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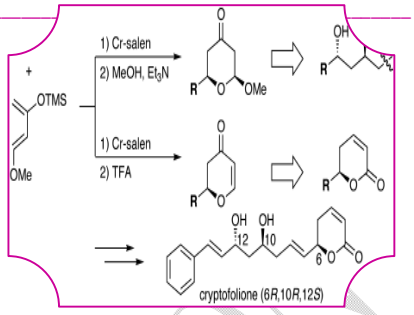
STUDIES ON COMPOUNDS CONSISTING QUINOLINE AND 2-PYRIDONE HETEROCYCLES



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ABSTRACT

Heterocycles incorporating a 2(1H)-pyridone framework constitute an extensively studied class of compounds owing to their diverse biological activities ranging from anti-HIV, antibacterial and antifungal to free radical scavengers. Pyridin- 2(1H)-ones are known to possess a wide range of biological activities such as analgesic, antimalarial, anti-inflammatory, anti-HIV, phytotoxic, antitumoral and antiviral properties. We have tried to designed a novel class of phenylacetic acid isomers possessing N-difluoromethyl-1,2-dihydropyrid-2-one pharmacophore attached to its C-2, C-3 or C-4 position for evaluation as anti-inflammatory agents.

KEYWORDS: *Quinoline derivatives, biological activities, anti-inflammatory agents.*

INTRODUCTION:

Quinoline is a hygroscopic, unpleasant-smelling, colorless, oily liquid. It occurs in coal tar and bone oil, and is made from phenyl amine and nitrobenzene. Quinoline is a basic compound, forming salts with mineral acids and forming quaternary ammonium compounds with haloalkanes. Quinolines and their derivatives are receiving increasing importance due to their wide range of biological and pharmacological activities.

Quinoline ring structure is obtained by *o*-condensation of benzene ring with pyridine. It is also called l-azanaphthalene or benzo[b]pyridine. In quinoline, the nitrogen atom is one atom away from the position at which the rings are fused.

In an isomer, isoquinoline, the nitrogen atom is positioned two atoms away from the fused ring. The numbering in quinoline commences from the nitrogen atom which is assigned first position

Quinoline and isoquinoline are related to pyridine exactly as is benzene related to naphthalene i.e. in the aromatic system, both the molecules contain 10π electrons. The presence of electron donating groups at 2- and 4-positions of quinoline increases the basicity. The pyridine ring in quinoline is electron deficient.

Therefore, nucleophilic attack takes place at the 2- and 4-positions. The π electron densities have been calculated for quinoline by the molecular orbital method and show electron deficiency at these two positions. The electrophilic attack preferably takes place at 5 and 8-positions.

Quinoline is a base since, as for pyridine, the lone pair of electrons on the nitrogen atom is not utilized in its internal resonance. Quinoline is an aromatic compound with resonance energy of 46.8 kcal/mol. The presence of the pyridine nucleus is reflected by the inclusion of doubly charged canonical forms.

Quinoline derivatives are also used for the preparation of nano- and mesostructures having enhanced electronic and photonic properties. Quinolines and their derivatives are very important compounds because of their wide occurrence in natural products**4** and biologically active compounds.

The quinoline nucleus can also be frequently recognized in the structure of numerous naturally occurring alkaloids having interesting pharmacological activity. A large variety of quinolines have displayed interesting physiological activities and found attractive applications as pharmaceuticals and agrochemicals, as well as being general synthetic building blocks.

SYNTHESIS OF QUINOLINE

Recently, more and more new simple and elegant syntheses of substituted quinolines have been described.

Quinolines from arylamine and 1,3-dicarbonyl compounds

Anilines react with 1,3-dicarbonyl compounds to give intermediates, which can be cyclized with acid to give substituted quinolines.

Conard-Limpach-Knorr synthesis uses β-keto esters and leads to quinolones. Anilines and β-keto esters can react at low temperature to give a kinetic product, β-aminoacrylate, cyclization of which gives 4-quinolone.

At higher temperature, β-keto ester anilides are formed and cyclization of these affords 2-quinolones. β-Aminoacrylates, for cyclization to 4-quinolones, are also available via the addition of anilines to acetyllinic esters.

Condensation of a 1,3-dicarbonyl compound with an aryl amine gives a high yield of β-amino-enone, which can then be cyclized with con. acid. Mechanistically, cyclization step can be viewed as an electrophilic substituition by the ortho protonated amino-enone, as showed, followed by loss of water to give aromatic quinoline

Quinolines from aryl amine and α,β-unsaturated carbonyl compounds

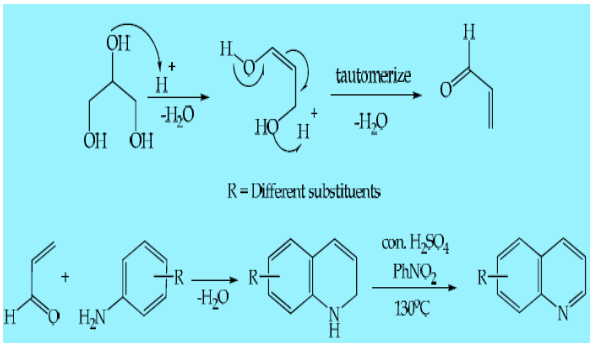
Arylamines react with an α, β-unsaturated carbonyl compound in the presence of an oxidizing agent to give quinolines. When glycerol is used as an in situ source of acrolein, quinolines carrying no substituents on the heterocyclic ring are produced.

In this amazing reaction, quinoline is produced when aniline, concentrated sulphuric acid, glycerol and mild oxidizing agent are heated together.

The reaction has been shown to proceed by the dehydration of glycerol to acrolein to which aniline then adds in a conjugate fashion.

Acid-catalyzed cyclization produces 1,2-dihydro quinoline finally dehydrogenated to quinoline by the oxidizing agent.

The corresponding nitrobenzene or arsenic acid has been used classically, though with the inclusion of a little sodium iodide, the sulfuric acid can serve as oxidant.



Biological outline of quinoline

Quinolines and their derivatives are important constituents of pharmacologically active synthetic compounds, as these systems have been associated with a wide spectrum of biological activities such as antibacterial, antifungal, anti-inflammatory, anticancer, etc.

2-Pyridone is an organic colourless solid compound, used in peptide synthesis.

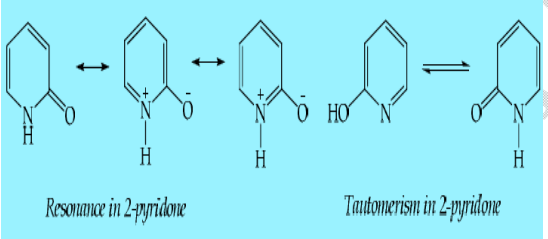
2-Pyridone is a multiple bioactive small molecule and an important pharmacophore that can form hydrogen bonded structures related to the base-pairing mechanism found in DNA and RNA. The most prominent feature of 2-pyridone is the amide group; a nitrogen with a hydrogen bound to it and a keto group next to it.

In peptides, amino acids are linked by this pattern, a feature responsible for some remarkable physical and chemical properties.

In this and similar molecules, the hydrogen bound to the nitrogen is suitable to form strong hydrogen bonds to other nitrogen and oxygen containing species. 2-Pyridones are in tautomeric equilibrium with isomers bearing hydroxyl group at second position. It is because it retains aromaticity within the nitrogen atom donating its lone pair electrons to the aromatic sextet.

The two forms are interchanged via the intramolecular proton transfer between the amine hydrogen and the carbonyl oxygen of the molecule.

The pyridone forms are favoured in ionic solvents and also in the solid state. 2-Pyridones are weak acids having pKa≈11. Deprotonation in a basic medium produces ambident anions, which can be attacked by electrophiles O, N and C.



The 2(1*H*)-pyridone ring system and the corresponding dihydro and tetrahydro derivatives are found abundantly in a wide variety of naturally occurring alkaloids and novel synthetic biologically active molecules.

A new pyridone alkaloid, militarinone A, has a pronounced neurotrophic effect. Lyconadin A, a Lycopodium alkaloid with a unique pentacyclic skeleton that contains a 2-pyridone moiety was demonstrated to possess modest anticancer activity.

Harzianopyridone is representative of the atpenin class of penta-substituted pyridine based natural product that was reported to be potent inhibitor of SQR.

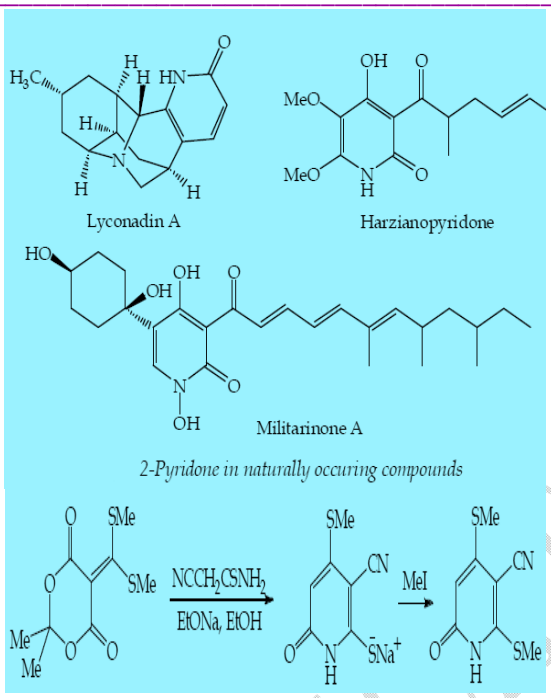
Harzianopyridone is generally represented in the literature as the 4-hydroxy-2-pyridone tautomer. Substituted 2-pyridones represent useful scaffolds for drug discovery and are also versatile synthetic building blocks. 2-Pyridones constitute important core units in a large number of pharmaceuticals, agrochemicals, and functional materials.

Methods for the preparation of 2-oxopyridine

Krivokolysko S G et al. have used Meldrum's acid to synthesize sulfur containing partially hydrogenated pyridones.

They have prepared non-hydrogenated pyridones by the reaction of di(methylthio) methylenesubstituted Meldrum's acid with cyanothioacetamide by boiling in ethanol in the presence of sodium ethoxide.

The synthesized sodium pyridine-2-thiolate was converted into the corresponding sulphide by alkylation with methyl iodide.



PHYSICAL CONSTANTS OF
6-AMINO-1-((2-CHLORO-6-ETHOXYQUINOLIN-3-YL)
METHYLENEAMINO)-4-(ARYL)-2-OXO-1,2- DIHYDROPYRIDINE-3,5-DICARBONITRILES

EXPERIMENTAL PROCEDURE:

Synthesis of *N*'-((2-chloro-6-ethoxyquinolin-3-yl)methylene)-2-cyanoacetohydrazide (III)

To a solution of compound in 1,4-dioxan, 2-cyanoacetohydrazide was added portion-wise with stirring. The resulting mixture was refluxed for one hr and cooled down to room temperature.

The separated solid was filtered and
recrystallized from the mixture of chloroform and methanol.

Yield: 88%; m.p.: 205°C; Elemental anal. obs. C, 56.56%; H, 4.01%; N, 17.56%. Calcd. For C15H13ClN4O2: C, 56.88%; H, 4.14%; N, 17.69%.

The progress of the reaction and the purity of the compound was checked on TLC plates using ethyl acetate:n-hexane (2:8) as an irrigator and the plates were developed in an iodine chamber.

Synthesis of 6-amino-1-((2-chloro-6-ethoxyquinolin-3-yl)methyleneamino)-4-(4-methoxyphenyl)-2-oxo-1,2-dihydropyridine-3,5-dicarbonitrile (JH5-3)

A mixture containing compound (0.01 mole), 2-(4-methoxybenzylidene) malononitrile(0.01 mole) and 2 drops of piperidine in absolute ethanol (50 mL) was
refluxed for 2-3 hrs.

The mixture was then cooled down to room temperature and the crystals formed were filtered, air dried and recrystallized from aqueous DMF.

Yield: 60%; m.p.: 248°C; Elemental anal. obs. C, 62.41%; H, 3.67%; N, 16.56%. Calcd. for C26H19ClN6O3: C, 62.59%; H, 3.84%; N, 16.84%.

The progress of the reaction and the purity of the compound was checked on TLC plates using ethyl acetate:n-hexane (2:8) as an irrigator and the plates were developed in an iodine chamber.

All other compounds of this series were prepared by using the same method and their physical data are recorded.

-R	Molecular Formula	Yield (%)	M.P. (°C)	Elemental Analysis					
				% Carbon		%Hydrogen		% Nitrogen	
				Req	Obs	Req	Obs	Req	Obs
-H	$C_{25}H_{17}ClN_6O_2$	59	243	64.04	63.86	3.65	3.55	17.92	17.78
-4-CH_3	$C_{26}H_{19}ClN_6O_2$	58	250	64.66	64.44	3.97	3.65	17.40	17.21
-4-OCH_3	$C_{26}H_{19}ClN_6O_3$	60	248	62.59	62.41	3.84	3.67	16.84	16.56
-3,4,5-$(OCH_3)_3$	$C_{28}H_{23}ClN_6O_5$	61	240	60.16	59.98	4.15	4.02	4.15	3.97
-3-OH	$C_{25}H_{17}ClN_6O_3$	58	241	61.92	61.67	3.53	3.34	17.33	17.22
-4-OH	$C_{25}H_{17}ClN_6O_3$	59	247	61.92	61.70	3.53	3.40	17.33	17.22
-3-NO_2	$C_{25}H_{16}ClN_7O_4$	59	258	58.43	58.01	3.14	2.97	19.08	18.87
-4-NO_2	$C_{25}H_{16}ClN_7O_4$	62	256	58.43	58.21	3.14	2.99	19.08	18.88
-4-F	$C_{25}H_{16}ClFN_6O_2$	58	245	61.67	61.45	3.31	3.03	17.26	17.00
-2-Cl	$C_{25}H_{16}Cl_2N_6O_2$	60	239	59.66	59.33	3.20	3.00	16.70	16.50

CONCLUSION:

In this article we have described a rapid, efficient, environmentally and economically benign method for the synthesis of quinoline derivatives by the condensation under solvent-free conditions with the excellent yields.

REFERENCES:

1. Bansal K R, "*Test book of Heterocyclic Chemistry",* New age International Publishers, New Delhi, 389, **2001**.
2. Malcolm S, "*Heterocyclic Chemistry*", Royal Society of Chemistry, Cambridge, UK, 43, **2001**.
3. (a) Zhang X, Shetty A S, Jenekhe S A, *Macromolecules*, 32, 7422, **1999**; (b) Jenekhe S A, Lu L, Alam M M, *Macromolecules*, 34, 7315, **2001**.
4. (a) Morimoto Y, Matsuda F, Shirahama H, *Synlett*, 202, **1991**; (b) Balasubramanian M, Keay J G In "*Comprehensive Heterocyclic Chemistry II*", Katritzky A R, Rees C W, Scriven E F V (ed.) Pergamon, New York, 5, 245, **1996**; (c) Michael J P, *Nat. Prod. Rep.*, 14, 605, **1997**.
5. (a) Markees D G, Dewey V C, Kidder G W, *J. Med. Chem.*, 13, 324, **1970**; (b) Campbell S F, Hardstone J D, Palmer M J, *J. Med. Chem.*, 31, 1031, **1988**; (c) Maguire M P, Sheets K R, McVety K, Spada A P, Zilberstein A, *J. Med. Chem.*, 37, 2129, **1994**; (d) Kalluraya B, Sreenivasa S, *Farmaco,* 53, 399, **1998;** (e) Roma G, Braccio M D, Grossi G, Mattioli F, Ghia M, *Eur. J. Med. Chem.*, 35, 1021, **2000**; (f) Chen Y L, Fang K C, Sheu J Y, Hsu S L, Tzeng C C, *J. Med. Chem.*, 44, 2374, **2001**.
6. (a) Shiokawa K, Tsuboi S, Moriya K, In *8th International Congress of Pesticide Chemistry Option, **2000***; Ragsdale N N, Kearney P C, Plimmer J R, ed., *Am. Chem. Soc.*, Washington DC, U. S. A., p 49, **1995**; (b) Werbitzky O, Studer P, U. *S. Patent,* 6022974, Feb. 8, 2000; *Chem. Abstr.*, 120, 134302, **1997**.
7. Dinesh K R, Kanak K M, Thota S and Chien-Hong C, *J. Org. Chem.,* 66, 3646, **2001**.
8. (a) Hart F A, *J. Chem. Soc.*, 3324, **1960**. (b) Witting G, Benz E, *Chem. Ber.*, 92, 1999, **1959**; (c) Kakusawa N, Sakamoto K, Kurita J, Tsuchiya T, *Heterocycles*, 43, 2091, **1996**; (d) Yamashita Y, Hayashi T, MasumuraM, *Chem. Lett.*, 9, 1133, **1980**.
9. Ozturk G, Erol D D, Uzbay T, Aytemir M D, *Farmaco*, 56, 251, **2001**.
10. Findlay J A, Tam W H J, Krepinsky J, *Can. J. Chem.*, 56, 613, **1978**.
11. Abadi A, Al-Deeb O, Al-Afify A, El-Kashef H, *Farmaco*, 54, 195, **1999**.
12. Storck P, Aubertin A, Grierson D S, *Tetrahedron Lett.*, 46, 2919, **2005**.
13. Macdonald G E, Puri A, Shillinget D G, *Weed Sci.,* 56, 189, **2008**.
14. Wakabayashi K, Böger P, *Weed Biol. Manag.*, 4, 59, **2004**.
15. Evidente A, Fiore M, Bruno G, Sparapano L, Motta A, *Phytochemistry*, 67, 1019, **2006**.
16. Cocco M T, Congiu C, Onnis V, *Eur. J. Med. Chem.*, 35, 545, **2000**.
17. Cocco M T, Congiu C, Onnis V, *Eur. J. Med. Chem.*, 38, 37, **2003**.
18. Edward E K, Gang Y, Morshed A C, Khaled R A, Abdellatif, *Bioorg. Med. Chem. Lett.*, 20, 896, **2010**.
19. Makoto A, Nagaaki S, Tsuyoshi N, Keita N, Shiho I, *Bioorg. Med. Chem.*, 17, 6106, **2009**.
20. Cocco M T, Congiu C, Onnis V, *Eur. J. Med. Chem.*, 35, 545, **2000**.

21. Collins I, Moyes C, Davey W B, Rowley M, *J. Med. Chem.*, 45, 1887, **2002**.
22. KimK S, Zhang L, Schmidt R, Wei D,Williams D K, *J.Med. Chem.*, 51, 5330, **2008**.
23. Ammar Y A, Ismail M M F, El-Sehrawi H M, Noaman E, *Arch. Pharm. Chem. Life Sci.*, 339, 429, **2006**.
24. Rollas S and Küçükgüzel S G, *Molecules,* 12, 1910, **2007**.
25. Gürsoy E, Güzeldemirci-Ulusoy N, *Eur. J. Med. Chem.*, 42, 320, **2007**.