180 °C for another 1 h. The mixture was cooled and the solid obtained was crystallized (cf. Table 1).

REFERENCES

Some New Quinolones of Expected Pharmaceutical Importance Derived from 1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde

E. A. MOHAMED

Department of Chemistry, Faculty of Education,
Ain-Shams University, Roxy, Cairo, Egypt

Received 7 July 1993

The title compound was condensed with various amino derivatives giving rise to new quinolones of expected biological activity, especially the condensation products of thiosemicarbazide and its derivatives. For the purpose of inducing and/or improving the pharmaceutical importance of the latter products, they were subjected to certain cyclization reactions, affording new quinolones substituted with heterocyclic rings. The structures of certain other new quinolones were elucidated by preparing them by two different routes, using interesting reagents. Condensation of 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline with certain compounds having active methylene groups was also studied.

It is reported in the literature that 1,2-dihydro-4-hydroxy-2-oxoquinolines are of great medicinal importance [1—6]. On the other hand, thiosemicarbazones, triazinoindoles, bariuric acid, thio-barbituric acid, and pyrazolones show antimicrobial, antitumour activities and possess a wide spectrum of medicinal properties [7—10]. This led to the decision to combine quinoline with each of these mentioned and some other heterocyclic substrates with the aim to obtain new compounds of higher and modified biological activities.

In order to achieve this purpose, it was necessary to synthesize a formyl derivative of quinolone and condense it with thiosemicarbazides and other reagents. Thus 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline (I, Scheme 1), which was synthesized according to the novel method described by the author [11], was formylated following the procedure, reported by Tomita [1] to give 1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde (II).

This aldehyde II condensed readily with thiosemicarbazide, phenyl, p-anisyl, and allylthiosemicarbazide to afford the desired thiosemicarbazones IIa—IIIId, which were also obtained when the hydrazone IV (preliminarily produced by condensing the aldehyde II with excess hydrazine hydrate) was

reacted with isothiocyanates. It is of interest herein to report that if the condensation of the aldehyde II with hydrazine hydrate was carried out at the mass ratio 2 : 1 the bis-azine derivative V was obtained. It was planned for the cyclization of the thiosemicarbazone III to certain heterocyclic ring, aiming to synthesize new quinolones bearing heterocycles, which may have certain chemotherapeutic properties. This was achieved by heating IIb in DMF, leading to the loss of one molecule of water and formation of the triazepine derivative VI. Another cyclization was carried out by reacting IIIa with oxalyl chloride producing the imidazolidine derivative VII. Cyclization to thiobarbituric acid derivative VIII, was affected by action of diethyl malonate on IIIa.

Other interesting quinolones of expected biological activity were prepared by reacting the formyl compound II with certain ammonia derivatives. So when II was reacted with ethyl carbamate, it gave the imino ester IX, which underwent condensation with hydrazine hydrate, affording X, which is impossible to be obtained from the direct condensation of II with semicarbazide. Indeed when condensation was carried out between II and semicarbazide, it gave rise to the semicarbazone XI which is completely different when compared to X. An interesting compound, of expected medicinal properties, was obtained when X was reacted with phenyl isothiocyanate, that is the phenylthiocarbamoyl derivative XII.

In continuation of condensation of the aldehyde II with some biologically active ammonia derivatives, II was subjected to react with isatin-3-hydrazone [12], 3-hydrazino-5H-1,2,4-triazinoindole [13], and oxalyl dihydrazide to produce the azines XIII, XIV, and the oxalyl dihydrazide XV (Scheme 2), respectively. The azine XIII was also obtained by reacting the hydrazone IV with isatin, similarly XV was obtained by condensing IV with oxalyl chloride, however many trials had failed to produce XIV by reacting IV with (2H,5H)-1,2,4-triazino [5,6-b] indole-3-thione.

Again the aldehyde II was used in the production of heterocycles fused or substituted to quinolone, by its condensation with some compounds having active methylene group, aiming to obtain new members of this category of compounds which may have important applications. It was planned to synthesize...
NEW QUINOLONES

the barbituric acid derivative XVIII (Scheme 3) by condensing the aldehyde II with malonate ester with the aim to obtain a simple condensation product XVI', which may react with thiourea to give the target compound XVIII. On doing so the resultant compound was not the thiobarbituric acid derivative XVIIIa but a half ester derivative XVII. This may be explained by the following facts: The obtained compound of the reaction between II and malonate was found to be a condensation-cyclization product XVI, where the expected simple condensation product XVI' was formed as an intermediate in this reaction which cyclized readily to XVI. This pyrano ester XVI was identical in every respect to an authentic sample synthesized according to Hans and Hans [14] by reacting I with ethoxymethylenediacetyl malonate. This pyrano ester derivative XVI was hydrolyzed to the half ester XVII when treated with thiourea in the presence of sodium ethoxide where thiourea did not play any role, but it was only the effect of the alkali, which was proved by treating XVI with dilute sodium hydroxide solution on cold, to give one and the same

Scheme 3

E. A. MOHAMED

product XVII. The target compound XVIIa, XVIIb was prepared by direct condensation of the aldehyde II with thiobarbituric acid or barbituric acid.

A similar cyclo-condensation reaction occurred when the aldehyde II was treated with malononitrile, giving rise to the pyrononitrile derivative XIX, which is identical to an authentic sample prepared according to the method described by Hans and Hans [14].

A similar cyclo-condensation reaction occurred when the aldehyde II was treated with malononitrile, giving rise to the pyrononitrile derivative XIX, which is identical to an authentic sample prepared according to the method described by Hans and Hans [14].

The formation of XIX by the action of malononitrile on II, may happen via cyclization of the dicyano compound XIX', which is preliminarily formed, into the pyrazoline derivative XIX'', followed by the hydrolysis of the latter compounds, though neither XIX' nor XIX'' could be separated.

An interesting group of condensation reagents, which have active methylene group are pyrazolones and especially those substituted at the positions 1 and 3. From these reagents, 3-methyl-, 3-phenyl-, and 1,3-diphenyl-5-pyrazolinone were selected for condensation with formylquinolone II to afford compounds XXa—XXc.

The pyrazolinone ring of XX is decomposed, when this compound is treated with sulfuryl chloride, this ring opening is accompanied with chlorination of the quinolone ring at the position 3, giving rise to the acid XX'/.

EXPERIMENTAL

Melting points are uncorrected and were measured in open capillary tubes. IR spectra (KBr discs) were recorded on a Perkin—Elmer, model 593, spectrometer.

$^1$H NMR spectra were taken on a Varian EM 390 spectrometer (90 MHz), using TMS as an internal standard and DMSO-$d_6$ as solvent. 1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde (II) was prepared as described by Tomita [1]. The physical and spectral data of all new synthesized compounds are listed in Table 1.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde Thiosemicarbazone (IIa), Phenylthiosemicarbazone (IIb), p-Anisylthiosemicarbazone (IIc), and Allylthiosemicarbazone (IIId)

A mixture of the aldehyde II (0.01 mol) and thiosemicarbazide, phenylthiosemicarbazide, p-anisylthiosemicarbazide or allylthiosemicarbazide (0.012 mol) in ethanol (30 cm$^3$) was refluxed on a water bath for 1 h. The yellowish solid mass formed was filtered off and recrystallized from the proper solvent.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde Hydrazone (IV)

A hot solution of the aldehyde II (0.01 mol) in 50 cm$^3$ of ethanol was mixed with hydrazine hydrate (0.2 mol) and the reaction mixture was then refluxed for 4 h. The pale yellow crystals formed were filtered off and recrystallized.

Formation of III from IV

To a suspension of the hydrazone IV (0.01 mol) in ethanol (30 cm$^3$) phenyl or allylthiocarbamate (0.01 mol) was added and the mixture was refluxed for 20 min. The solid formed was filtered off and crystallized to afford compounds IIIb and IIId, respectively, identified by their melting point, mixed melting point, and spectral data.

Bis(1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde)azine (V)

A solution of the aldehyde II (0.01 mol) in ethanol (50 cm$^3$) was refluxed with hydrazine hydrate (0.005 mol) for 4 h. The yellow deposit was filtered off and crystallized.

7-Methyl-1-phenyl-6-oxo-2-thioxo-1,3,7-trihydroquino[4,3-e]-1,2,4-triazepine (VI)

The thiosemicarbazone derivative IIIb (1 g) was refluxed for 1 h in DMF (15 cm$^3$), upon cooling this solution VI was deposited.

1,2-Dihydro-3-(4,5-dioxo-2-thioxo-1-imidazolidinyliminomethyl)-4-hydroxy-1-methyl-2-oxoquinoline (VII)

To a suspension of compound IIIa (0.005 mol) in dry benzene (25 cm$^3$), oxalyl chloride (0.008 mol) was added with stirring. The reaction mixture was then refluxed for 2 h and the canary yellow solid product was filtered off, washed with methylene chloride, dried and crystallized.

1,2-Dihydro-3-(4,6-dioxo-2-thiohydropyrimidin-1-yl)-4-hydroxy-1-methyl-2-oxoquinoline (VIII)

A mixture of thiosemicarbazone IIIa (0.01 mol), diethyl malonate (0.015 mol), and diphenyl ether (15 cm$^3$) was heated under reflux for 6 h. The mixture was cooled and triturated with diethyl ether (30 cm$^3$). After standing for 12 h the precipitate was filtered off, washed with diethyl ether and recrystallized.

1,2-Dihydro-3-ethoxycarbonyliminomethyl-4-hydroxy-1-methyl-2-oxoquinoline (IX)

A suspension of the aldehyde II (0.01 mol) in methanol (50 cm$^3$) was treated with ethyl carbamate (0.011 mol) and the reaction mixture was refluxed...
### NEW QUINOLONES

**Table 1. Physical Data and Spectral Analysis of the New Compounds**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>Molecular Weight</th>
<th>Yield</th>
<th>M.p.</th>
<th>IR, $\nu/cm^{-1}$</th>
<th>$^1H$ NMR, $\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIa</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>276</td>
<td>52.17</td>
<td>4.35</td>
<td>20.29</td>
<td>11.59</td>
</tr>
<tr>
<td>IIIb</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>352</td>
<td>61.36</td>
<td>4.65</td>
<td>15.91</td>
<td>9.09</td>
</tr>
<tr>
<td>IIIc</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>382</td>
<td>59.69</td>
<td>4.71</td>
<td>14.66</td>
<td>8.38</td>
</tr>
<tr>
<td>IIId</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>316</td>
<td>57.10</td>
<td>5.20</td>
<td>19.28</td>
<td>10.00</td>
</tr>
<tr>
<td>IV</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>217</td>
<td>60.83</td>
<td>5.07</td>
<td>19.35</td>
<td>74</td>
</tr>
<tr>
<td>V</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>402</td>
<td>65.67</td>
<td>4.48</td>
<td>13.93</td>
<td>91</td>
</tr>
<tr>
<td>VI</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>334</td>
<td>64.40</td>
<td>3.90</td>
<td>14.60</td>
<td>9.30</td>
</tr>
<tr>
<td>VII</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>330</td>
<td>50.91</td>
<td>3.03</td>
<td>16.67</td>
<td>8.70</td>
</tr>
<tr>
<td>VIII</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>344</td>
<td>52.33</td>
<td>3.49</td>
<td>16.28</td>
<td>9.30</td>
</tr>
<tr>
<td>IX</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>274</td>
<td>61.31</td>
<td>5.11</td>
<td>10.22</td>
<td>62</td>
</tr>
<tr>
<td>X</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>260</td>
<td>55.38</td>
<td>4.62</td>
<td>21.54</td>
<td>54</td>
</tr>
<tr>
<td>XI</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>260</td>
<td>55.38</td>
<td>4.62</td>
<td>21.54</td>
<td>54</td>
</tr>
<tr>
<td>XII</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>395</td>
<td>57.72</td>
<td>4.20</td>
<td>17.72</td>
<td>8.10</td>
</tr>
<tr>
<td>XIII</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>346</td>
<td>65.90</td>
<td>4.05</td>
<td>16.18</td>
<td>64</td>
</tr>
<tr>
<td>XIV</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>385</td>
<td>62.34</td>
<td>3.90</td>
<td>25.45</td>
<td>71</td>
</tr>
<tr>
<td>XV</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>408</td>
<td>59.02</td>
<td>4.10</td>
<td>17.21</td>
<td>90</td>
</tr>
<tr>
<td>XVI</td>
<td>C$_7$H$_6$N$_2$O$_5$S</td>
<td>299</td>
<td>64.21</td>
<td>4.35</td>
<td>4.68</td>
<td>60</td>
</tr>
</tbody>
</table>
filtered off and crystallized.

266

refluxed for 2 h. The canary yellow solid formed was precipitated upon cooling was filtered off and crystallized.

Table 1 (Continued)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Formula</th>
<th>w(\text{calc})/%</th>
<th>w(\text{found})/%</th>
<th>Yield</th>
<th>M.p. °C</th>
<th>IR, v/cm⁻¹</th>
<th>¹H NMR, δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>XVII</td>
<td>C₁₈H₂₁NO₆ 317</td>
<td>60.57 4.73 4.42</td>
<td>57 233—236</td>
<td>3500—2550 br, 1775, 1715, 1650, 1590, 1455, 1325, 1210, 1100</td>
<td>3.7 (s, 3H, CH₃), 6.9—8.1 (m, 5H, H_{meta} and H_{para}), 11.1—12.5 (br, 3H, OH and 2 x NH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XVIIia</td>
<td>C₁₈H₂₁NO₆ 313</td>
<td>57.51 3.61 13.42</td>
<td>73 &gt; 300</td>
<td>3400—3180, 2780—2840 br, 1715, 1685, 1670, 1640, 1600</td>
<td>11.30.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XVIIib</td>
<td>C₁₈H₂₁NO₆ 329</td>
<td>54.71 3.01 12.77</td>
<td>75 &gt; 300</td>
<td>3400, 3200, 3180—2500, 1720, 1670, 1640, 1600, 1375, 1250, 1140, 750</td>
<td>21 (s, 3H, CH₂), R², 3.6 (s, 3H, CH₃), 5.6 (s, 1H, olefinic), 7.1—8.2 (m, 4H, H_{meta}), 10.5—11.0 (br, 2H, OH and NH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XIX</td>
<td>C₁₈H₂₁NO₆ 252</td>
<td>66.67 3.17 11.11</td>
<td>52 298—300</td>
<td>3080—3020 w, 2940 w, 2220, 1780, 1650, 1010</td>
<td>2.1 (s, 3H, CH₂), R²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXa</td>
<td>C₁₈H₂₁NO₆ 285</td>
<td>63.60 4.59 14.84</td>
<td>78 &gt; 300</td>
<td>3200—3160 br, 2700 br, 1655, 1640, 1615, 1800</td>
<td>2.3 (s, 3H, CO—CH₃), 3.7 (s, 3H, CH₃), 6.2 (s, 1H, olefinic), 11.5—12.5 (br, 3H, OH and NH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXb</td>
<td>C₁₈H₂₁NO₆ 345</td>
<td>69.57 4.35 12.17</td>
<td>80 255—257</td>
<td>3250—3160 br, 2720 br, 1660, 1640, 1620, 1600</td>
<td>13.5 (br, 1H, COOH)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXc</td>
<td>C₁₈H₂₁NO₆ 421</td>
<td>74.11 4.51 9.98</td>
<td>80 248—249</td>
<td>3060 w, 2940 w, 2700 br, 1650, 1610, 1590</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>XXI</td>
<td>C₁₈H₂₁NO₆ 321.5</td>
<td>55.99 3.73 4.35</td>
<td>65 &gt; 300</td>
<td>3500—2800 br, 1735, 1880, 1685 and 1640—1630, 1595, 1455, 1380, 1310, 1240</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

for 4 h. Upon standing at room temperature overnight a solid was deposited which was filtered off and crystallized.

1,2-Dihydro-3-hydrazinocarbonyliminomethyl-4-hydroxy-1-methyl-2-oxoquinoline (X)

The ester IX (0.005 mol) was mixed with hydrazine hydrate (0.01 mol) in ethanol (25 cm³) and this mixture was refluxed for 1 h. The yellow deposit which was precipitated upon cooling was filtered off and crystallized.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde Semicarbazone (XI)

Following the same procedure described for preparation of III, compound XI was synthesized from II (0.01 mol) and semicarbazide hydrochloride (0.0117 mol).

1,2-Dihydro-4-hydroxy-1-methyl-3-(4-phénylthiosemicarbazidocarbonyliminomethyl)-2-oxoquinoline (XII)

To a suspension of the isosemicarbazone X (0.005 mol) in ethanol (25 cm³), phenyl isothiocyanate (0.0057 mol) was added and the mixture was refluxed for 2 h. The canary yellow solid formed was filtered off and crystallized.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde oxalyldihydrazide (XIII)

a) To a solution of the aldehyde II (0.01 mol) in ethanol (50 cm³) containing 1 cm³ of glacial acetic acid, isatin-3-hydrazone (0.01 mol) was added and the mixture was refluxed for 5 h. The deposit separated was filtered off and recrystallized.

b) A mixture of the hydrazone IV (0.0023 mol), isatin (0.0023 mol), and DMF (10 cm³) was refluxed for 3 h. On standing to cool to room temperature XIII was separated and identified by its melting point, mixed melting point, and spectral data.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinoline-3-carbaldehyde (5H-1,2,4-Triazino[5,6-b]indol)-3-yloxydihydrazine (XIV)

A mixture of II (0.01 mol), DMF (2 cm³), and 3-hydrazono-5H-1,2,4-triazinoindole (0.01 mol) in 50 cm³ of ethanol was refluxed for 4.5 h. The solid mass that formed was filtered off, washed with cold ethanol and recrystallized.

N,N'-Bis(1,2-dihydro-4-hydroxy-1-methyl-2-oxoquinolymethyl)oxalylhydrazide (XV)

a) To a warm solution (60—85 °C) of the aldehyde II (0.005 mol) in ethanol (50 cm³), oxalylhydrazide

266


E. A. MOHAMED
(0.0025 mol) was added portionwise. The reaction mixture was then refluxed for 3 h and the product formed was filtered off, while the mixture was still hot to afford XV.

b) To a suspension of the hydrazone IV (0.0023 mol) in dry benzene (10 cm³), oxalyl chloride (0.00115 mol) was added and the mixture was refluxed for 2 h, then left to cool to room temperature. The yellow product so formed was filtered off and recrystallized to produce compound XV, identified by its melting point, mixed melting point, and spectral data.

General Procedure for the Reaction of the Aldehyde II with Active Methylene Compounds: Formation of Compounds XVI, XVIIa, XVIIIb, XIX, and XX

A mixture of equimolar amounts of II and the active methylene compounds in ethanol was refluxed for 4 h in the presence of catalytic amounts of piperidine (or sodium ethoxide). The solid that separated upon cooling of the reaction mixture was collected and recrystallized.

1,2-Dihydro-4-hydroxy-1-methyl-2-oxoquinolyl-methylenemalonic Acid Monoethyl Ester (XVII)

A mixture of the ester XVI (0.5 g) and sodium hydroxide solution (20 cm³; 15 %) was stirred at 50—60 °C for 30 min. The cooled clear solution was then acidified and the obtained solid was filtered off and crystallized.

2-Acetyl-3-(3-chloro-1,2-dihydro-1-methyl-2,4-dioxoquinol-3-yl)propenoic Acid (XXI)

A suspension of XXa (0.002 mol) in dioxane (10 cm³) was warmed to 50—55 °C and sulfuryl chloride (0.006 mol) was then added dropwise, so that temperature did not exceed 60 °C. The reaction mixture was then stirred for 10 min, poured into ice-cold water, washed several times with water and crystallized.

REFERENCES