutic importance as anticancer, antiinflammatory and other pharmacological properties (1-5). Also, it has been reported that pyridin-amine, pyridone and pyridine-thione derivatives were found to possess many biological and pharmacological

activities [6-13]. These facts led me to study the synthesis of indanocyanopyridine derivatives of expected biological activity.

Results and Discussion :

Synthesis of the desired compounds was achieved by allowing 1-indanone I to react with malononitrile in the presence of ammonium acetate and different aromatic or heterocyclic aldehydes, namely, p-nitrobenzaldehyde, 3,4,5-trimethoxybenzaldehyde, and thiophene-2-carbox aldehyde to afford 3-cyano-4-substituted aryl- or thienyl-pyridine derivatives IIa-c, respectively (Scheme).

On the other hand, condensation of 1-indanone I with ethylcyanoacetate in the presence of ammonium acetate and different aromatic or heterocyclic aldehydes, namely, p-methoxybenzaldehyde, p-nitro-benzaldehyde, p-dimethylaminobenzaldehyde, 2-nitro-3-methoxybenz-aldehyde, 3, 4, 5-trimethoxybenzaldehyde and thiophene-2-carboxaldehyde, afforded 3-cyano-4-substituted aryl- or thienyl-2(1H)pyridone derivatives IIIa-f, respectively (Scheme).

Finally, the reaction of 1-indanone I with arylmethylenecyano-thioacetamides[13], namely, p-methoxyphenyl, p-nitrophenyl, p-dimethylaminophenyl, 3-methoxy-4-hydroxy-5-bromophenyl or 2-(2-thienyl)methylene cyanothioacetamides, in the presence of ammonium

acetate, afforded 3-cyano-4-substituted aryl- or thienyl-2(1H)pyridine thione derivatives IVa-e, respectively (Scheme).

Antimicrobial activity :

The prepared compounds were tested for local strains of Gram-positive bacteria and Gram-negative bacteria, fungi and yeast according to the modified cup plate method (14,15).

The measured values of preliminary screening for antimicrobial activity are indicated in Table (4).

The results showed that compounds IIa-c and IIIa-f possess slight activity towards Gram-positive bacteria. While compounds IVa-d are inactive towards Gram-positive bacteria. All the tested compounds are inactive. Compounds IIa-c and IIIa-f possess moderate activity against yeast while compounds IVa-d possess slight activity. Finally, compounds IIa,b and IIIb,d-f possess slight activity against fungi while compounds IIc and IIIa,c possess moderate activity. Compounds IVa-d are inactive towards fungi.

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Experimental

All melting points were determined in open capillary tubes and uncorrected. Microanalysis were performed by the Micro Analytical Center of Cairo University. IR spectra were recorded on Carlzeise spectrometer model "UR 10" using KBr discs. ^{1}H-NMR spectra were determined on Varian EM-360 NMR spectrometer 60 MHz, using tetramethylsilane as an internal standard. Mass spectra were determined on a Finnigan SSQ 7000 GC-MS.

Synthesis of 3-cyano-4-substituted aryl pyridine derivatives IIa-c :

A mixture of 1-indanone I (0.01 mol), malononitrile (0.01 mol), the appropriate aldehyde (0.01 mol) and ammonium acetate (0.08 mol) in 30 ml n-butanol was refluxed for 6 h. The solid formed was collected by filteration, washed with water and finally with pet. ether, dried and recrystallized from the proper solvents. The physical and analytical data of these compounds are shown in Tables (1-3).

Synthesis of 3-cyano-4-substituted aryl-2(1H)pyridine derivatives IIIa-f :

A mixture of equimolar amounts of I, ethyl cyanoacetate, the appropriate aldehyde (0.01mol), and ammonium acetate (0.08 mol) in 30 ml n-butanol was refluxed for 5 h. The solid separated on cooling, was filtered off, dried and crystallized from the proper solvents. The physical and analytical data of these compounds are listed in Tables (1-3).

Synthesis of 3-cyano-4-substituted aryl-2(1H)pyridine thione derivatives IV(a-e) :

A mixture of 1-indanone I (0.01 mol), the appropriate arylidenecyano-thioacetamide (0.01 mol), and ammonium acetate (0.08 mol) in 40 ml n-butanol was refluxed for 8 h. The reaction mixture was cooled, and the solid separated was filtered off, dried and then crystallized from the proper solvent. The physical and analytical data of these compounds are shown in Tables (1-3).

Table 1: The physical and analytical data of the prepared compounds :

Comd. No.	M.P.(°C) solvent for crystallisation	Yield %	Molecular Formula (Mol. wt.)	Analysis Calcd. / Found		
				C	H	N
IIa	215-217 A.A.	75	$C_{19}H_{12}N_4O_2$ (328.35)	69.50 69.82	3.69 3.92	17.07 17.30
IIb	300-302 A.A.	80	$C_{22}H_{19}N_3O_3$ (373.44)	70.75 70.96	5.14 5.35	11.26 11.47
IIc	255-257 A.A.	78	$C_{17}H_{11}N_3S$ (289.38)	70.55 70.88	3.84 4.05	14.52 14.77
IIIa	31-312 A.A.	76	$C_{20}H_{14}N_2O_2$ (314.36)	76.41 76.73	4.50 4.71	8.91 9.23
IIIb	> 360 A..A.	60	$C_{19}H_{11}N_3O_3$ (329.33)	69.29 69.32	3.37 3.40	12.76 12.79
IIIc	> 360 A.A.	65	$C_{21}H_{17}N_3O$ (327.41)	77.03 77.18	5.24 5.57	12.84 13.07
IIId	300-302 D.M.F.	70	$C_{20}H_{13}N_3O_4$ (359.36)	66.84 67.16	3.65 3.98	11.70 12.02
IIIe	307-309 A.A.	73	$C_{22}H_{18}N_2O_4$ (374.42)	70.57 70.92	4.86 5.07	7.48 7.69
IIIf	350-352 A.A.	68	$C_{17}H_{10}N_2OS$ (290.36)	70.32 70.64	3.48 3.83	9.65 9.98
IVa	185-187 A.A.	73	$C_{20}H_{14}N_2OS$ (330.43)	72.69 72.91	4.28 4.49	8.48 8.69

Table 1 : cont.

Comd. No.	M.P.(°C) solvent for crystalliation	Yield %	Molecular Formula (Mol. wt.)	Analysis Calcd. / Found		
				C	H	N
IVb	302-304 D.M.F.	68	$C_{19}H_{11}N_3O_2S$ (345.40)	66.07 66.28	3.22 3.34	12.17 12.29
IVc	285-287 D.M.F.	63	$C_{21}H_{17}N_3S$ (343.48)	73.43 73.66	5.00 5.21	12.24 12.45
IVd	270-272 A.A.	61	$C_{20}H_{13}N_2O_2SBr$ (425.33)	56.47 56.68	3.09 3.30	6.59 6.80
IVe	295-297 A.A.	66	$C_{17}H_{10}N_2S_2$ (306.43)	66.63 66.84	3.30 3.51	9.14 9.36

A.A. = Acetic acid, D.M.F. = Dimethylformamide.

Table 2 : The IR data of the prepared compounds.

Compd. No.	IR (KBr) cm^{-1}
IIc	3437, 3356, 3248 (NH, NH2), 2211 (C≡ N), 1636 (C=N), 1558 (C=C).
IIIa	3439 (NH), 2220 (C≡ N), 1684 (C=O), 1567 (C=C).
IIIb	3398 (NH),2218 (C≡ N), 1682 (C=O), 1640 (C=C).
IIIc	3411 (NH), 2363 (C≡ N), 1669 (C=O), 1637 (C=C).
IIId	3433 (NH) , 2220 (C≡ N), 1645 (C=O), 1567 (C=C).
IIIe	3204 (NH), 2214 (C≡ N), 1642 (C=O), 1520 (C=C).
IIIf	3449 (NH), 2217 (C≡ N), 1629 (C=O), 1556 (C=C).
IVa	3418 (NH), 2209 (C≡ N), 1642 (C=N), 1613 (C=S), 1560 (C=C).
IVb	3400 (NH), 2362 (C≡ N), 1694 (C=N), 1629 (C=S), 1513 (C=C), 1343 (NO_2).
IVc	3390 (NH), 2361 (C≡ N), 1612 (C=N), 1565 (C=S), 1526 (C=C).
IVd	3460 (OH), 3371 (NH), 2210 (C≡ N), 1621 (C=N), 1564 (C=S), 1501 (C=C), 755 (Br).

The spectra supported the keto form in accordance with previous reports, which reported that 2-hydroxypyridine exists in the keto form [16,17].

Table 3 : ^{1}H-NMR data of the prepared compounds :

Compd. No.	^{1}H-NMR (δ ppm, DMSO)
IIb	1.9 (s, 2H, CH_2); 3.3-3.8 (m, 9H, 3 OCH_3); 7.45-7.65 (m, 6H, aromatic) and at 8.4 (s, 2H, 2-NH).
IIIC	1.9 (s, 2H, CH_2); 2.75-3.95 (m, 6H, 2 N-CH_3); 7.3-7.7 (m, 8H, aromatic) and at 8.2 (s, 1H, -NH).

The mass spectrum of IIa showed the following ion fragments m/z (peak / relative abundance) : 328 / 100 (M^+), 313 / 31.98, 227 / 15.82, 200 / 3.31, 154 / 2.77, 115 / 20.97 and 86 / 2.57.

The mass spectrum of IIc showed the following ion fragments : 289 / 100 (M^+), 274 / 35.8, 227 / 56.68, 205 / 25.68, 169 / 15.61, 154 / 78.24, 115 / 55.06, 97 / 48.75 and 86 / 31.53.

The mass spectrum of IIIe showed the following ion fragments: 374 / 100 (M^+), 343 / 15.82, 227 / 5.97, 206 / 3.36, 170 / 2.55, 154 / 14.51, 115 / 4.41 and 86 / 14.28.

The mass spectrum of IVb showed the following ion fragments : 344 / 3.22 (M^+-1), 313 / 7.09, 227 / 3.98, 200 / 1.39, 170 / 0.69.

Table 4: The antimicrobial activity of some prepared compounds.

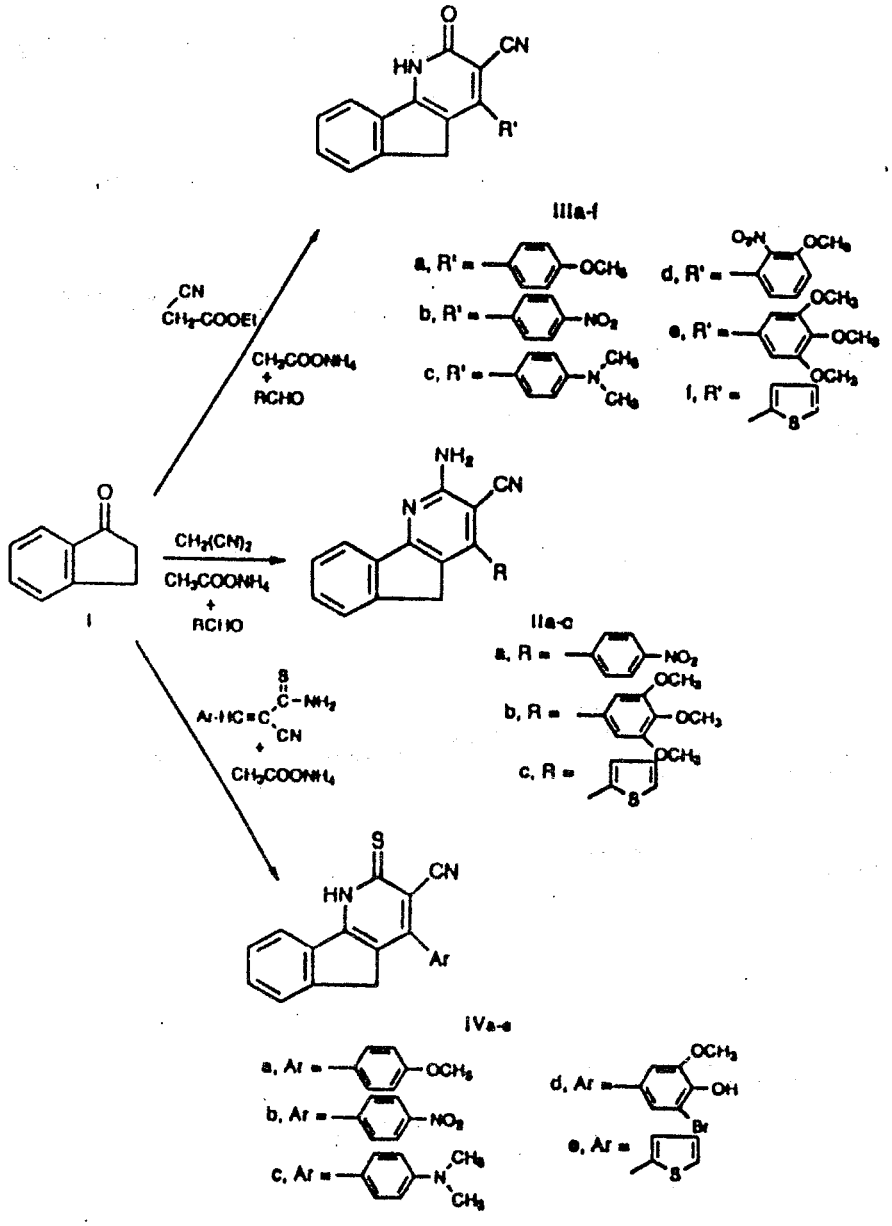
Compound No.	*Bacillus subttilis* (G-positive)	*Escherichia coli* (G-negative)	*Candida albicans* (yeast)	*Aspergillus flavs* (fungi)
IIa	+	-	++	+
IIb	+	-	++	+
IIc	+	-	++	++
IIIa	+	-	++	++
IIIb	+	-	++	+
IIIc	+	-	++	++
IIId	+	-	++	+
IIIe	+	-	++	+
IIIf	+	-	++	+
IVa	-	-	+	-
IVb	-	-	+	-
IVc	-	-	+	-
IVd	-	-	+	-

+++ = Highly sensitive (inhibition zone 12-15 mm).

++ = Moderately sensitive (inhibition zone 9-12 mm).

\+ = Slightly sensitive (inhibition zone 6-9 mm).

– = Not sensitive.


IIIa-f
a, R' = OCH3
b, R' = NO2
c, R' = N(CH3)2
d, R' = O2N, OCH3
e, R' = OCH3, OCH3
f, R' = S
CN
CH2-COOEt
CH3COONH4
+
RCHO
CH2(CN)2
IIa-c
a, R = NO2
b, R = OCH3, OCH3
c, R = OCH3, S
Ar-HC=C(CN)-C(=S)-NH2
IVa-e
a, Ar = OCH3
b, Ar = NO2
c, Ar = N(CH3)2
d, Ar = OCH3, OH, Br
e, Ar = S

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تشييد بعض مشتقات ٣- سيانوبيريدين من ١- أندانون والمتوقع لها فعلية بيولوجية

عماد محمد محمد قاسم

قسم الكيمياء العلاجية - المركز القومى للبحوث - الدقى - القاهرة

تم فى هذا البحث تشييد بعض مركبات ٣- سيانو - ٤- اريل -٢ (١يد) بيريدين II_{a-c} وكذلك مركبات ٣- سيانو - ٤ - اريل-٢ (١يد) بيريدون III_{a-f} ومركبات ٣- سيانو - ٤ - اريل-٢ (١يد) بيريدون ثيون III_{a-f} بيريدين ثيون VI_{a-c}من - اندانون.

أمكن أثبات التركيب الكيميائى لكل المركبات الجديدة عن طريق التحليل الكيميائى الدقيق وكذلك دراسة أطياف الاشعة تحت الحمراء والرنين النووى المغناطيسى وكذلك مقياس طيف الكتلة.

تم إختبار بعض المركبات المشيدة الجديدة لدراسة تأثيرها المضاد للبكتيريا والفطريات وقد لوحظ أن لبعضها بعض التأثير الملموس وللبعض الأخر عدم التأثير .