SYNTHESIS OF SOME NEW 3-SUBSTITUTED-4-HYDROXY-1--METHYL-QUINOLIN-2-ONE DERIVATIVES AS POTENTIAL ANTIBACTERIAL AND ANTIFUNGAL AGENTS

Margret Mansour GIRGES[a], Mokhtar Ayad HANNA[b,*], Hussien Mohamed HASSAN[a] and Evelin Boshra MOAWAD[a]

Chemistry Department,
[a] Mansoura and [b] Damiatta Faculties of Science,
Mansoura University, Mansoura, Egypt

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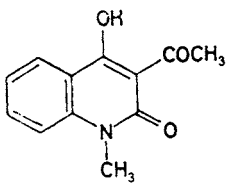
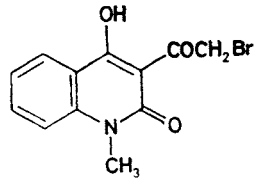
3-Acetyl-4-hydroxy-1-methylquinolin-2-one (*I*) and its bromo derivative *II* were allowed to react with different reagents to get new quinoline derivatives that have different heterocyclic moieties at position 3. The antibacterial and antifungal activities of the products were also evaluated.

The chemotherapeutic activities of 4-hydroxyquinolin-2-one derivatives[1-4] led us to study the various changes in their structures in order to synthesize more potent drugs. One of these variations is the introduction of different heterocyclic moieties at the position 3 of the quinoline nucleus. So, 3-bromoacetyl-4-hydroxy-1-methylquinolin-2-one (*II*) and its precursor *I* generate great interest as a versatile intermediate in synthesis of compounds *III* – *VIII* with a view of evaluating their antibacterial and antifungal activities.



I

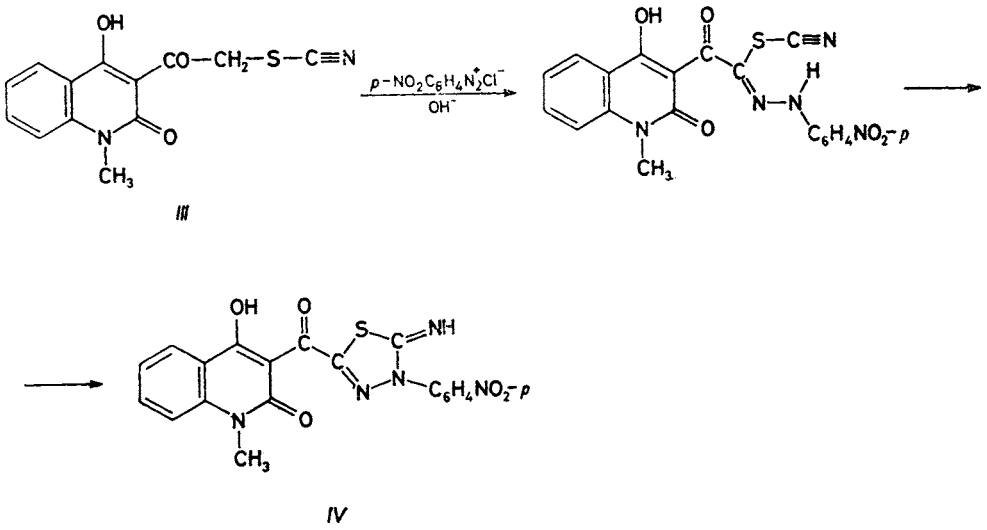


II

In view of the reported synthesis of 1,3,4-thiadiazolines[5] via the reaction of arene diazonium salts with active methylene thiocyanate compounds, it seemed of interest to study the possibility of synthesizing 3-thiadiazolinoylquinolinone derivative *IV* using quinolinoylmethyl thiocyanate *III* as a key intermediate. The desired thio-

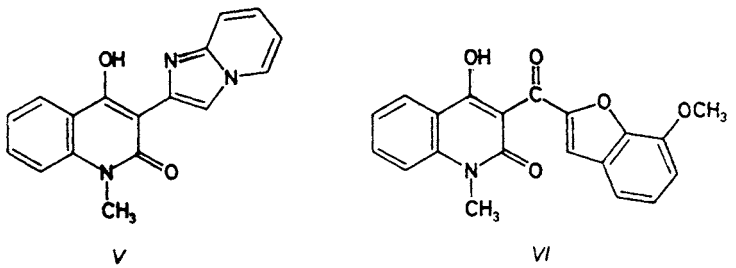
* To whom correspondence should be addressed.

cyanate *III* was obtained from *II* and subjected to coupling as depicted by Scheme 1. The structure of compound *IV* as well as the intermediate compound *III* was confirmed by elemental and spectral data.



SCHEME 1

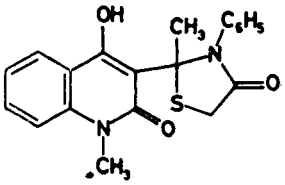
The use of phenacyl halides[6,7] for alkylation on ring nitrogen atom of 2-aminopyridine with the formation of intermediate product that is easily cyclized by heating to imidazo[1,2-*a*]pyridine, was promptive to study the possibility of using 3-(bromoacetyl)quinoline derivative for alkylation of 2-aminopyridine, aiming to get new quinoline derivative that include the imidazopyridyl moiety in position three of its structure. Thus, when 3-bromoacetyl-4-hydroxy-1-methylquinolin-2-one (*II*) was heated with 2-aminopyridine in ethanol, 4-hydroxy-3-(imidazo[1,2-*a*]pyrid-2-yl)--1-methylquinolin-2-one (*V*) was formed in good yield.



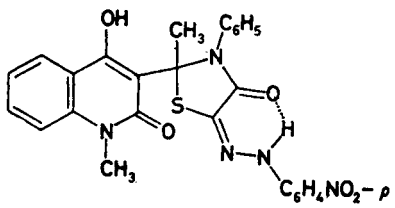
V *VI*

Freudenberg[8] reported the synthesis of benzofuran derivatives by condensation of salicylaldehyde or its derivatives with phenacyl bromide. Accordingly compound *II* was treated with *o*-vaniline – taken as an example for salicylaldehyde derivative – to introduce a benzofuranoyl moiety in the position 3 of compound *I*. The product proved to be 4-hydroxy-3-(7-methoxybenzofuran-2-oyl)-1-methylquinolin-2-one (*VI*).

The pharmacological activity of 4-thiazolidinone derivatives[9-11] was promptive to synthesize 4-hydroxy-3-(2-methyl-4-oxo-3-phenylthiazolidin-2-yl)-1-methylquinolin-2-one (*VII*). The latter was obtained through condensation of *I* with aniline and mercaptoacetic acid. A further thiazolidinone derivative *VIII* was obtained via coupling of arene diazonium salt, namely, *p*-nitrobenzenediazonium chloride with *VII*.



VII



VIII

The compounds prepared were also tested in vitro for antibacterial and/or antifungal activities. The microorganism and the minimum inhibitory concentrations in μg/ml are given unless they exceed 100 μg/ml: *Staphylococcus albus*, *I* 25, *II* 75, *III* 7·5, *IV* 50, *V* 7·5, *VI* 25, *VII* 25, *VIII* 7·5; *Staphylococcus aureus*, *I* 50, *II* 75, *III* 100, *IV* 75, *VII* 25, *VIII* 25; *Escherichia coli*, *I* 50, *II* 50, *IV* 25, *V* 50, *VI* 25, *VII* 50; diplococcal *Neisseria catarrhalis*, *I* 7·5, *III* 7·5, *IV* 50, *V* 7·5, *VI* 75, *VII* 7·5, *VIII* 7·5; *Saccharomyces cerevisiae*, *VI* 100, *VII* 7·5.

EXPERIMENTAL

Temperature data are uncorrected. Melting points were determined on a Fisher–Johns apparatus. IR spectra (KBr) were recorded on an SP 2000 Pye–Unicam spectrometer. ^{1}H NMR spectra ($CDCl_3$) were performed on Varian EM 360 NMR spectrometer (60 MHz).

3-(Bromoacetyl)-4-hydroxy-1-methylquinolin-2-one (*II*)

A mixture of 3-acetylquinolinone derivative *I* (ref.[12]) (2·2 g; 0·01 mol), N-bromosuccinimide (1·93 g; 0·01 mol) and a catalytic amount of benzoyl peroxide (two crystals) in carbon tetrachloride (40 ml) was refluxed for six hours, after which the precipitated succinimide was removed by filtration and the filtrate was cooled. The yellow crystals that formed after short time were removed by filtration and recrystallized from light petroleum (60/80) as pale yellow crystals; yield 1·95 g (66%); m.p. 177°C. For $C_{12}H_{10}BrNO_3$ (296·1) calculated: 48·67% C, 3·40% H, 26·99% Br, 4·73% N; found: 48·62% C, 3·44% H, 27·28% Br, 4·69% N. IR spectrum (cm^{-1}): 3 450 (enolic OH), 1 710 (CO of bromoacetyl group), 1 665 (amidic CO).

4-Hydroxy-1-methyl-3-(thiocyanatoacetyl)quinolin-2-one (*III*)

A solution of 3-bromoacetyl derivative *II* (2·96 g; 0·01 mol) in ethanol (30 ml) was added to a solution of potassium thiocyanate (1·54 g; 0·01 mol) in ethanol (10 ml) and the mixture was heated for 2 h while stirring on a water bath. The precipitated solid that separated on cooling was filtered off and recrystallized from ethanol to give the product as yellowish brown crystals; yield 2·47 g (90%); m.p. above 300°C. For $C_{13}H_{10}N_2O_3S$ (274·3) calculated: 56·92% C, 3·67% H, 10·22% N, 11·69% S; found: 57·09% C, 3·64% H, 10·32% N, 11·98% S. IR spectrum (cm^{-1}): 3 500 (enolic OH), 2 130 (—SCN), 1 700 (CO of thiocyanatoacetyl), 1 660 (amidic CO).

4-Hydroxy-3-(5-imino-4-*p*-nitrophenyl-Δ^2-1,3,4-thiadiazolin-2-oyl)-1-methylquinolin-2-one (*IV*)

To a stirred, cooled solution of the active methylene thiocyanate *III* (1·48 g; 0·005 mol) in pyridine (10 ml), *p*-nitrobenzenediazonium chloride (0·005 mol — prepared from 0·8 g *p*-nitroaniline) was added protionwise over a period of 30 min without allowing the temperature to rise above 5°C. When the addition was complete, the reaction mixture was stirred for an additional 15 min and left overnight in a refrigerator. Acidification with dil. HCl yielded orange solid which was filtered and recrystallized from ethanol to give 1·48 g (70%) of the product; m.p. 150°C. For $C_{19}H_{13}N_5O_5S$ (423·4) calculated: 53·89% C, 3·09% H, 16·54% N, 7·57% S; found: 53·74% C, 2·99% H, 16·63% N, 7·33% S. IR spectrum (cm^{-1}): 3 500 (—C=C—OH), 3 325 (imino NH), 1 670 (unsat. CO), 1 660 (amidic CO), 1 625 (C=N). ^{1}H NMR (δ, ppm): 2·9 s, 3 H (N—CH_3); 5·8 s, 1 H (=NH); 7·2—7·6 m, 8 H (aromatic); 11·9 s, 1 H (OH).

4-Hydroxy-3-(imidazo[1,2-*a*]pyrid-2-yl)-1-methylquinolin-2-one (*V*)

To a solution of 2-aminopyridine (0·2 g; 0·002 mol) in ethanol (15 ml) the bromoacetyl derivative *II* (0·6 g; 0·002 mol) was added and the mixture was refluxed for 2 h. Evaporation of solvent followed by heating the residue with aqueous sodium acetate solution (10%, 20 ml for 15 min) gave brown solid which was crystallized from ethanol as brown crystals; yield 0·35 g (60%); m.p. above 300°C. For $C_{17}H_{13}N_3O_2$ (291·3) calculated: 70·09% C, 4·50% H, 14·42% N; found: 70·32% C, 4·59% H, 14·36% N. IR spectrum (cm^{-1}): 3 500—3 300 (enolic OH), 1 670 (CO, amidic), 1 580 (C=N).

4-Hydroxy-3-(7-methoxybenzofuran-2-oyl)-1-methylquinolin-2-one (*VI*)

Potassium hydroxide (0·6 g) was added carefully to a mixture of 3-bromoacetyl derivative *II* (2·96 g; 0·01 mol), *o*-vaniline (0·012 mol) in ethanol (20 ml). The mixture was heated on water bath for 5 h, cooled and poured into stirred water (150 ml). The resulting granular brown solid was filtered and recrystallized as yellowish green crystals; yield 3·49 g (100%); m.p. 156°C. For $C_{20}H_{15}NO_5$ (349·3) calculated: 68·77% C, 4·33% H, 4·01% N; found: 68·63% C, 4·30% H, 4·17% N. IR spectrum (cm^{-1}): 3 600 (enolic OH), 1 670 (unsat. CO), 1 660 (amidic CO). ^{1}H NMR (δ, ppm): 2·9 s, 3 H (N—CH_3); 3·8 s, 3 H (OCH_3); 6·2 s, 1 H (H-3 of benzofuran); 7—7·8 m, 7 H (aromatic); 11·8 s, 1 H (OH).

4-Hydroxy-3-(2-methyl-4-oxo-3-phenylthiazolidin-2-yl)-1-methylquinolin-2-one (*VII*)

A mixture of 3-acetylquinoline derivative *I* (0·01 mol), aniline (0·01 mol), thioglycollic acid (0·01 mol) and a catalytic amount of anhydrous zinc chloride in benzene (100 ml) was refluxed for 10 h. The solvent was evaporated in vacuo and the residue washed successively with 10 ml

dil. HCl, 10% sodium bicarbonate solution (50 ml) and triturated with ethanol. The produced solid was collected by filtration and recrystallized from ethanol to give *VII* as yellow solid; yield 3·04 g (83%); m.p. 240°C. For $C_{20}H_{18}N_2O_3S$ (366·4) calculated: 65·56% C, 4·95% H, 7·65% N, 8·75% S; found: 65·82% C, 4·82% H, 7·73% N, 8·61% S. ^{1}H NMR spectrum (δ, ppm): 1·2 s, 3 H (C—CH_3); 2·8 s, 3 H (N—CH_3); 4·25 s, 2 H (CH_2); 7·1—7·9 m, 9 H (Ar); 11·8 s, 1 H (OH). IR spectrum (cm^{-1}): 3 600 (enolic OH), 1 675 (CO), 1 660 (CO-amidic).

4-Hydroxy-3-(4,5-dioxo-2-methyl-3-phenyl-5-*p*-nitrophenylhydrazonothiazolidin-2-yl)-1--methylquinolin-2-one (*VIII*)

p-Nitroaniline (0·005 mol) dissolved in conc. HCl (2 ml) and water (2 ml) was diazotised with sodium nitrite (0·25 g in 20 ml of water) in an ice bath. The diazo solution thus prepared was added gradually with stirring to a previously cooled solution of thiazolidinone derivative *VII* (0·005 mol). The azodye separated was filtered, dried and recrystallized from ethanol as orange crystals; yield 1·96 g (76%); m.p. 256°C. For $C_{26}H_{21}N_5O_6S$ (515·5) calculated: 60·57% C, 4·11% H, 13·59% N, 6·22% S; found: 60·75% C, 4·04% H, 13·70% N, 6·02% S. IR spectrum (cm^{-1}): 3 600 (enolic OH), 1 705 (CO, thiazolidinone moiety), 1 655 (amidic CO). The bathochromic shift for the carbonyl absorption in thiazolidinone moiety is due to hydrogen bonding.

In vitro Studies of Antibacterial and Antifungal Activities for the Prepared Compounds

The bacteriostatic effect for the prepared compounds were determined by the agar diffusion sensitivity test. The microorganisms were purely cultured on bactonutrient broth and bactonutrient agar[13]. The antifungal activity was tested using the turbidimetric method[14].

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