Synthesis of 6-(4-Methyl-1-piperazinyl)-7*H*-indeno[2,1-*c*]-quinoline Derivatives as Potential 5-HT Receptor Ligands

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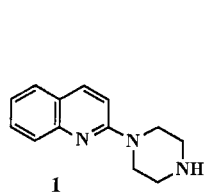
Received April 11, 1991

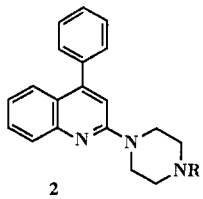
Two synthetic pathways for the achievement of the title compounds are reported. The key intermediate, namely 3-carboxy-4-phenyl-2(1*H*)-quinolinone **9**, was directly cyclized into the corresponding 6-chloro-7*H*-indeno[2,1-*c*]quinolin-7-one **10** or alternatively it was esterified, reduced to the alcohol, chlorinated and cyclized into the 6-chloro-7*H*-indeno[2,1-*c*]quinoline **8**. Further reaction of the chloroindenoquinoline derivatives with *N*-methylpiperazine afforded the piperazinyl derivatives **4a-c**.

J. Heterocyclic Chem., **28**, 1809 (1991).

In the last decade several papers have been devoted to quipazine **1**, the well known serotoninergic agent whose pharmacological activity resembles that of tricyclic antidepressants [1]. Japanese authors have reported the synthesis and antidepressant properties of quipazine derivatives **2** [2], bearing a phenyl group in the 4-position of the quinoline nucleus. Furthermore, the antiinflammatory activity of compound **3** having an indenoquinoline structure, has been recently described [3]. As a part of our continuing interest in the biological activity of fused heterocyclic ring systems, containing the quinoline moiety [4], we wish to report the synthesis of 6-(4-methyl-1-piperazinyl)-7*H*-indeno[2,1-*c*]quinoline derivatives **4**, structurally related to **2** and **3**.

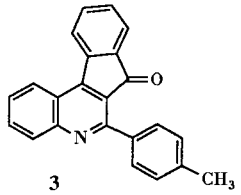


1



2

R = H,Me, Et



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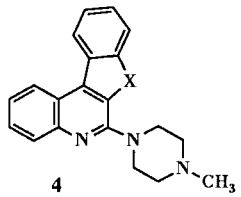


4

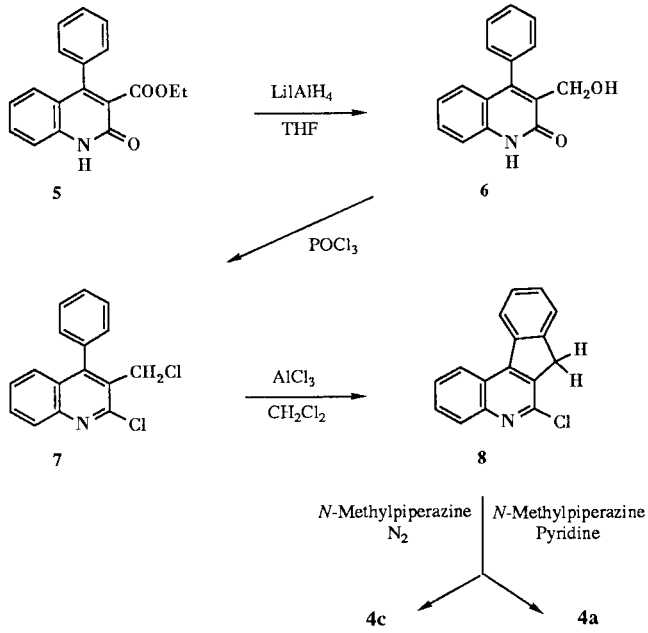
4a X = CO
b X = CHOH
c X = CH_2

The title compounds, regarded as rigid analogues of **2** in which the aromatic substituent of **3** has been replaced by a piperazine moiety, could represent potential 5-HT receptor ligands or new antiinflammatory agents.

Chemistry.

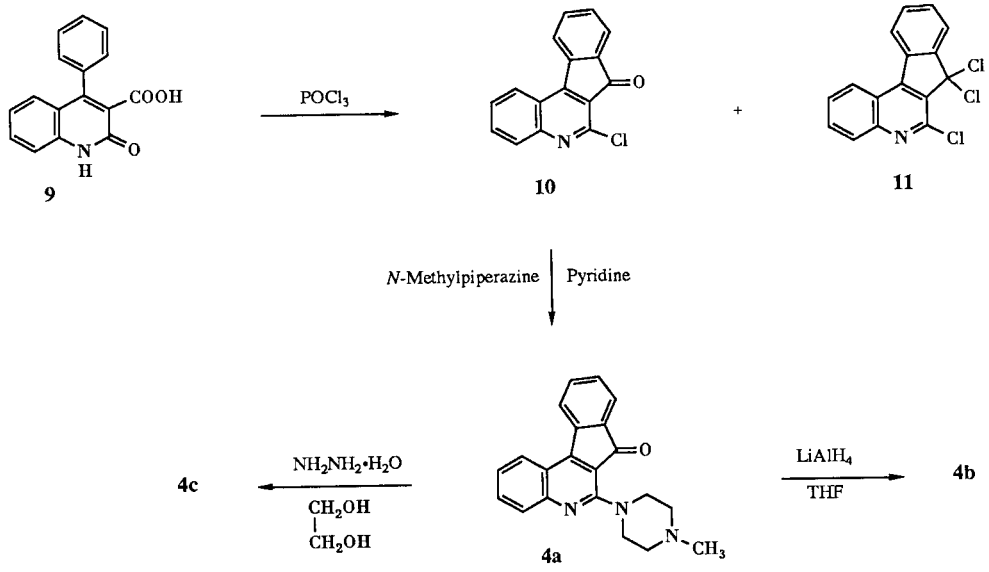
The first approach to the synthesis of indenoquinoline nucleus **4** is depicted in Scheme I. Lithium aluminium hydride reduction in THF of 3-carbethoxy-4-phenyl-2(1*H*)-quinolinone **5**, prepared following the literature [5], afforded the corresponding alcohol **6**, which by reaction with phosphorus oxychloride at reflux was converted into the chloroquinoline **7**. The cyclization of **7** under the Friedel-Crafts conditions gave the chloroindenoquinoline **8** in moderate yield (30-57%). When **8** was allowed to react with *N*-methylpiperazine in refluxing pyridine, the oxidized compound **4a** was obtained (60%) along with minor amount of **4c** (30%). However, the expected 6-(4-methyl-1-piperazinyl)-7*H*-indenoquinoline **4c** was obtained in good yield (80%), when the reaction was performed at 120-130° without solvent and under a nitrogen atmosphere. A more efficient synthetic route to compounds **4a-c** is illustrated in Scheme II. As an earlier paper reported [5] the possibility to obtain the key intermediate **10**, by cyclization under the Friedel-Crafts conditions of the acid chloride of 3-car-

Scheme 1



5 **6** **7** **8** **4c** **4a**

Scheme 2



boxy-2-chloro-4-phenylquinoline, we attempted the direct cyclization of compound **9** in refluxing phosphorus oxychloride and **10** was obtained in good yield. This reaction also gave trichloroindenoquinoline **11** as a byproduct. Compound **10** was easily converted into the piperazinyl derivative **4a** by reaction with *N*-methylpiperazine in pyridine as the solvent. Such a reaction ran faster than that performed on compound **8**, probably because the electron withdrawing effect of the carbonyl group activates the chloro derivative **10** towards nucleophiles. Lithium aluminium hydride reduction of **4a** afforded the unstable carbinol **4b**, which in solution converted again into **4a**; while the reduction of the same product under the Wolff-Kishner conditions gave compound **4c** in fairly good yield.

A preliminary biological screening of the synthesized compounds, for their potential serotoninergic properties, is still in progress and the results will be published elsewhere.

EXPERIMENTAL

Melting points were determined in open capillaries on a Büchi apparatus and are uncorrected. Microanalyses were carried out on a Perkin-Elmer 240C Elemental Analyzer. Anhydrous sodium sulphate was used as the drying agent. Merck silica gel 60 (70-230 mesh) was used for column chromatography. The ir spectra were recorded in nujol mulls on a Perkin-Elmer 398 spectrometer. The ^{1}H-nmr spectra were recorded on a Varian XL 200 spectrometer in the indicated solvents. Chemical shifts are given in ppm from TMS as internal standard, and coupling constants (J) in Hz. Mass spectra (EI, 70 eV) were recorded on a VG 70-250S spectrometer. The ir, nmr spectra and elemental analyses were performed by Dipartimento Farmaco Chimico Tecnologico-Universitá di Siena. Mass spectra were performed by Centro di Analisi e Determinazioni Strutturali-Universitá di Siena.

3-Hydroxymethyl-4-phenyl-2(1*H*)-quinolinone (**6**).

To a suspension of lithium aluminium hydride (1.2 g, 31.6 mmoles) in anhydrous tetrahydrofuran (10 ml) a solution of compound **5** (2 g, 6.8 mmoles) in anhydrous tetrahydrofuran (50 ml) was slowly added. The mixture was stirred at room temperature for 2 hours, cooled and then quenched by the addition of water. The hydroxide formed was filtered off and the organic layer, washed with saturated aqueous ammonium chloride, was dried and concentrated *in vacuo* to yield **6** as a white solid (yield 98%). An analytical sample crystallized from ethyl acetate/chloroform melted at 238-239°; ir: 3440 cm^{-1} (bm, OH and NH), 1650 cm^{-1} (s, C=O); ^{1}H-nmr (deuteriochloroform): 4.30 (t, 1H, OH, J = 6.6), 4.52 (d, 2H, CH_2, J = 6.6), 7.12-7.56 (m, 9H, arom), 12.59 (s, 1H, NH); ms: m/z 251 (23, M$^+$).

Anal. Calcd. for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.67; H, 5.26; N, 5.56.

2-Chloro-3-chloromethyl-4-phenylquinoline (**7**).

A mixture of compound **6** (1.1 g, 4.4 mmoles) and phosphorus oxychloride (6 ml) was refluxed for 1 hour, cooled and then poured into crushed ice. The gummy precipitate was extracted with chloroform and the organic layer washed with water, dried and concentrated *in vacuo*. Purification by chromatography of the residue, eluting with dichloromethane, gave **7** as a white solid. An analytical sample crystallized from cyclohexane melted at 178-179°; ^{1}H-nmr (deuteriochloroform): 4.60 (s, 2H, CH_2), 7.35-7.77 (bm, 8H, arom), 8.06 (d, 1H, J = 9.2, H_8); ms: m/z 287 (40, M$^+$).

Anal. Calcd. for $C_{16}H_{11}Cl_2N$: C, 66.69; H, 3.85; N, 4.86. Found: C, 66.91; H, 3.86; N, 4.86.

6-Chloro-7*H*-indeno[2,1-*c*]quinoline (**8**).

A mixture of compoud **7** (0.4 g, 1.39 mmoles) in anhydrous dichloromethane (30 ml) and aluminium chloride (1.5 g, 11 mmoles)

was stirred at room temperature overnight and refluxed for an additional hour. After cooling, the reaction mixture was poured into ice-water and the gummy precipitate extracted with chloroform. The usual workup of the organic layer gave a pale yellow oil which was purified by chromatography using dichloromethane as the eluent. A recrystallization from cyclohexane of the solid obtained (30-57%) afforded an analytical sample melting at 121-122°; ^{1}H-nmr (deuteriochloroform): 4.08 (s, 2H, CH_2), 7.51-7.78 (m, 5H, arom), 8.16 (d, 1H, J = 9.0), 8.38-8.43 (m, 1H), 8.67 (d, 1H, J = 8.9); ms: m/z 251 (100, M^+).

Anal. Calcd. for $C_{16}H_{10}ClN$: C, 76.35; H, 4.00; N, 5.56. Found: C, 76.60; H, 4.04; N, 5.69.

6-(4-Methyl-1-piperazinyl)-7*H*-indeno[2,1-*c*]quinoline (**4c**).

Procedure A.

A solution of **8** (1.0 g, 3.97 mmoles) in *N*-methylpiperazine (5 ml) was heated at 120-130° under a nitrogen atmosphere for 7 hours. After cooling the reaction mixture was poured into ice-water, made alkaline with concentrated sodium hydroxide and extracted with diethyl ether. The organic layer, washed to neutrality with water, was dried and concentrated *in vacuo* to give an oil, which was chromatographed using ethyl acetate/triethylamine (8:2) as eluent to afford compound **4c** (yield 80%).

Procedure B.

A mixture of **4a** (1.0 g, 3.04 mmoles) in ethylene glycol (10 ml) and hydrazine hydrate (2 ml) was heated at 120° for an hour and then at 180° for 4 hours. After being cooled, the reaction mixture was poured into ice-water and extracted with dichloromethane. The organic layer was thoroughly washed with water, dried and concentrated *in vacuo*. Purification by chromatography of the residue, eluting with ethyl acetate/triethylamine (8:2) gave **4c** (yield 89%). An analytical sample crystallized from *n*-hexane melted at 101-102.5°; ^{1}H-nmr (deuteriochloroform): 2.40 (s, 3H, CH_3), 2.65 (t, 4H, J = 5.0), 3.75 (t, 4H, J = 5.0), 4.03 (s, 2H, CH_2), 7.43-7.62 (m, 5H, arom), 7.95 (d, 1H, J = 8.0), 8.39 (d, 1H, J = 7.0), 8.58 (d, 1H, J = 8.3); ms: m/z 315 (7, M^+).

Anal. Calcd. for $C_{21}H_{21}N_3$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.82; H, 6.75; N, 13.26.

6-Chloro-7*H*-indeno[2,1-*c*]quinolin-7-one (**10**).

A mixture of **9** (1 g, 3.77 mmoles) in phosphorus oxychloride (7 ml) was refluxed for 72 hours, cooled and poured onto crushed ice. The aqueous mixture was made alkaline with concentrated sodium hydroxyde and extracted with chloroform. The organic layer, washed with water, dried and concentrated *in vacuo* gave a yellow solid. Purification by chromatography, eluting with dichloromethane gave **10** (yield 60%) as yellow solid. An analytical sample crystallized from chloroform/ethyl acetate melted at 225-227° (literature 215-217° [5]); ir: 1730 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): 7.50-7.87 (bm, 5H, arom), 8.07 (d, 1H, J = 8.0), 8.14 (d, 1H, J = 7.3), 8.50 (d, 1H, J = 8.4); ms: m/z 265 (100, M^+).

Anal. Calcd. for $C_{16}H_8ClNO$: C, 72.33; H, 3.03; N, 5.27. Found: C, 72.47; H, 2.97; N, 5.16.

6,7,7-Trichloro-7*H*-indeno[2,1-*c*]quinoline (**11**).

This compound, obtained as a byproduct in the reaction of **10** was isolated by chromatography and crystallized from cyclohexane to give colorless needles (yield 25%) melting at 181-182°; ^{1}H-nmr (deuteriochloroform): 7.59-7.74 (bm, 3H, arom), 7.79-7.88 (m, 1H), 7.97-8.01 (m, 1H), 8.13 (d, 1H, J = 7.9), 8.23-8.27 (m, 1H), 8.58 (d, 1H, J = 8.9); ms: m/z 319 (9, M^+).

Anal. Calcd. for $C_{16}H_8Cl_3N$: C, 59.94; H, 2.52; N, 4.37. Found: C, 60.30; H, 2.52; N, 4.36.

6-(4-Methyl-1-piperazinyl)-7*H*-indeno[2,1-*c*]quinolin-7-one (**4a**).

Procedure A.

A solution of **8** (0.5 g, 2 mmoles) in pyridine (10 ml) and *N*-methylpiperazine (2 ml) was refluxed for 2 hours and then stirred at room temperature overnight. The reaction mixture was poured into ice-water and extracted with chloroform; the organic layer was washed with water, dried and concentrated *in vacuo*. Purification by chromatography of the residue, eluting with ethyl acetate/triethylamine (8:2), gave **4a** (yield 60%) and **4c** (yield 30%).

Procedure B.

To a solution of **10** (1 g, 3.76 mmoles) in pyridine (15 ml), *N*-methylpiperazine (2 ml) was added. The reaction mixture was refluxed for 45 minutes and then poured into ice-water. A red-brown precipitate formed, was collected by filtration, washed with water to neutrality, dried, and crystallized from cyclohexane (yield 89%). An analytical sample melted at 125-126°; ir: 1710 cm^{-1} (C=O); ^{1}H-nmr (deuteriochloroform): 2.38 (s, 3H, CH_3), 2.68 (t, 4H, J = 5.0), 3.70 (t, 4H, J = 5.0), 7.33-7.67 (bm, 5H, arom), 7.75 (d, 1H, J = 7.6), 8.03 (d, 1H, J = 7.3), 8.3 (d, 1H, J = 7.8); ms: m/z 329 (38, M^+).

Anal. Calcd. for $C_{21}H_{19}N_3O$: C, 76.57; H, 5.81; N, 12.76. Found: C, 76.30; H, 5.79; N, 12.63.

7-Hydroxy-6-(4-methyl-1-piperazinyl)-7*H*-indeno[2,1-*c*]quinoline (**4b**).

To a suspension of lithium aluminium hydride (0.5 g, 13 mmoles) in anhydrous tetrahydrofuran (10 ml), a solution of **4a** (0.5 g, 1.52 mmoles) in anhydrous tetrahydrofuran (20 ml) was slowly added. The mixture was refluxed for 24 hours, cooled and quenched by the addition of water. The hydroxide was filtered off and the organic layer, washed with brine, was dried and concentrated *in vacuo*. Purification by chromatography of the residue, eluting with ethyl acetate/triethylamine (8:2) gave **4b** (yield 50%). Recrystallization from ethyl acetate afforded an analytical sample melting at 165°; ir: 3120 cm^{-1} (bs, OH); ^{1}H-nmr (deuteriochloroform): 1.66 (bs, 1H, OH), 2.31 (s, 3H, CH_3), 2.49-2.73 (m, 4H), 3.47-3.87 (m, 4H), 5.81 (s, 1H, CH), 7.38-7.76 (bm, 5H, arom), 7.88 (d, 1H, J = 8.5), 8.22 (d, 1H, J = 7.2), 8.45 (d, 1H, J = 8.2); ms: m/z 331 (10, M^+).

Anal. Calcd. for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68. Found: C, 76.36; H, 6.42; N, 12.59.

Acknowledgements.

This work was supported by grants from Ministero dell'Universitá e della Ricerca Scientifica e Tecnologica and the Consiglio Nazionale delle Ricerche. The authors wish to thank Prof. F. Ponticelli for the recording of the mass spectra and fruitful discussion.

REFERENCES AND NOTES

[1] R. Rodriguez and E. G. Pardo, *Psychopharmacologia*, **21**, 81 (1971).

[2] K. Hino, K. Furukawa, Y. Nagai and H. Uno, *Chem. Pharm. Bull.*,

28, 2648 (1980).

[3] M. A. Quraishi and S. N. Dhawan, *J. Indian Chem. Soc.*, **66**, 390 (1989); *Chem. Abstr.*, **112**, 138893 (1990).

[4a] M. Anzini, S. Vomero, A. Garofalo, A. Cappelli and A. Cagnotto, *Farmaco, Ed. Sci.*, **44**, 555 (1989); [b] S. Vomero, M. Anzini and A. Cappelli, *J. Heterocyclic Chem.*, **27**, 1099 (1990); [c] M. Anzini, A. Cappelli, S. Vomero, M. Botta and A. Cagnotto, *Farmaco, Ed. Sci.*, **45**, 1169 (1990).

[5] W. Borsche and W. Noll, *Liebigs Ann. Chem.*, **532**, 127 (1937).