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The Behavior of 2-Chloroquinoline-3-carboxaldehyde towards Certain Primary Amines and Activated Methylenes

Nabila M. Ibrahim, H. A. A. Yosef and M.R. H. Mahran
Department of Organometallic and Organometalloid Chemistry, National Research Centre, Giza, 12622, Egypt.

THE REACTIVITY of 2-chloroquinoline-3-carboxaldehyde (1b) towards primary amines (2a-d, 3, 4), hydrazines (5a-d, 6) and active methylene compounds (7,8) has been investigated. Assignments of the appropriate structures to the new reaction products have been assisted by compatible analytical and spectroscopic measurements.

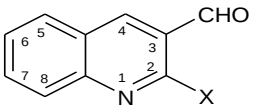
Keywords: 2-Chloroquinoline-3-carboxaldyde, Primary amines, Hydrazines, Activated methylenes, Reactions and Structural Elucidations.

Quinolines and their annelated derivatives are of particular importance by virtue of their occurrence in numerous natural products along with their wide ranging applications as drugs, pharmaceuticals and agrochemicals[1-6]. Recently,[7] we have reported on the synthesis of new quinoline compounds derived from 2-azido-3-quinolinecarboxaldehyde (1a). In pursuance to our growing interest in the chemistry of polyfunctional substrates[8-10], we have now studied the behavior of 2-chloro- quinoline-3-carboxaldyde (1b) towards certain primary amines (2a-d, 3, 4), hydrazines (5a-d, 6) and active methylenes (7, 8) (Scheme1). It is also worthy to mention that compound 1b occupies a prominent position as a key intermediate for various functional group interconvertions[11-13] .

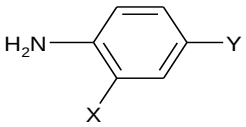
Results and Discussion

It has been now found that the reaction of 1b with aniline (2a) in absolute ethanol yields 2-chloro-3-[(phenylamino)methylene]quinoline (9) almost exclusively. This finding is in complete variance to the case of performing the same reaction in DMF which is known to afford dibenzo[b,g][1,8] naphthyridine(10) as the sole product[14] .

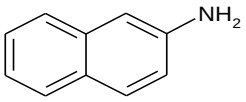
*Corresponding author: E-mail: mrh_mahran@yahoo.com



1a, X = N_3
b, X = Cl



2a, X = Y = H
b, X = NH_2; Y = H
c, X = H; Y = NH_2
d, X = H; Y = COOH



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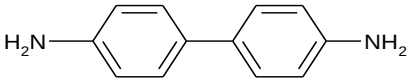

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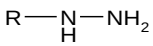
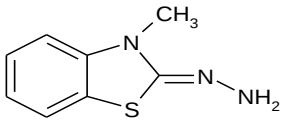


5a, R = H
b, R = CH_3
c, R = C_6H_5
d, R = $C_6H_3(NO_2)_2$-2,4



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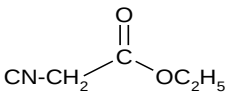

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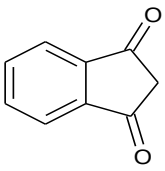

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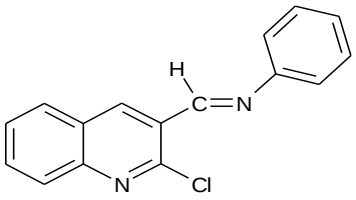
Scheme 1



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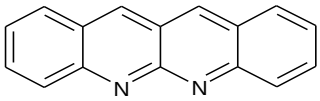

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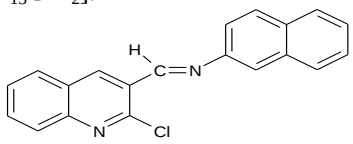
Correct elementary and molecular weight determination (MS) for 9 corresponded to $C_{16}H_{11}ClN_2$. Its IR spectrum (KBr, cm^{-1}) showed strong absorption bands at 3059 (CH, aromatic), 1613 (C=N), 1572, 1482 (C=C, aromatic) and at 749 (Cl-C=). The latter absorption was recorded at 754 cm^{-1} in the spectrum of 1b. Moreover, the strong carbonyl band present in the spectrum of 1b at 1686 cm^{-1} was absent in the spectrum of 9. The ^1H NMR spectrum of 9 (DMSO, δ ppm) showed signals at 9.18 (s, 1H, CH-4, quinoline ring) and at 8.45 (s, 1H, CH=N-). The aromatic protons (9H) appeared as a multiplet in the 8.30 -7.35 ppm region.

On the other hand, compound 1b condensed with β-naphthylamine (3) upon stirring in absolute ethanol at ambient temperature or refluxing in DMF at 75°C to give one and the same product almost exclusively which was formulated as 2-chloro-3-[(β-naphthyl -amino)methylene]quinoline (11) [MS: m/z 316 (68.70 %), 318 (59.71%), M^+, $C_{20}H_{13}ClN_2$].



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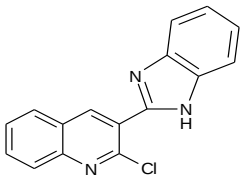
Its IR spectrum (KBr, cm^{-1}) showed bands at 3045 (CH, aromatic), 1608 (C=N), 1561 (C=C, aromatic) and 767 (Cl-C=). Its ^1H NMR spectrum (DMSO, δ ppm) revealed protons of the quinoline ring[7] at 9.36 (s, 1H, CH-4), 8.31, 8.02 (2d, each with J_{HH} = 8.90 Hz , 2H, CH-8,CH-5,), 7.92, 7.74 (2t, 2H, CH-7, CH-6), and the azomethine proton appeared as a singlet at δ 9.01. The spectrum also showed protons of the naphthyl moiety (7H) at 8.38, 7.95 (2dd, 2H), 7.86, 7.32 (2d, each with J_{HH} = 7.65 Hz, 2H) and 7.60 - 7.54 (m, 3H).

The reaction of 1b with *o*-phenylenediamine (2b)[15] is now repeated in a 2:1 molar ratio in absolute ethanol at ambient temperature and yielded two products (Scheme 2) which could be separated by column chromatography.

The first product (65%) was proved to be 3-(1H-benzimidazol-2-yl)-2-chloro-quinoline (13)[15] for the following reasons: correct elemental analyses and molecular weight determination (MS) corresponded to $C_{16}H_{10}ClN_3$ [MS: m/z 279 (100%), 281 (31%), M^+]. Its IR spectrum (KBr, cm^{-1}) showed the NH band at 3441 cm^{-1} and the Cl-C= band at 748 cm^{-1}.The ^1H NMR spectrum of 13 (DMSO, δ ppm) showed a signal at 12.9 (1H, NH, D_2O-exchangeable).



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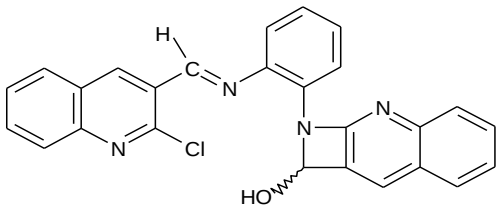
The second product (20%) was assigned structure 16 for the following reasons: (a) Its elemental analyses and molecular weight determination (MS) corresponded to $C_{26}H_{17}ClN_4O$ [MS: m/z 436 (36.90%), 438 (15%), M^+].

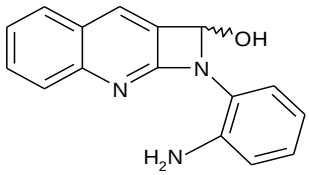


16

(b) Its IR spectrum (KBr, cm^{-1}) showed the OH group as a weak band at 3741 and the C=N group(s) as a strong band at 1662[16]. The strong Cl-C= present at 754 cm^{-1} in the spectrum of 1b was recorded at 747 in the spectrum of 16. (c) The ^1H NMR spectrum of 16 (DMSO, δ ppm) showed signals at 11.80 (1H, OH, D_2O-exchangeable) and at 5.28 due to the methine proton (sp^3 -CH-OH)[16]. Moreover, a multiplet corresponding to 15H (14H, aromatic protons and 1H, HC=N) also appeared in the spectrum in the 8.85 - 7.08 ppm region.

On the other hand, the reaction of 1b with *o*-phenylenediamine (2b) in a 1:1 molar ratio in absolute ethanol at room temperature yielded also two products which could be separated by column chromatography. The first product (65%) was proved to be 3-(1H-benzimidazol-2-yl)-2-chloroquinoline (13) (mp., mmp., comparative IR and mass spectra).

The second product (15%) was assigned structure 18 for the following reasons: (a) Its elemental analyses and molecular weight determination (MS) corresponded to $C_{16}H_{13}N_3O$ [MS: m/z 263, M^+, <5%]. (b) Its IR spectrum (KBr, cm^{-1}) showed bands around 3224 (OH, NH_2), 3062, 3024 (CH, aromatic), 1619 (C=N) and at 1590, 1528 (C=C, aromatic). (c) The ^1H NMR spectrum of 18 (DMSO, δ ppm) showed a signal at 12.00 (1H, OH, D_2O-exchangeable) and the characteristic pattern of the quinoline ring protons (5H) appeared at 8.72 (s, 1H, CH-4), 7.71, 7.46 (2d, each with J_{HH} = 8.00 Hz, 2H, CH-8, CH-5) and at 7.52 (t, 1H, CH-7). The spectrum also showed signals at 8.30 (d, J_{HH} = 5.70 Hz, 1H, aminophenyl moiety) and at 7.36 - 6.86 (m, 7H, CH-6 of quinoline ring, 3H of aminophenyl moiety, 2H of NH_2 and 1H of sp^3- CH-OH).



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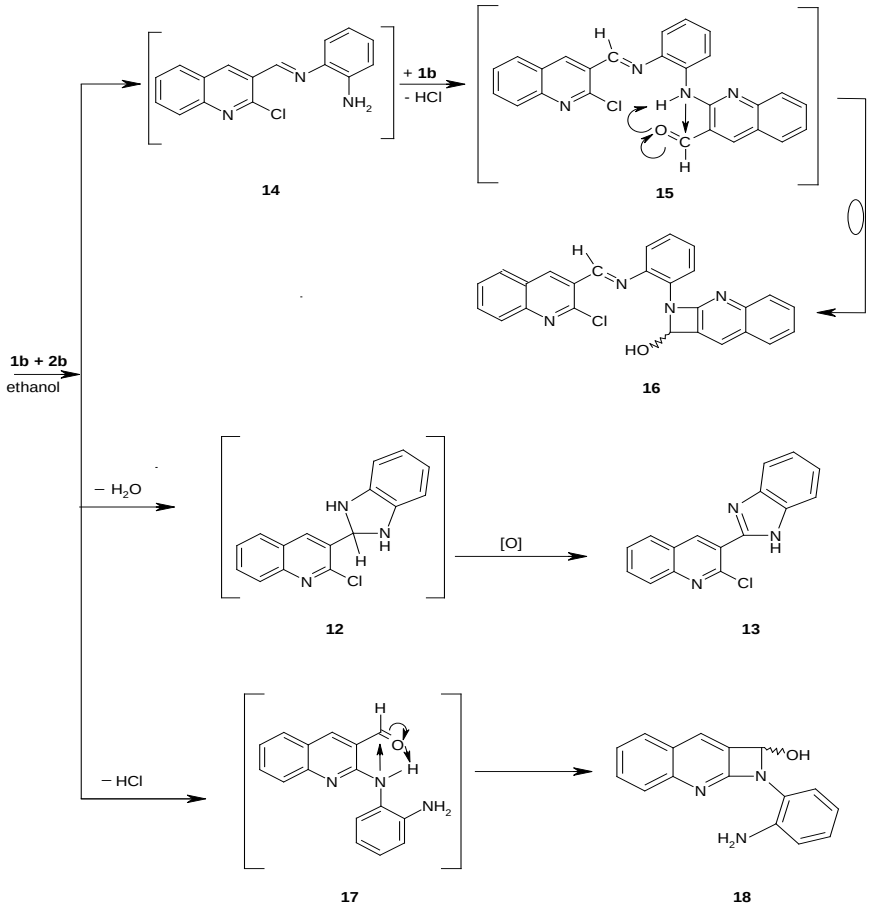
The mechanism for formation of compounds 13, 16 and 18 from the reaction of compound 1b with *o*-phenylenediamine (2b) is depicted in Scheme 2.

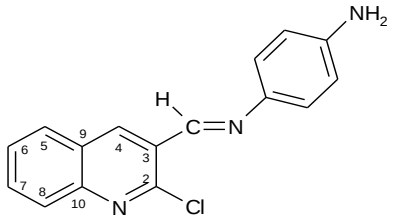
Condensation of 1b with 2b can proceed *via* dehydration to give an intermediate like 12 which undergoes auto oxidation[15] to afford compound 13. Condensation of 1b with 2b can also proceed *via* initial formation of anil 14 which can condense with another molecule of 1b *via* removal of HCl molecule to give an intermediate like 15. Intramolecular rearrangement of the latter can produce compound 16.

Meanwhile, formation of compound 18 can be interpreted in terms of the dehydrochlorinative condensation of 1b with 2b followed by intramolecular rearrangement of intermediate 17 so formed.



Scheme 2

Condensation of 1b with *p*-phenylenediamine (2c) was completed in ethanol at room temperature in a 1:1 molar ratio to give a mixture of two products. The first (80%) was formulated as 2-chloro-3- [(*p*-aminophenylamino) methylene] quinoline (19).



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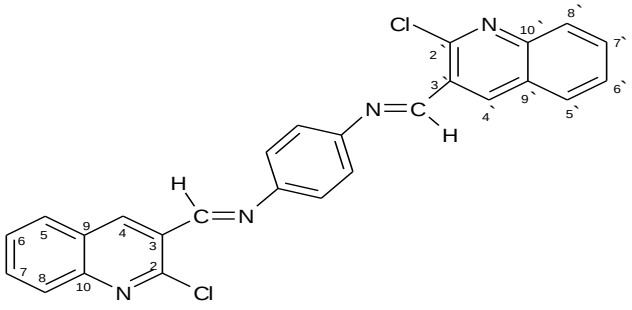
Its mass spectrum recorded the molecular ion peak at m/z 281 (283) which corresponds to $C_{16}H_{12}ClN_3$. The ^{1}H NMR spectrum (DMSO, δ ppm) showed signals at 9.08 (s, 1H, CH-4), 8.92 (s, 1H, CH=N), 8.22, 7.95 (2d, each with J_{HH} = 8.0 Hz, 2H, CH-8, CH-5,), and 7.85, 7.70 (2t, 2H, CH-7, CH-6). The AB system of the p-disubstituted benzene ring gave two doublets (each with J_{HH} = 8.50) at 7.25 (2H) and 6.60 (2H). The NH_2 protons gave a broad signal at 3.50 (D_2O-exchangeable).

The second product (10%) was formulated as N,N`-bis-[(2-chloroquinolin-3-yl)- methylidene]-*p*-phenylenediamine (20) for the following reasons: (a) Elementary analyses and molecular weight determination (MS) corresponded to $C_{26}H_{16}Cl_2N_4$ [MS: m/z 454 (100%), 458 (11.63%), M^+]. (b) Its IR spectrum (KBr, cm^{-1}) revealed the presence of strong bands at 1611 (C=N), 1576 (C=C, aromatic) and 738 (Cl-C=). (c) The ^{1}H NMR spectrum of 20 (DMSO, δ ppm) showed four singlets at 9.17, 9.02, 9.00 and 8.88 (CH-4, CH-4`, 2 CH=N), a multiplet corresponding to 8 protons in the 8.20 - 7.49 region (protons of the two quinoline moieties) and two doublets each with J_{HH} = 10.85 Hz at 7.23 (2H) and 6.64 (2H) of the AB system due to protons of the 1,4-disubstituted benzene ring.



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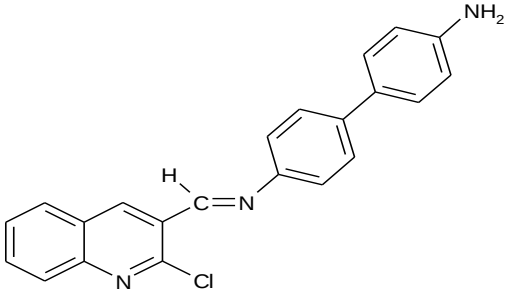
When condensation of 1b with *p*-phenylenediamine (2c) was proceeded in DMF at 75°C, two products were gained. The first (10%) was proved to be 2-chloro-3- [(*p*-aminophenylamino) methylene]quinoline (19) (mp., mmp.,

comparative IR and mass spectra). Meanwhile, the second product (80%) was proved to be N,N`-bis-[(2-chloroquinolin-3-yl)methylidene]-*p*-phenylenediamine (20) (mp., mmp., comparative IR and mass spectra).

On the other hand, the reaction of 1b with 4,4`-diaminodiphenyl (benzidine, 4) in ethanol yielded a 1:1 condensation product for which structure 21 is assigned. [MS: m/z 358 (M+H), < 5%]. Its IR spectrum (KBr, cm^{-1}) disclosed the presence of absorption bands at 3436 (NH_2), 1617 (C=N), 1488 (C=C, aromatic) and 739 (Cl-C=). Its ^1H NMR spectrum (DMSO, δ ppm) showed signals at 9.14 (s,1H, CH-4, quinoline ring), 8.97 (s, 1H, CH=N), 8.25, 7.98 (2d, each with J_{HH} = 6.3 Hz, 2H, CH-8, CH-5, quinoline ring), 7.88, 7.70 (2t, 2H, CH-7, CH-6, quinoline ring) and 7.62 - 5.25 (m, 10H, 8H of the biphenyl ring and 2H of NH_2 group).



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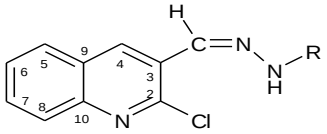
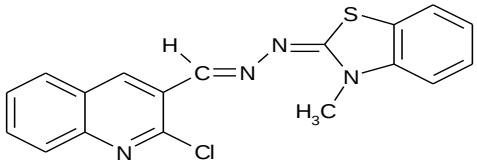
The condensation of 1b with hydrazines 5a-d was completed in absolute ethanol at room temperature (except in the case with 5a which proceeded at the reflux temperature of the solvent) to yield crystalline products for which structures 22a-d were respectively postulated. Correct elementary analyses and molecular weight determinations (MS) were recorded for all products. Thus, the MS of 22b, taken as an example, showed the molecular ion peak at 219 (49.35%), 221 (16%), M^+, which corresponds to $C_{11}H_{10}ClN_3$. Loss of Cl-radical from M^+ yielded the base peak m/z 184 (100%). Its IR spectrum (KBr, cm^{-1}) showed strong absorption bands at 3303 (NH), 3124 (CH, aromatic), 2919, 2879 (CH, aliphatic) 1566, 1512 (C=N, C=C, aromatic) and at 747 (Cl-C=). The ^1H NMR spectrum of 22b (DMSO, δ ppm) showed the NH proton as a singlet at 8.05 (D_2O-exchangeable). The azomethine proton appeared at δ 7.60, while protons of the methyl group appeared at δ 2.97 (s, 3H).



22 a, R = H
b, R = CH_3
c, R = C_6H_5
d, R = $C_6H_3(NO_2)_2$-2,4

Moreover, compound 1b reacted also with 2-hydrazinylidene-3-methyl-2,3-dihydro-1,3-benzothiazole (6) in absolute ethanol to give a yellow product for which structure 23 is assigned. The IR spectrum of 23 showed strong absorption bands at 2924 (CH, aliphatic, 1604 (C=N), 1526 (C=C, aromatic) and at 744 (Cl-C=N). Its mass spectrum showed an ion peak at m/z 317 (M -˙Cl), 19.20%. The characteristic features of its ^{1}H NMR spectrum (DMSO, δ ppm) were presence of signals at 9.65 (s, 1H, CH-4 of quinoline ring), 8.84 (s, 1H, azomethine proton) and at 3.59 (s, 3H, N-CH_3). Protons of the fused benzene rings (8H) gave a multiplet in the 8.62 - 7.11 ppm region.



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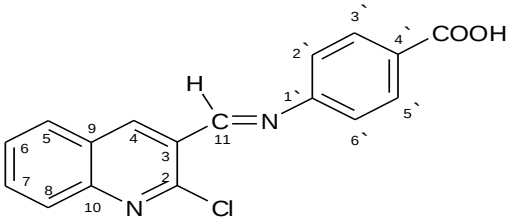
The reaction of 1b with p-aminobenzoic acid (2d) was completed in absolute ethanol at ambient temperature to give golden yellow crystals for which structure 24 is assigned. Compatible analytical and spectroscopic results were gained for 24.



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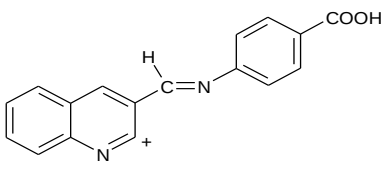
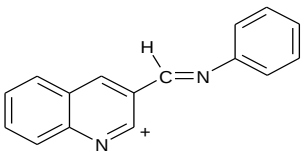
The molecular ion peak was present in its mass spectrum at m/z 310 (100%), 312 (42.40%) which corresponds to a molecular formula of $C_{17}H_{11}ClN_2O_2$. The parent peak suffers loss of Cl-radical followed by loss of a neutral CO_2 molecule to give cations a (m/z 275, 17.60%) and b (m/z 231, 10.15%), respectively.



a

m/z 275 (17.6 %)



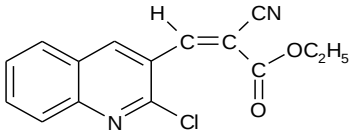
b

m/z 231 (10.15 %)

The IR spectrum of 24 (KBr, cm^{-1}) showed absorption bands at 3063 (CH, aromatic), 1694 (C=O), 1596 (C=N), 1574 (C=C, aromatic), 1289 (C-O, stretching)

and 749 (Cl-C=). Its ^{1}H NMR spectrum (DMSO, δ ppm) showed signals at 13.00 (bs, 1H, OH, D_2O-exchangeable), 9.20 (s, 1H, CH-4, quinoline ring) and 8.94 (s, 1H, azomethine proton). The ^{13}C NMR spectrum of 24 (DMSO, δ ppm) showed signals of the carbon skeleton of the quinoline nucleus (9C)[7] at 158.15 (C-2), 149.99 (C-4), 148.48 (C-10), 133.27 (C-7, C-9), 131.28 (C-3), 130.13 (C-5, C-6) and 127.44 (C-8). Signals due to the N-phenyl carbon atoms (6C) appeared at 155.27 (C-4`), 139.01 (C-1`), 129.30 (C-2`), 128.58 (C-6`), 128.26 (C-3`) and 127.31 (C-5`). The azomethine carbon atom (N=C-H) gave a signal at 121.74 and the carbonyl carbon atom (O=C-OH) gave a signal at 167.45.

The reaction of 1b with ethyl cyanoacetate (7) in ethanol yielded a mixture of two products which could be separated by column chromatography. The first (65%) was formulated as ethyl 3-(2-chloroquinolin-3-yl)-2-cyanoprop-2-enoate (25) for the following reasons: (a) Its elemental analyses and molecular weight determination (MS) corresponded to $C_{15}H_{11}ClN_2O_2$ [MS: m/z 286 (20.90%), 288 (8.58%) M^+]. (b) The IR spectrum of 25 (KBr, cm^{-1}) showed strong absorption bands at 2923, 2854 (CH, ethyl), 2225 (CN), 1724 (C=O, ester) and 758 (Cl-C=N). (c) Its ^{1}H NMR spectrum (DMSO, δ ppm) disclosed protons of the ethoxy group at 1.31 (t, 3H, ethoxy-CH_3) and 4.34 (q, 2H, ethoxy-CH_2). The exocyclic methine proton appeared as a singlet at δ 8.56 ppm.



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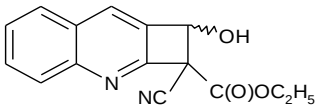
The second product (15%) was assigned structure 27 for the following reasons: (a) Its elemental analyses and molecular weight determination (MS) corresponded to $C_{15}H_{12}N_2O_3$ [MS: m/z 268 (9.93%), M^+]. (b) Its IR spectrum (KBr, cm^{-1}) disclosed the presence of strong absorption bands at 3337 (OH), 2921, 2854 (CH, ethyl), 2205 (CN), 1744 (C=O, ester), 1658, 1621 (C=N, C=C, aromatic) and 1241 (C-O, stretching). The strong Cl-C= band present at 754 in the spectrum of 1b and at 758 in the spectrum of 25 was absent in the spectrum of 27. (c) The ^{1}H NMR spectrum of 27 (DMSO, δ ppm) disclosed the presence of signals at 1.31(t, 3H, ethoxy-CH_3), 4.43 (q, 2H, ethoxy-CH_2), 5.14 (s, 1H, sp^3 CH-OH) and at 7.35 (s, 1H, OH, D_2O-exchangeable).



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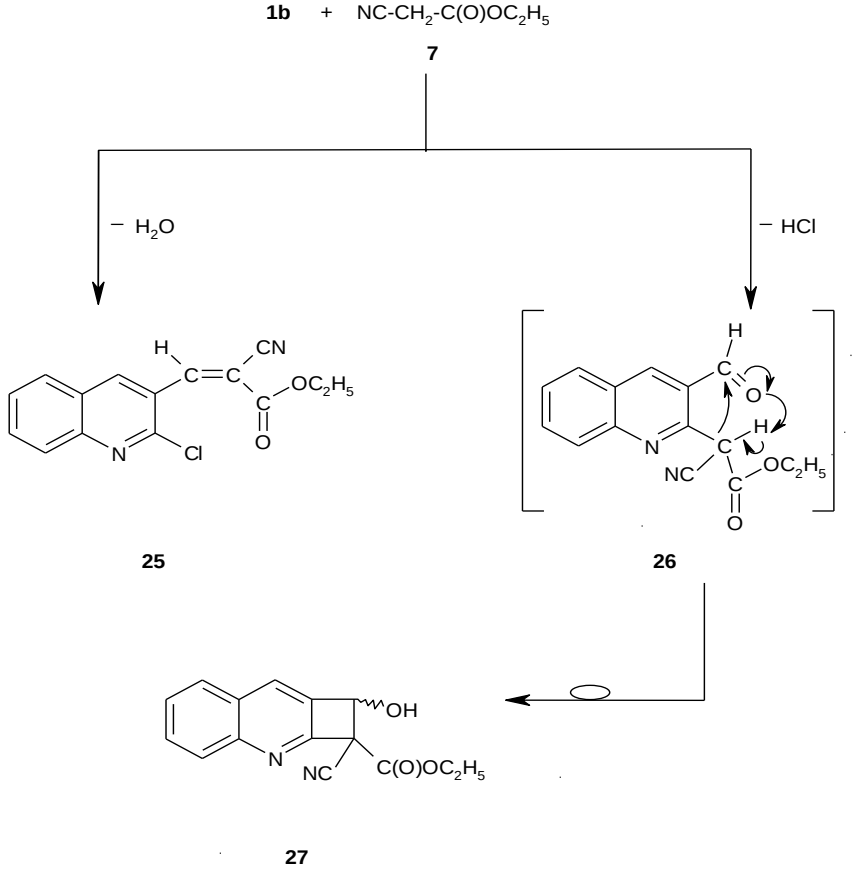
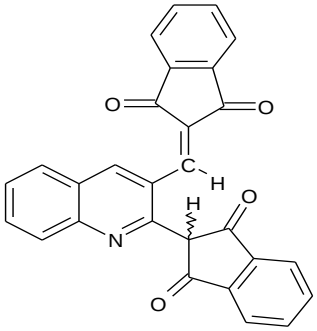
The mechanism for formation of compounds 25 and 27 from the reaction of compound 1b with ethyl cyanoacetate (7) is depicted in Scheme 3. The reaction can proceed either *via* dehydration to give 25 directly or *via* dehydrochlorination to yield an intermediate like 26 which undergoes then intramolecular rearrangement to yield 27.



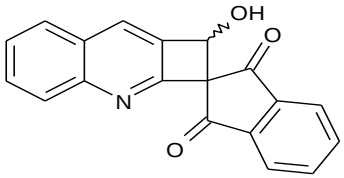
Scheme 3

Reaction of compound 1b with indane-1,3-dione (8) in a 1:1 molar ratio was performed in absolute ethanol in presence of TEA to give a mixture of two products which could be separated by column chromatography. The first (25%) was assigned structure 28 for the following reasons: Its mass spectrum recorded the molecular ion peak at m/z 429 (3.70%) matching a molecular formula of $C_{28}H_{15}NO_4$. The IR spectrum of 28 disclosed strong absorption bands at 1705, 1644 (C=O, aryl) and at 1593, 1494 (C=N, C=C, aromatic). Its ^{1}H NMR spectrum (DMSO, δ ppm) recorded signals at 8.40 (s, 1H, CH-4 of the quinoline ring), 8.23 (s, 1H, exocyclic methine proton). 7.89-7.29 (m, 12H, 4H of quinoline ring and 8H of the two indanyl moieties) and at 5.21 (s, 1H, O=C-CH-C=O).



28

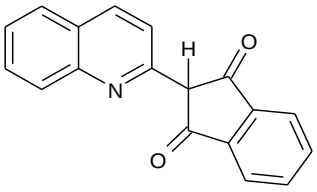
The second product (50%) was assigned structure 29 whose mass spectrum recorded the molecular ion peak at m/z 301 (60.40%) corresponding to a molecular formula of $C_{19}H_{11}NO_3$. The IR spectrum of 29 (KBr, cm^{-1}) showed strong absorption bands at 3436 (OH), 2935, 2851 (CH, aliphatic) , 1685, 1644 (C=O, aryl), 1596, 1536 (C=N, C=C, aromatic) and at 1227 (C-O, stretching).



29

When the reaction of 1b with indane-1,3-dione (8) was performed in a 1:2 molar ratio in absolute ethanol, compound 28 (mp., mmp., comparative IR and mass spectra) was gained as the sole product.

It is worthy to state that compounds 28 and 29 bear marked structural resemblance to that of Quinophthalone (30) which is an essential constituent in externally applied drugs and cosmetics[17a].



30

Conclusion

From results of the present investigation, it could be concluded that the formyl function in 2-chloroquinoline-3-carboxaldeyde (1b) is the most vulnerable site of attack by the investigated primary amines (2a-d and 3-6). On the other hand, active methylenes (7 and 8) can attack the formyl and/or the chlorine atom in 1b to give new condensation products of types 25, 27, 28 and 29. Furthermore, use has been made in the present investigation to incorporate two heterocyclic moieties of anticipated biological activities in one and the same molecule (*cf.* 13, 16, 18, 20 and 23). Thus, the molecule of compound 23 incorporates both of the quinoline moiety found in many drugs (*e.g.* Amodiaquin, antimalarial)[17b] as well as the benzothiazolyl moiety which is found in a variety of pharmaceutical agents [*e.g.* Talipexole (antiparkinsonism)[17c] and Riluzole (neuro-protective)[17d]]. Formation of compounds of types 16, 18 and 27 *via* molecular rearrangement of their corresponding precursors (15, 17 and 26), contributes the chemistry of functionally substituted azetidines which are relatively few in number[18].

Experimental

Melting points were determined on an Electrothermal digital melting point apparatus and were uncorrected. Analytical data were obtained at the Analytical Laboratory of the National Research Centre. Satisfactory elemental analyses (combustion values) (C: $\pm$ 0.3%, H: $\pm$ 0.2%, Cl: $\pm$ 0.4%, N: $\pm$ 0.3% and S: $\pm$ 0.3%) were gained for the new products. The IR spectra were recorded in KBr disks on a Jasco Fourier Transform Infrared Spectrophotometer model FT/IR-3000E. The ^{1}H NMR spectra were recorded in dimethylsulfoxide (DMSO) on JOEL 500 AS (at 500 MHz) Spectrometer using tetramethylsilane (TMS) as an internal reference. ^{13}C NMR spectra were recorded on JOEL 500 AS (at 125 MHz). Mass spectra (EI-MS) were determined at 70 eV on a Finnigan MAT SSQ 7000 spectrometer. 2-Chloroquinoline-3-carboxaldehyde (1b) was prepared according to an established method[19] .

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with aniline (2a)

A solution of aniline (2 mmole) in ethanol (5 ml) was added to a solution of compound 1b (2 mmole) in ethanol (20 ml) and the mixture was stirred at room temperature for 3 hr. The formed precipitate was filtered and recrystallized from ethanol to give compound 9.

2-Chloro-3-[(phenylamino)methylene]quinoline (9)

Pale yellow crystals, mp.128-130^{o}C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ= 9.18 (s, 1H, CH-4, quinoline moiety), 8.45 (s, 1H, CH=N), 8.30 -7.35 (m, 9H, aromatic protons). IR (KBr): 3059, 1613, 1572, 1482, 749. Molecular Formula: $C_{16}H_{11}ClN_2$ (266.72). MS: m/z 266 (100%), [M^+].

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with β-naphthylamine (3)

A solution of β-naphthylamine (2 mmole) in ethanol (10 ml) was added to a solution of 1b (2 mmole) in ethanol (10 ml) and the mixture was stirred at room

temperature for 3-5 hr. The formed precipitate was filtered and recrystallized from ethanol to give compound 11.

2-Chloro-3-[(β-naphthylamino)methylene]quinoline (11)

Yellow crystals, mp. 158-160^{o}C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ = 9.36 (s, 1H, CH-4, quinoline ring), 9.01 (s, 1H, azomethine proton), 8.31, 8.02 (2d, each with J_{HH} = 8.90 Hz, 2H, CH-8,CH-5, quinoline ring), 7.92, 7.74 (2t, 2H, CH-7, CH-6, quinoline ring), 8.38,7.95 (2dd, 2H, naphthyl moiety), 7.86,7.32 (2d, each with J_{HH} = 7.65 Hz, 2H, , naphthyl moiety) and 7.60-7.54 (m, 3H, naphthyl moiety). IR (KBr): 3045, 1608, 1561, 767. Molecular Formula: $C_{20}H_{13}ClN_2$ (316.78). MS: m/z 316 (68.70 %), [M^{+}].

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with o-phenylenediamine (2b)

In 2:1 molar ratio

To a stirred solution of 1b (2 mmole) in ethanol (10 ml) was added a solution of *o*-phenylenediamine (1mmole) in ethanol (5 ml) and the mixture was stirred at room temperature for about 5 hr. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using a mixture of petroleum ether (b.p. 60-80^{o}C) and acetone as an eluent to give compound 13 (60%) at 90:10 v/v pet. ether/acetone and compound 16 (10%) at 75:25 v/v pet. ether/acetone.

3-(1H-Benzimidazol-2-yl)-2-chloroquinoline (13)

Colorless crystals, mp. 199-201^{o}C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ = 12.9 (s, 1H, NH, D_2O-exchangeable), 8.99 (s, 1H, CH-4 of the quinoline moiety) and 8.20-7.28 (m, 8H, protons of the two fused benzene rings). IR (KBr): 3441, 3048, 2978, 2893, 1412, 748. Molecular Formula: $C_{16}H_{10}ClN_3$ (279.72). MS: m/z 279 (100%), [M^{+}].

1-({[(2-Chloroquinolin-3-yl)methylidene]amino} phenyl) -1,2-dihydroazeto [2,3-b] quinolin-2-ol (16)

White powder, mp. 316-319^{o}C (DMF/H_2O). ^{1}H NMR (500 MHz, DMSO) δ= 11.80 (1H, OH, D_2O-exchangeable), 8.85 - 7.08 (m, 15H) and 5.28 (s, 1H, sp^3 - CH-OH). IR (KBr): 3741, 3158, 3110, 3059, 2997, 1662, 1137, 747. Molecular Formula: $C_{26}H_{17}ClN_4O$ (436.89). MS: m/z 436 (36.90 %), [M^{+}].

In 1:1 molar ratio

To a stirred solution of compound 1b (1 mmole) in ethanol (10 ml) was added a solution of *o*-phenylenediamine (1mmole) in ethanol (5 ml) and the mixture was stirred at room temperature for about 5 hr. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using a mixture of petroleum ether (bp. 60-80^{o}C) and acetone as an eluent to give compound 13 (60%) at 90:10 v/v pet. ether/acetone and compound 18 (10%) at 60:40 v/v pet. ether/acetone.

1-(2-Aminophenyl)-1,2-dihydroazeto [2,3-b] quinolin-2-ol (18)

Yellowish-brown powder, mp. > 300°C (DMF/H_2O). ^{1}H NMR (500 MHz, DMSO) δ = 12.00 (s, 1H, OH), 8.72 (s, 1H, CH-4 of quinoline ring), 8.30 (d, J_{HH} = 5.7Hz,1H, aminophenyl moiety) 7.71, 7.46 (2d, each with J_{HH} = 8Hz, 2H, CH-8, CH-5 of quinoline ring), 7.52 (t, 1H, CH-7 of quinoline ring) and 7.36 -6.86 (m, 7H, CH-6 of quinoline ring, 3H of aminophenyl moiety, 2H of NH_2 and 1H of sp^3 CH-OH). IR (KBr): 3224, 3062, 3024, 1619 1590, 1528. Molecular Formula: $C_{16}H_{13}N_3O$ (263.29). MS: m/z 263 (< 5 %), [M^+].

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with p-phenylenediamine (2c)

In ethanol

To a stirred solution of 1b (2 mmole) in ethanol (10 ml) was added a solution of *p*-phenylenediamine (2c) (1 mmole) in ethanol (5 ml). The mixture was stirred at room temperature for about 4 hr. The formed precipitate was filtered, washed with cold ethanol, then boiled in ethanol and filtered. The solid that remained was collected, dried and recrystallized from DMF/H_2O to give compound 19 (major product 80%), while the filtrate was concentrated and cooled to give compound 20 (minor product 10%).

In DMF

A mixture of compound 1b (2 mmole) and p-phenylenediamine (2c) (1 mmole) in DMF (15 ml) was heated on a steam bath at 75°C for about 3 hr. The mixture was then cooled and poured onto ice-cooled water. The formed precipitate was filtered, washed with water, dried, then boiled in ethanol and filtered. The solid that remained was collected, dried and recrystallized from DMF/H_2O to give compound 19 (minor product 5%), while the filtrate was concentrated and cooled to give compound 20 (major product 75%).

2-Chloro-3-[(p-aminophenylamino)methylene]quinoline (19)

Brownish-yellow powder, mp. > 300 (DMF/H_2O). ^{1}H NMR (500 MHz, DMSO) δ = 9.08 (s, 1H, CH-4), 8.92 (s, 1H, CH=N), 8.22, 7.95 (2d, each with J_{HH}= 8.0 Hz , 2H, CH-8, CH-5), 7.85, 7.70 (2t, 2H, CH-7, CH-6), 7.25, 6.60 (2d, each with J_{HH} = 8.50, 4H, AB system of the *p*-disubstituted benzene ring) and at 3.50 (bs, 2H, NH_2, D_2O-exchangeable). IR (KBr): 3401, 3359, 3059, 3023, 1612, 1053,740. Molecular Formula: $C_{16}H_{12}ClN_3$ (281.73). MS: m/z 281 (100%), [M^+].

N,N`-Bis-[(2-chloroquinolin-3-yl)methylidene]-p-phenylenediamine (20)

Greenish-yellow crystals, mp. 283-285°C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ = 9.17, 9.02, 9.00 and 8.88 (4s, 4H, CH-4, CH-4`, 2 CH=N), 8.20 - 7.49 (m, 8H, protons of the two quinoline rings) and 7.23, 6.64 (2d, each with J_{HH}= 10.85 Hz, 4H, AB system of the 1,4-disubstituted benzene ring). IR (KBr): 1611, 1576 and 738. Molecular Formula: $C_{26}H_{16}Cl_2N_4$ (455.33). MS: m/z 454 (100 %), [M^+ based on Cl 35].

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with 4,4`-diaminodiphenyl (benzidine, 4)

A mixture of compound 1b (2 mmole) and benzidine (4) (2 mmole) in ethanol

(20ml) was stirred at room temperature for about 3 hr. The formed precipitate was filtered, washed with ethanol and recrystallized from DMF/H_2O to give compound 21.

N-[(2-Chloroquinolin-3-yl)methylidene]-4,4`-diaminobiphenyl (21)

Yellow powder, mp. 319-322^{o}C (DMF/H_2O). ^{1}H NMR (500 MHz, DMSO) δ= 9.14 (s,1H, CH-4, quinoline ring), 8.97 (s, 1H, CH=N), 8.25, 7.98 (2d, each with J_{HH}= 6.3Hz, 2H, CH-8, CH-5, quinoline ring), 7.88, 7.70 (2t, 2H, CH-7, CH-6, quinoline ring) and 7.62-5.25 (m,10H, 8H of the biphenyl ring and 2H of NH_2 group). IR (KBr): 3436, 3059, 2990, 1617, 1488, 739. Molecular Formula: $C_{22}H_{16}ClN_3$ (357.83). MS: m/z 358 (< 5%), [M+H].

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with hydrazine hydrate (5a)

A mixture of compound 1b (1 mmole) and hydrazine hydrate (5a) (1 mmole) in ethanol (15ml) was refluxed for about 10 hr. The reaction mixture was then cooled and the formed precipitate was filtered, washed with ethanol and recrystallized from DMF/H_2O to give compound 22a.

2-Chloro-3-(hydrazinylidenemethyl)quinoline (22a)

Golden yellow crystals, mp. 223-225^{o}C (DMF/H_2O). ^{1}H NMR (500 MHz, DMSO) δ = 8.60 (s, 1H, CH-4), 8.07 (s, 1H, CH=N), 8.05 (d, J_{HH} = 8.1Hz, 1H, CH-8), 7.86 (d, J_{HH} = 8.4Hz, 1H, CH-5), 7.73, 7.59 (2t, 2H, CH-7, CH-6) and 7.54 (s, 2H, NH_2, D_2O-exchangeable). IR (KBr): 3327, 3190, 1590, 1559 and 750. Molecular Formula: $C_{10}H_8ClN_3$ (205.64). MS: m/z 205 (78.08%), [M^+].

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with hydrazine derivatives (5b-d,6)

General procedure

A solution of 2-chloroquinoline-3-carboxaldehyde (1b) (1mmole) in ethanol (10 ml) was mixed with a solution of the hydrazine derivative (5b,c,d and/or 6) (1mmole) in ethanol (10 ml) and stirred at room temperature for 3-5 hr. The formed precipitate was collected by filtration, washed with ethanol and recrystallized from the appropriate solvent to give compounds 22b-d and 23, respectively.

2-Chloro-3-[(2-methylhydrazinylidene)methyl]quinoline (22b)

Pale yellow crystals, mp. 174-176^{o}C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ = 8.68 (s, 1H, CH-4), 8.61,8.03 (2d, each with J_{HH} = 8.4 Hz, 2H, CH-8, CH-5) 8.05 (s, 1H, NH, D_2O-exchangeable), 7.88, 7.73 (2t, 2H, CH-7, CH-6) 7.60 (s, 1H, CH=N-) and 2.97 (s, 3H, CH_3). IR (KBr): 3303, 3124, 2919, 2879, 1566, 1512, 747. Molecular Formula: $C_{11}H_{10}ClN_3$ (219.67). MS: m/z 219 (49.35 %), [M^+].

2-Chloro-3-[(2-phenylhydrazinylidene)methyl]quinoline (22c)

Yellow crystals, mp. 172-174^{o}C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ = 11.00 (s, 1H, NH, D_2O-exchangeable), 8.93 (s, 1H, CH-4), 8.23 (s, 1H, exocyclic

azomethine proton), 8.15, 7.95 (2d, each with J_{HH} = 10.8 Hz, 2H, CH-8, CH-5), 7.80, 7.65 (2t, 2H, CH-7, CH-6) and 7.20, 6.85 (m, 5H, C_6H_5). IR (KBr): 3300, 3031, 2963, 1590, 1552, 1515, 760. Molecular Formula: $C_{16}H_{12}ClN_3$ (281.73). MS: m/z 281 (63.36%), [M^+].

2-Chloro-3-[{2-(2,4-dinitrophenyl)hydrazinylidene}methyl]quinoline (22d)

Orange powder, mp. 288-291°C (DMF/H_2O). ^{1}H NMR (500 MHz, DMSO) δ= 9.19 (s, 1H, CH-3 of the 2,4-dinitrophenyl ring), 9.13 (s, 1H, CH-4 of the quinoline moiety), 8.93 (s, 1H, azomethine protone) and 8.39 – 7.72 (m, 7H, 4H of the quinoline moiety, 2H of the dinitrophenyl ring and NH). IR (KBr): 3274, 1614, 1586, 1511, 1327, 756. Molecular Formula: $C_{16}H_{10}ClN_5O_4$ (371.73). MS: m/z 370 (100%), [M-H].

2-Chloro-3- [{(3-methyl-1,3-benzothiazole-2 (3H) -ylidene) hydrazinylidene}-methyl] quinoline (23)

Golden yellow crystals, mp. 226-228°C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ= 9.65 (s, 1H, CH-4, quinoline ring), 8.84 (s, 1H, exocyclic azomethine proton), 8.62 – 7.11 (m, 8H, protons of the fused benzene rings) and 3.59 (s, 3H, N-CH_3). IR (KBr): 2924, 1604, 1526, 744. Molecular Formula: $C_{18}H_{13}ClN_4S$ (352.84). MS: m/z 317 (19.20 %), [M -˙Cl].

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with p-aminobenzoic acid (2d)

To a stirred solution of compound 1b (2 mmole) in ethanol (10 ml) was added a solution of p-aminobenzoic acid (2d) (2 mmole) in ethanol (10 ml) and the mixture was stirred at room temperature for about 7 hr. The formed precipitate was filtered, washed with ethanol and recrystallized from ethanol to give compound 24.

4- [{(2-Chloroquinolin-3-yl)methylidene}amino]benzoic acid (24)

Golden yellow crystals, mp. 239-241°C. ^{1}H NMR (500 MHz, DMSO) δ = 13.00 (bs, 1H, OH, D_2O-exchangeable), 9.20 (s, 1H, CH-4, quinoline ring), 8.94 (s, 1H, exocyclic azomethine proton), 8.28 (d, J_{HH} = 9 Hz, 1H, CH-8, quinoline ring), 8.04 (d, J_{HH} = 9 Hz, 3H, CH-5, of the quinoline ring together with two protons of the 1,4-disubstituted benzene ring), 7.93, 7.73 (2t, 2H, CH-7,CH-6, quinoline ring) and 7,42 (d, J_{HH} = 9 Hz, 2H, 1,4-disubstituted benzene ring). ^{13}C NMR (125 MHz, DMSO): δ = 167.45, 158.15, 155.27, 149.99, 148.48, 139.01, 133.27 (2C), 131.28, 130.13 (2C), 129.30, 128.58, 128.26, 127.44, 127.31, 121.74. IR (KBr): 3063, 2986, 2667, 2545, 1694, 1596,1574, 1289, 749. Molecular Formula: $C_{17}H_{11}ClN_2O_2$ (310.73). MS: m/z 310 (100%), [M^+**]**.

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with ethyl cyanoacetate (7)

To a stirred solution of compound 1b (2 mmole) and piperidine (0.1 ml) in ethanol (15 ml) was added a solution of ethyl cyanoacetate (2 mmole) in ethanol (5 ml) and the mixture was stirred at room temperature for about 3 hr. The volatile materials were evaporated under reduced pressure and the residue was chromatographed on silica gel using a mixture of petroleum ether (bp 60-80°C) and acetone as an eluent to give compound 25 (65%) at (85:15 v/v) pet. ether/acetone and compound 27 (15%) at (80:20 v/v) pet. ether/acetone.

Ethyl 3-(2-chloroquinolin-3-yl)-2-cyanoprop-2-enoate (25)

Colorless crystals, mp. 292- 295°C (acetone/petroleum ether {bp. 60-80°C}). ^{1}H NMR (500 MHz, DMSO) δ = 9.06 (s, 1H, CH-4, quinoline ring), 8.56 (s,1H, exocyclic methine proton), 8.17, 8.02 (2d, each with J_{HH} = 8.40 Hz, 2H, CH-8,CH-5, quinoline ring), 7.94, 7.74 (2t, 2H, CH-7, CH-6, quinoline ring), 4.34 (q, 2H, ethoxy-$\underline{CH_2}$) and 1.31 (t, 3H, ethoxy-$\underline{CH_3}$). IR (KBr): 2923, 2854, 2225, 1724, 1600, 1575, 1266, 758. Molecular Formula: $C_{15}H_{11}ClN_2O_2$ (286.71). MS: m/z 286 (20.90%), [M^+].

Ethyl 2-cyano-1-hydroxy-1,2-dihydrocyclobuta[b]quinoline-2-carboxylate (27)

White powder, mp. >300°C (DMF/H_2O). ^{1}H NMR (500 MHz, DMSO) δ= 8.97–7.68 (m,5H, protons of quinoline ring), 7.35 (s, 1H, OH, D_2O-exchangeable), 5.14 (s, 1H, sp^3 $\underline{CH}$-OH), 4.43 (q, 2H, ethoxy-$\underline{CH_2}$) and 1.31 (t, 3H, ethoxy-$\underline{CH_3}$). IR (KBr): 3337, 2921, 2854, 2205, 1744, 1658, 1621, 1241. Molecular Formula: $C_{15}H_{12}N_2O_3$ (268.27). MS: m/z 268 (9.93 %), [M^+].

Reaction of 2-chloroquinoline-3-carboxaldehyde (1b) with indane-1,3-dione (8)

In 1:1 molar ratio

To a stirred solution of compound 1b (1mmole) in ethanol (10 ml) was added a solution of indan-1,3-dione (8) (1mmole) in ethanol (10 ml) and the mixture was stirred at room temperature for about 3 hr. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using a mixture of petroleum ether (bp 60–80°C) and acetone as an eluent to give compound 28 (25%) at (80:20 v/v) pet. ether/acetone and compound 29 (50%) at (65:35 v/v) pet. ether/acetone.

2-{3-[(1,3-Dioxo-1,3- dihydro-2H- inden-2-ylidene) methylquinolin-2-yl}-1H-indene-1,3 (2H)-dione (28)

Yellow crystals, mp. 275-277°C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ= 8.40 (s, 1H, CH-4 of the quinoline ring), 8.23 (s, 1H, exocyclic methine proton). 7.89-7.29 (m, 12H, 4H of quinoline ring, 8H of the two indane moieties) and at 5.21 (s, 1H, O=C-$\underline{CH}$-C=O). IR (KBr): 1705, 1644, 1593, 1494. Molecular Formula: $C_{28}H_{15}NO_4$ (429.42). MS: m/z 429 (< 5 %), [M^+].

1-Hydroxy- 1H-spiro (cyclobuta [b]quinoline -2,2`-indene) -1`,3`-dione (29)

Yellow crystals, mp.152-153°C (ethanol). ^{1}H NMR (500 MHz, DMSO) δ= 11.82 (s, 1H, OH), 7.84 - 7.25 (m, 9H, 5H of the quinoline ring and 4H of the indane moiety) and 5.36 (s, 1H, sp^3 $\underline{CH}$-OH). IR (KBr): 3436, 2935, 2851, 1685, 1644, 1596, 1536,1227. Molecular Formula: $C_{19}H_{11}NO_3$ (301.30). MS: m/z 301 (60.40%), [M^+**]**.

In 1:2 molar ratio

To a stirred solution of compound 1b (1 mmole) in ethanol (10 ml) was added a solution of indan-1,3-dione (8) (2 mmole) in ethanol (10 ml), and the mixture was stirred at room temperature for about 3 hr. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel using a mixture of petroleum ether (bp 60–80°C) and acetone as an eluent to give compound 28 (70%) at (80:20 v/v) pet. ether/acetone as the sole product.

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سلوك 2- كلوروكينولين -3- كاربوكسالدهيد نحو بعض الأمينات الأولية والمركبات ذات مجموعة الميثيلين النشطه

نبيلة مصطفى إبراهيم ، هشام عبد الله عبد المنعم يوسف ومحمد رفعت حسين مهران
قسم الكيمياء العضوية الفلزية – المركز القومى للبحوث – القاهرة – مصر.

تم دراسة نشاط 2- كلوروكينولين -3- كاربوكسالدهيد (Ib) نحوالأمينات الأولية (2a- d,3,4) والهيدرازينات (5a-d,6) والمركبات ذات مجموعة الميثيلين النشطة (7,8) . وقد تأيدت التركيبات الكيميائية للنواتج الجديدة بواسطة الأساليب التحليلية والطيفية المختلفة .