

ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS: A NOVEL SYNTHESIS
OF 4-AZOLOYL-2-AMINOQUINOLINES

Fathy M. ABDEL-GALIL, Bahia Y. RIAD, Sherif M. SHERIF and
Mohamed H. ELNAGDI*

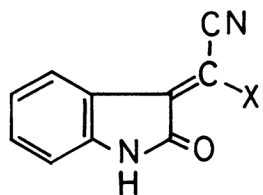
Department of Chemistry, Faculty of Science, Cairo University,
Giza, A.R. Egypt

A novel synthesis of 4-azoloyl-2-aminoquinolines via the
reaction of the 3-cyanomethylene derivatives of isatin with the
2-pyrazolin-5-one derivatives and 2-ethoxycarbonylmethyl-2-
thiazolin-4-one is reported.

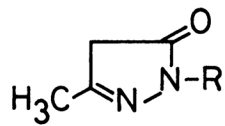
The considerable biological and medicinal activities of quinoline deriva-
tives in the past times have stimulated considerable research in this field.^{1,2}
As a part of a programme directed for exploring the synthetic potentiality, scope,
and limitation of activated nitriles in heterocyclic synthesis^{3,4} we report here
a novel synthesis of 4-azoloyl-2-aminoquinolines via the reaction of 3-cyano-
methylene derivatives of isatin (Ia,b) with the 2-pyrazolin-5-one derivatives
(IIa,b). The compounds obtained possess latent functional substituents and appear
promising for further chemical transformations.⁵ Moreover, they are of interest
for biological studies.

Thus, in a typical procedure, equimolar amounts (20 mmoles) of Ia and the
3-methyl-2-pyrazolin-5-one derivatives (IIa,b) are refluxed in ethanol (30 ml) in
the presence of catalytic amounts of triethylamine for 2-3 hrs. Removal of ethanol
and trituration with water affords products of molecular formulas corresponding to
addition of IIa,b to Ia.

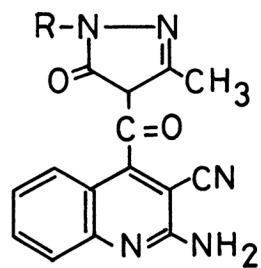
We took six alternate theoretically possible structures into consideration
(cf. structures III - VIII and Table 1). Structure III was readily established for
the reaction products based on the IR and ¹H-NMR data which revealed quinoline H-5
at a much lower field (δ 8.5 ppm) than that anticipatable for structures IV - VIII.
Moreover, the IR spectra revealed absorptions corresponding to NH₂, CN, and two CO



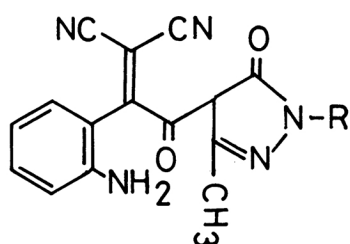
Ia, X=CN
b, X=CO₂Et



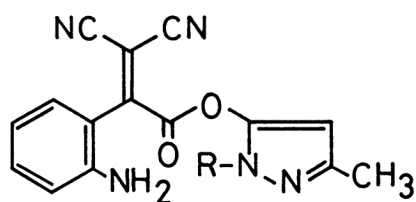
IIa, R=H
b, R=Ph



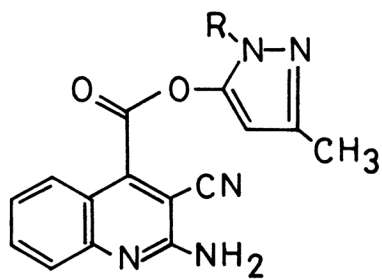
IIIa, R=H
b, R=Ph



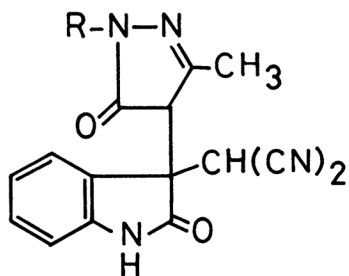
IV



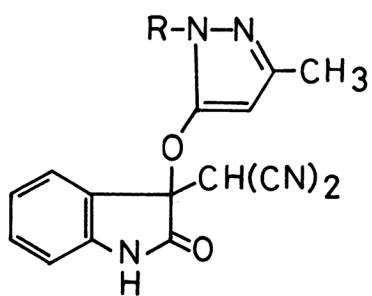
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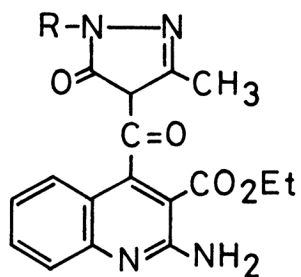
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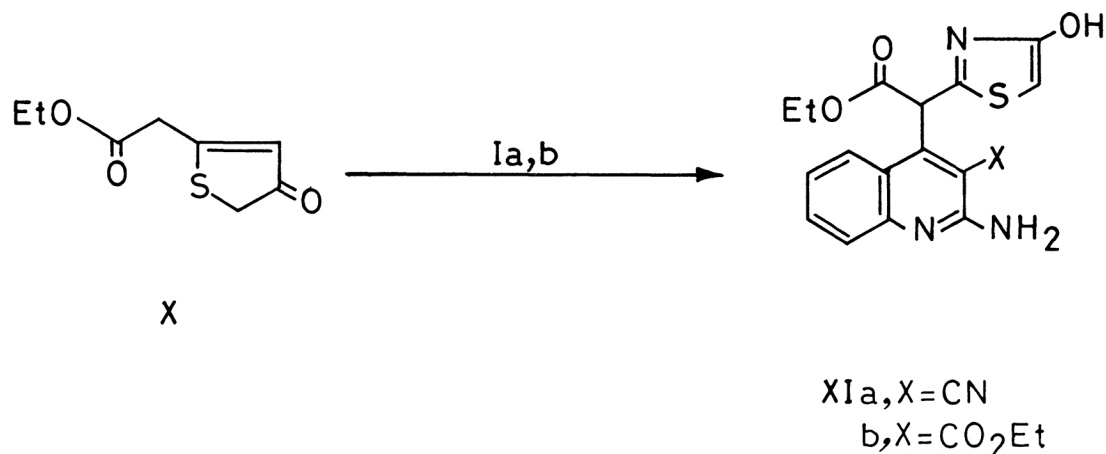
VII



VIII



IXa, R=H
b, R=Ph

Table 1. 4-Azoloyl-2-aminoquinoline derivatives IIIa,b, IXa,b and XIa,b

Compound*	Cryst. Solvent	M.p. [°C]	Yield [%]	Mol. Formula
<u>IIIa</u>	Ethanol	285-286	69	C ₁₅ H ₁₁ N ₅ O ₂
<u>IIIb</u>	Ethanol/H ₂ O	219	70	C ₂₁ H ₁₅ N ₅ O ₂
<u>IXa</u>	Ethanol	281-283	74	C ₁₇ H ₁₆ N ₄ O ₄
<u>IXb</u>	Ethanol	235	65	C ₂₃ H ₂₀ N ₄ O ₄
<u>XIa</u>	Ethanol	260-261	82	C ₁₈ H ₁₄ N ₄ O ₄ S
<u>XIb</u>	Acetic acid	276-277	71	C ₂₀ H ₁₉ N ₅ O ₆ S

*) Satisfactory elemental analyses for all the newly synthesised compounds were obtained.

groups (1680 and 1640 cm⁻¹) as required by structure III. The formation of IIIa,b from the reaction of IIa,b with Ia is assumed to proceed via the reaction of the active methylene in IIa,b with Ia to yield the acyclic intermediate IV which is then readily cyclised into the final isolable product III. The rearrangement of isatin into quinolines via the reaction with ketones is a well known reaction.⁶

Also rearrangement of Ia into quinolines via reaction with diazo compounds has been reported.⁷ However, to our knowledge this is the first reported conversion of indoles into quinolines via similar route.

In a fashion similar to the behaviour of Ia towards IIa,b, compound Ib reacted with IIa,b to yield the quinoline derivatives IXa,b.

Compounds Ia,b also reacted with 2-ethoxycarbonylmethyl-2-thiazolin-4-one (X) to yield 1:1 adducts. Several theoretically isomeric structures were considered; however, structure XI could only be intelligibly interpreted for this structure.

Now the behaviour of Ia,b towards a variety of other active methylene reagents is under investigation. Results will be included in another communication.⁵

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