SYNTHESIS OF 1,4-DIHYDRO-4-OXO-3-QUINOLINECARBOXYLIC ESTERS : REGIOSELECTIVITY PROBED BY THE X-RAY STRUCTURE OF A CYCLIZATION INTERMEDIATE.

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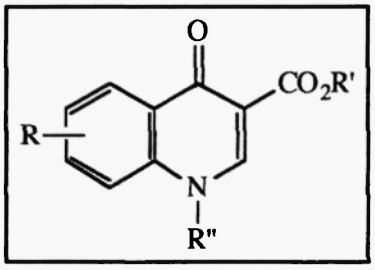
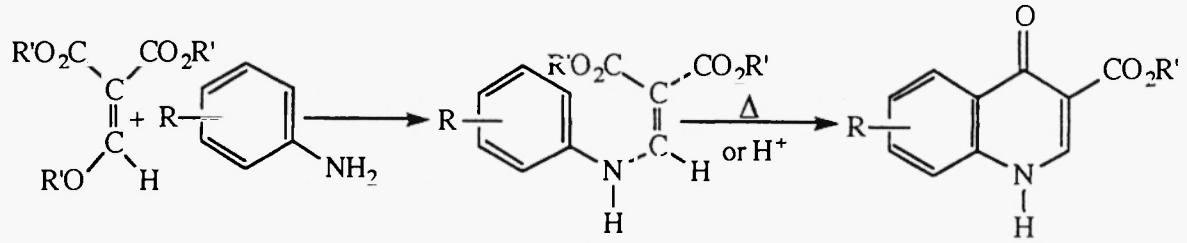
Abstract : 1,4-dihydro-4-oxoquinolines (quinolones) are prepared by cyclization of an arylaminomethylenemalonate precursor; this heterocyclization step is an intramolecular acylation with an ester as acylating reagent. The regioselectivity of ring closure is controled by the directing electronic effects of the substituents and by steric influences. With a precursor having a 3-benzyloxy and a 4-butyl group onto the benzene ring, the regioselectivity is complete and cannot be explained by the sole small steric effect of the benzyloxy group. The X-ray structure of the cyclization intermediate shows that the vicinal substituents present opposed conformations which explain the observed regioselectivity.

Substituted 1,4-dihydro-4-oxo-3-quinoline carboxylic acids and esters (**1**) are useful as drugs (anticoccidians)[1,2] and as intermediates in the synthesis of other medicinal compounds (antimalarian, antiinflammatory and antibacterial derivatives).[3-7]



1 - R= different substituents; R'= H or alkyl; R"= H

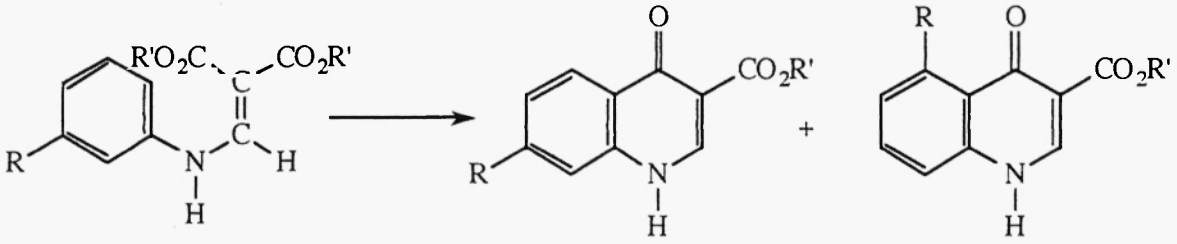
The synthetic process involves two steps where a substituted aniline reacts with an alkoxymethylenemalonic ester to give an intermediate arylaminomethylenemalonate (anilinomethylene dialkyl malonate) which is further cyclized by heating above 250°C (or in the presence of an acid catalyst), to give the 1,4-dihydro-4-oxoquinoline derivative (quinolone) as depicted in sheme 1.[8-12]



SCHEME 1

The heterocyclization step can be regarded as a Friedel-Crafts acylation using an ester as intramolecular acylating reagent.

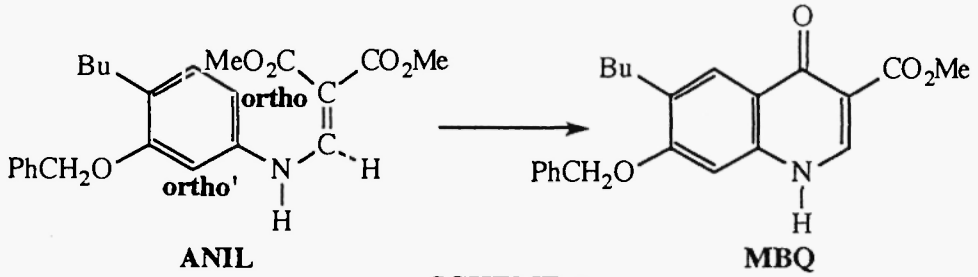
When the arylamino methylenemalonate is not symmetrically substituted on the aryl moiety, different regioisomers can result depending upon the nature of the substituents (sheme 2).[13]



SCHEME 2

This is the case when R is an alkyl or alkoxy substituent : an ortho-para directing effect occurs and two isomers should be obtained.[14]

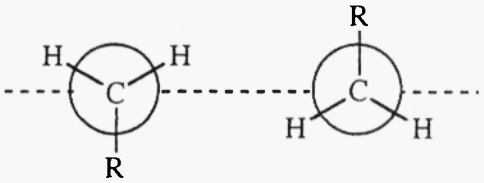
During a study on the improvement of the synthesis of MBQ or "methylbenzoquate" (6-butyl-1,4-dihydro-4-oxo-7-benzyloxy-3-quinoline carboxylic acid methyl ester), we obtained only one isomer in the cyclization step starting from the appropriate intermediate ANIL[15] (3-benzyloxy-4-butyl anilino methylene dimethyl malonate) as outlined in scheme 3.



ANIL **MBQ**

SCHEME 3

The electronic effect of the butyl group, in the 4-position, does not affect the regioselectivity and the electron-donating influence of the benzyloxy group directs the cyclization ortho and ortho' to the nitrogen (to almost comparable amounts based on electronic effects). However, the presence of this benzyloxy substituent reduces the cyclisation on the 2-position and favors the cyclization on the 6-position. The steric effect of the benzyloxy is not large enough (it is not a bulky α-substituted tertiary alkyl group) to explain the total regioselectivity observed. A prefered conformation of the benzyloxy group resulting in a much larger steric effect toward the carbon ortho' to the nitrogen could explain this result, but this was not self-evident, since most vicinal primary alkyl groups attached to a benzene ring, or more generally to a planar framework, are arranged alternatively above and below the plane so as to minimize repulsion.[16]



Therefore they do not display a large steric effect toward adjacent positions. An experimental evidence of the large steric effect of the benzyloxy was therefore needed. Working on the improvement of the synthesis of MBQ, we obtained a very pure cyclization intermediate (ANIL) from which we could grow a single crystal.

The ORTEP view of the X-ray crystallographic molecular structure of ANIL is shown in Figure 1.

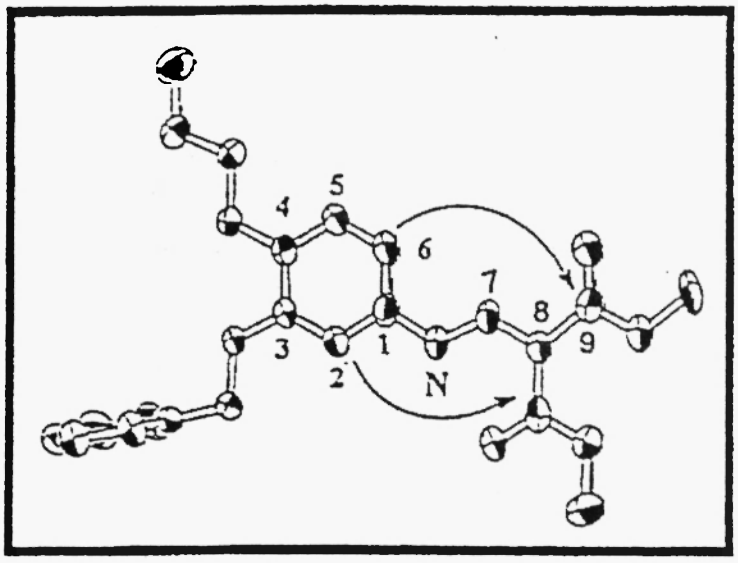
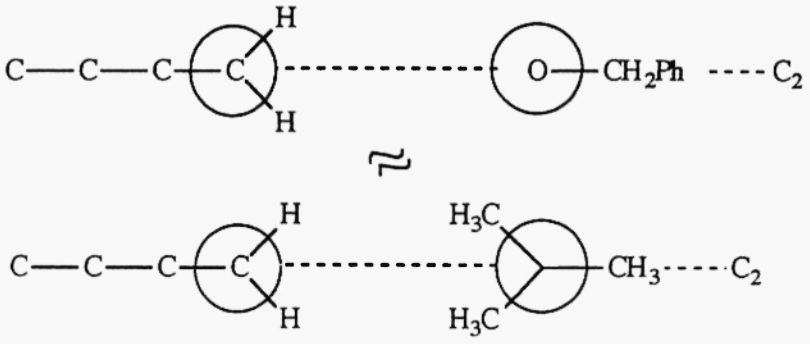


Figure 1- ORTEP view of the molecular structure of ANIL including the atom labelling scheme

The "East"part of the molecule (the aminomethylene malonate moiety) is planar as expected from the conjugation between the two ester groups, the double bond and the lone pair of the nitrogen atom. This conjugation appears by comparing the lengths of the bonds, since single bonds are shorter and double bonds are longer than the average of equivalent bonds[17] e.g. C_7-N : 1,336Å (C-N : 1,47Å); C_7=C_8 : 1,377Å (C=C : 1,335Å); C_8-C_9 : 1,474Å (C-C : 1,544Å).

The major feature concerning the regioselectivity of cyclisation is the relative arrangement of the two substituents butyl and benzyloxy which are in the plane of the ring pointing in opposite directions. When adopting these conformations, the two vicinal substituents display toward the adjacent carbons a very bulky face. In the case of the benzyloxy, the CH_2 (of OCH_2Ph) is in the plane pointing toward C_2 and is equivalent to (or even bulkier than) a tertiary butyl group having a CH_3 pointing in the same direction.



The large steric parameters of a tertiary butyl group (taken from Taft et al.(Es)[17], Charton et al. (υ)[18] or Berg et al. (S^o)[19]) are in full agreement with the total regioselectivity observed in the synthesis of MBQ.

In conclusion, the results reported in this note are a clear-cut evidence that vicinal substituents on aryl and heteroaryl molecules can adopt "opposed" conformations which give large steric effects on adjacent positions. Such conformations can induce a complete regioselectivity in the considered heterocyclization process.

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(20) The authors have deposited tables of crystallographic refinement parameters, atomic coordinates, thermal parameters, structure factors and complete geometry of the compound described in this note with the Cambridge Crystallographic Data Centre. The coordinates can be obtained on request from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB21EZ, UK.

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