A Novel Synthesis for Quinoline Derivatives [1]

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Condensation of ethyl 2-(2-oxo-2,3-dihydro-1*H*-indolid-3-ene)cyanoacetate and/or 2-(2-oxo-2,3-dihydro-1*H*-indolid-2-ene)malononitrile with 3-methylpyrazolin-5-one, 1-phenyl-3-methyl-pyrazolin-5-one, benzoyl acetonitrile or ethyl acetoacetate affords different substituted quinolines. The reaction is suggested to proceed through a nucleophilic addition followed by ring opening and recyclization steps.

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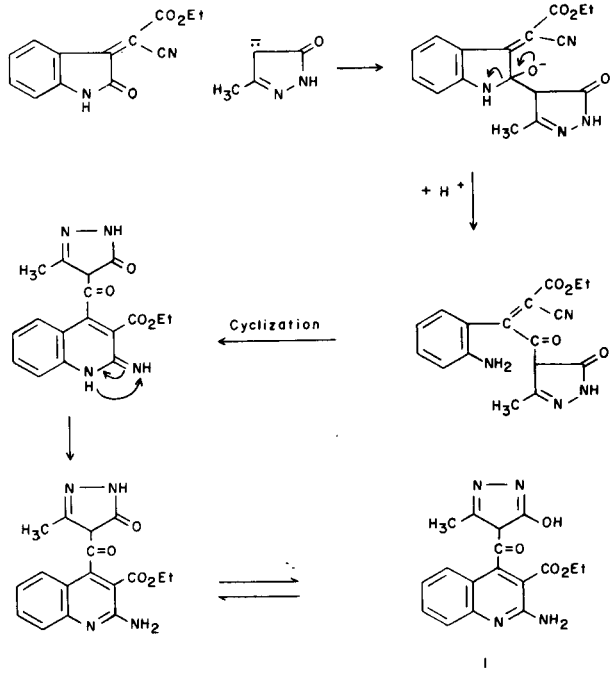
Quinoline derivatives have long been known for their chemotherapeutic activities [3], in addition to other versatile uses as dyestuffs and photographic sensitizers [4]. they can be synthesised by different methods among which one may mention the methods due to Skraup [5], Döbner-von Miller [6], and Friedlander [7].

The present work offers a novel method for the preparation of quinoline derivatives involving the reaction of yilidine derivatives of isatin as 2-(2-oxo-2,3-dihydro-1*H*-indolid-2-ene)malononitrile and/or ethyl 2-(2-oxo-2,3-dihydro-1*H*-indolid-3-ene)cyanoacetate with active methylene compounds.

Treatment of ethyl 2-(2-oxo-2,3-dihydro-1*H*-indolid-3-ene)cyanoacetate with 3-methylpyrazolin-5-one in the presence of triethylamine as a basic catalyst gives 2-amino-3-ethoxycarbonyl-4-quinolyl 5-hydroxy-3-methylpyraz-4-yl ketone (I) which was assigned this structure on the basis of elemental analysis which conforms to the molecular formula $C_{17}H_{16}N_4O_4$.

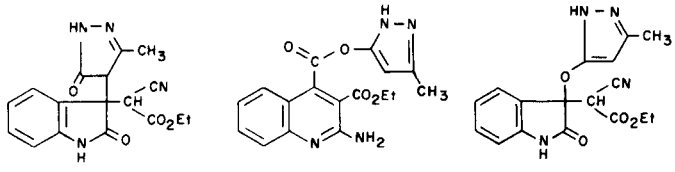
Its ir spectrum (Table 2) shows characteristic absorptions for strongly chelated NH and NH_2, CO groups and the absence of any absorptions for CN group at 2180 cm^{-1} whereas the absorption characteristic for OH may be due to the tautomerism present in the pyrazolinone moiety. Further proof for the suggested structure was derived from its electronic spectrum which exhibits characteristic quinoline maxima at 323, 307, and 275 nm [8] although with some bathochromic shift due to substituent effects. Moreover, the ^{1}H-nmr spectra in DMSO gives a clue to the assigned structure since the signals due to the aromatic protons were separated into two downfield protons at 8.0-8.2 ppm and three upfield protons at 6.9-7.3 ppm. This is interpreted in terms of the deshielding of H_5 and H_8 in the quinoline nucleus and by anisotropy of both the CO and N=C groups whereas the other aromatic protons, H_6, H_7 of the quinoline and the pyrazoline H_4 appeared in the aromatic region.

The formation of I may be rationalized in terms of a carbanion attack at the carbonyl carbon of ethyl 2-(2-oxo-2,3-dihydro-1*H*-indolid-3-ene)cyanoacetate followed by ring opening and recyclization affording the final product I.



I

Attack of the carbanion nucleophile on the olefinic carbon of the yilidines to give product VIII is excluded according to the recorded spectral and nmr analytical data in Table 2. On the same basis, nucleophilic attack of the carbonyl carbon or the olefinic carbon of ethyl 2-(2-oxo-2,3-dihydro-1*H*-indolid-3-ene)cyanoacetate by an alternative pyrazoloxy anion to give the corresponding products IX and X are also excluded.



VIII IX X

Table 1

2-Amino-3-cyano-(or Ethoxycarbonyl)-4-acylquinolines

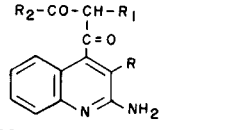
Compound No.	Mp, °C solvent	Yield %	Molecular formula	Analysis % Calcd. C	H	N	Found C	H	N
I	230 DMF	62	$C_{17}H_{16}N_4O_4$	60.00	4.70	16.47	59.80	4.91	16.00
II	240 DMF	63.3	$C_{23}H_{20}N_4O_4$	66.30	4.80	13.46	65.90	5.20	13.40
III	255 acetone	74	$C_{18}H_{18}N_2O_5$	63.15	5.26	8.18	63.10	5.70	8.00
IV	285 DMF	60	$C_{15}H_{11}N_5O_2$	61.43	3.40	23.89	60.90	3.40	23.70
V [a]	250 DMF	61	$C_{21}H_{15}N_5O_2$	68.29	4.06	18.97	67.80	4.50	18.40
VI	240 ethyl acetate	62	$C_{20}H_{12}N_4O_2$	70.58	3.50	16.47	70.40	4.00	16.42
VII [b]	270 acetone	61	$C_{17}H_{15}N_3O_4$	62.76	4.60	12.70	62.70	4.60	12.70

[a] Pale buff needles. [b] Pale yellow needles; all others were colorless needles.

Similar treatment of ethyl 2-(2-oxo-2,3-dihydro-1*H*-indolid-3-ene)cyanoacetate with 3-methyl-1-phenylpyrazolin-5-one affords 2-amino-3-ethoxycarbonyl-4-quinolyl-1-phenyl-5-oxo-2-pyrazolin-4-yl ketone (II), whereas with acetylacetone it affords 1-(2-amino-3-ethoxycarbonylquinolin-4-yl)-2-acetyl-1,3-butanedione (III).

The assigned structures for these products (II, III) were based on grounds similar to those for I (*c.f.* Tables 1 and 2) taking into consideration that ir absorption due to the CN group originally present in ethyl 2-(2-oxo-2,3-dihydro-1*H*-indolid-3-ene)cyanoacetate is lacking in the products I-III, *i.e.* the cyano group became incorporated into the quinoline ring system.

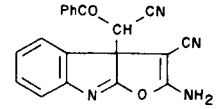
The reaction of 2-(2-oxo-2,3-dihydro-1*H*-indolid-2-ene)-malononitrile with different nucleophiles was also examined. Thus, with 3-methylpyrazolin-5-one it gives 2-amino-3-cyanoquinolin-4-yl 5-oxo-3-methyl-2-pyrazolin-4-yl ketone (IV), whereas with 1-phenyl-3-methylpyrazolin-5-one it affords 2-amino-3-cyanoquinolinyl-4-yl 5-oxo-3-methyl-1-phenyl-2-pyrazolin-4-yl ketone (V), while with benzoylacetonitrile it gives two compounds. A major product (60% yield) mp 240° was identified as 1-(2-amino-3-cyanoquinolin-4-yl)-2-cyano-3-phenyl-1,3-propanedione (VI) and a minor product (20% yield) mp 100° which was identified as 2-amino-3-cyanofuro[2,3-*b*]-3-benzoylacetonitrile indole (XI). Its ir spectrum showed absorption bands at 3350, 3140 cm^{-1} (NH_2), at 2150 cm^{-1} (CN), at 1710 cm^{-1} (CO) and at 1650 cm^{-1} for (CN). *Anal.* Calcd. for $C_{20}H_{12}N_4O_2$: C, 70.58; H, 3.5; N, 16.47. Found: C, 70.39; H, 3.55; N, 16.40. The mechanism of its formation will be discussed in a future publication. Interaction of 2-(2-oxo-2,3-dihydro-1*H*-indolid-2-ene)malononitrile with ethyl acetoacetate gives 1-(2-amino-3-cyanoquinolin-4-yl)-2-ethoxycarbonyl-1,3-butanedione (VII).



III, R = CO_2Et, R_1 = $COCH_3$, R_2 = CH_3

VI, R = R_1 = CN, R_2 = Ph

VII, R = CN, R_1 = CO_2Et, R_2 = CH_3



XI

EXPERIMENTAL

All melting points are uncorrected. The ir (potassium bromide) and uv (absolute ethanol) were recorded on Beckmann 408 and 26 spectrophotometers respectively. The ^{1}H-nmr (spectra (DMSO) were recorded on a Varian T-60A spectrophotometer using TMS as the internal standard.

Ethyl 2-(2-Oxo-2,3-dihydro-1*H*-indolid-3-ene)cyanoacetate [9].

This compound was obtained as dark red crystals from ethanol, mp 215°.

2-(2-Oxo-2,3-dihydro-1*H*-indolid-2-ene)malononitrile [9].

This compound was obtained as red crystals from ethanol, mp 235°.

Preparation of Quinoline Derivatives I-VII.

A mixture of ethyl cyanoacetate or 2-(2-oxo-2,3-dihydro-1*H*-indolid-2-ene)malononitrile (0.02 mole) in absolute ethanol (50 ml) and the appropriate nucleophile (0.02 mole) together with few drops of triethylamine was refluxed for 3-4 hours. The reaction product was filtered off, washed with a little ethanol and crystallized from a suitable solvent as shown in Table 1. Molecular structures of the derivatives prepared were established by various spectral analyses (Table 2).

Table 2

Spectral Data of the 2-Amino-3,4-disubstituted-quinolines (in Table 1)

Compound	UV Spectra [a] λ max (log ε)	IR (potassium bromide) cm^{-1}	^{1}H-NMR (DMSO-d_6) [b] (δ/ppm)
I	323 (4.25) 307 (4.19) 275 (4.21)	(NH_2) br (3500-2700) (CO) 1710	0.8 (t, 3H, ester CH_3) 1.6 (s, 3H, CH_3) 3.33- 4.1 (q, 2H, CH_2) 6.9-7.3 (m, 3 upfield ArH) and 8.0-8.2 (m, 2 downfield ArH)
II	320 (4.81) 302 (4.49) 278 (4.72)	(NH_2) 3360, 3150, (CO) 1700	0.7-0.8 (t, 3H, ester CH_3) 1.6 (s, 3H, pyrazoline CH_3) 6.8-8.3 (m, 10H, ArH and pyrazoline CH
III	316 (4.39) 304 (4.27) 278 (4.31)	(NH_2) 3400, 3150, (CO) 1710, 1690	0.7-1.1 (t, 3H, ester CH_3) 3.7-4.2 (q, 2H, ester CH_2) 2.1-2.2 (s, 6H, CO CH_3), 3.1-3.4 (m, 2H, NH_2), 7.0-8.0 (m, 4H, ArH), 9.68 (s, 1H, CH)
IV	318 (4.38) 302 (4.26) 278 (4.30)	(OH) 3430, (NH_2) 3400, 3200, (NH) 3140 (CN) 2180, (CO) 1710 and (pyrazoline ring- CO) 1640	1.6 (s, 3H, CH_3), 3.15, 3.75 (m, 2H, NH_2), 6.4 (s, 1H, NH), 6.8-7.4 (m, 4H, ArH) 8.25 (s, 1H, CH)
V	318 (4.67) 303 (4.26) 277 (4.23)	(NH_2) 3400, 3200, (CN) 2180, (CO) 1710 and 1640	1.6 (s, 3H, CH_3), 3.15 3.5 (m, 9H, ArH), 8.0 (m, 9H, ArH), 8.25 (s, 1H, pyrazoline CH)
VI	314 (4.90) 278 (4.81)	(NH_2) 3400, 3150 (CN) 2180, (CO) 1715 and 1670	3.3-3.45 (s, 2H, NH_2), 6.9-8.0 (s, 9H, ArH) 8.33 (s, 1H, CH)
VII		(NH_2) 3300, 3150, (CN), 2200, (CO) 1710 and 1690	0.6-0.9 (t, 3H, ester CH_3) 3.5-4 (q, 2H, CH_2) 2.2-2.4 (s, 3H, -$COCH_3$) 3.2-3.3 (s, 2H, -NH_2) 8.0 (s, 1H, CH)

[a] Solvent used, Butan-1-ol. [b] s = Singlet, m = multiplet, q = quartets, t = triplet.

REFERENCES AND NOTES

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