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Synthesis of Some Novel Substituted Quinolines as Potent Analgesic Agents

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Summary. 2-Chloroquinoline-3-carbaldehyde and 2-chloro-4-methylquinoline-3-carbaldehyde have been prepared from acetanilide and acetoacetanilide *via a Vilsmeier-Haack* reaction. Upon reaction with phenyl hydrazine, hydroxylamine, urea, and thiourea in presence of acetic acid, these chloroaldehydes afforded the title compounds which exhibit a several times higher analgesic activity than noramidopyrine (*NAP*).

Keywords. Quinolinyl substituted heterocycles; Analgesic agents.

Synthese einiger neuer substituierter Chinoline als stark analgetisch wirkende Substanzen

Zusammenfassung. 2-Chlorchinolin-3-carbaldehyd und 2-Chlor-4-methylchinolin-3-carbaldehyd wurden, ausgehend von Acetanilid und Acetylacetanilid, über eine *Vilsmeier-Haack*-Reaktion hergestellt. Reaktion dieser chlorsubstituierten Aldehyde mit Phenylhydrazin, Hydroxylamin, Harnstoff und Thioharnstoff ergab die Titelverbindungen, deren analgetische Aktivität jene von Noramidopyrin (*NAP*) um ein Mehrfaches übertrifft.

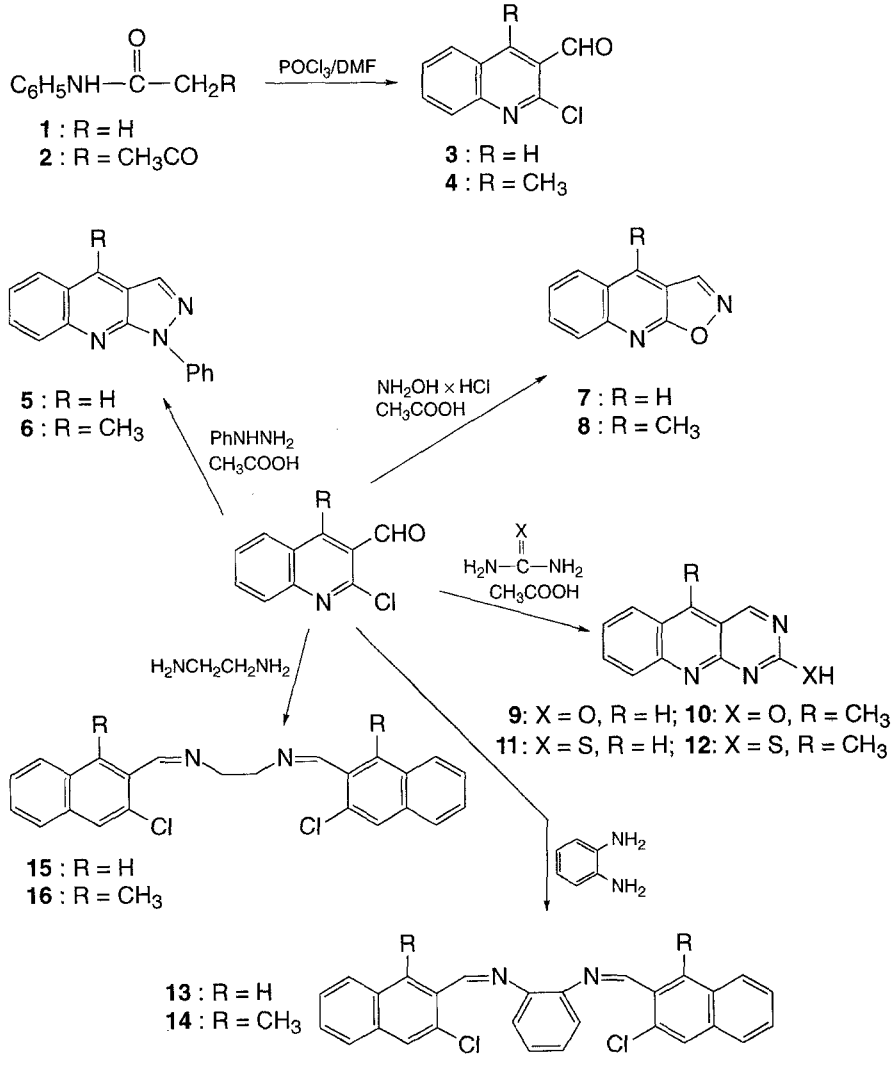
Introduction

Compounds containing pyrazole, isoxazole, and pyrimidine moieties are associated with diverse pharmaceutical and agrochemical application [1–5]. The importance of these substances prompted us to synthesize some new heterocycles and *Schiff* bases starting from 2-chloroquinoline-3-carbaldehyde (**3**) and 2-chloro-4-methylquinoline-3-carbaldehyde (**4**). The resulting compounds (**5**–**16**) were screened for their biological activity and found to be promising analgesic agents.

Results and Discussion

2-Chloroquinoline-3-carbaldehyde (**3**) and 2-chloro-4-methyl-quinoline-3-carbaldehyde (**4**) were prepared from acetanilide and acetoacetanilide by a method reported earlier [6]. Reaction of **3** and **4** with phenyl hydrazine [7] yielded 1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**5**) and 4-methyl-1-phenyl-1*H*-pyrazolo[3,4-*b*]quinoline (**6**), whereas interaction with hydroxylamine hydrochloride afforded isooxazolo[5,4-*b*]quinoline (**7**) and 4-methyl-isooxazolo[5,4-*b*]quinoline (**8**). The ^{1}H NMR spectrum of compound **8** show a singlet at 2.45 ppm due to the CH_3

protons; the aromatic multiplet appears at 7.4–8.0 ppm. Reaction of **3** and **4** with urea and thiourea in the presence of sodium hydroxide gave 2-hydroxy-pyrimido[3,4-*b*] quinoline (**9**), 2-hydroxy-5-methyl-pyrimido[3,4-*b*]quinoline (**10**), 2-mercaptopyrimido[3,4-*b*]quinoline (**11**), and 2-mercapto-5-methylpyrimido[3,4-*b*)quinoline (**12**). The ^{1}H NMR spectra of compounds **9** and **10** show a singlet in the region of 10.25–10.50 ppm; for **13** and **14** a singlet in the region of 9.98–10.10 ppm is observed. Reaction of **3** and **4** with *o*-phenylenediamine and ethylenediamine in a 2:1 molar ratio afforded N, N'-*bis*-(2-chloroquinolin-3-yl-methylene)-*o*-phenylenediamine (**13**), N, N'-*bis*-(2-chloro-4-methylquinoline-3-yl-methylene)-*o*-phenylene diamine (**14**), N, N'-*bis*-(2-chloroquinoline-3-yl-methylene)-ethylenediamine (**15**), and N, N'-*bis*-(2-chloro-4-methylquinoline-3-yl-methylene)-ethylenediamine (**16**). The ^{1}H NMR spectra of compounds **13**–**16** show a singlet in the region of 8.45–8.75 ppm due to –CH protons. The reaction route is depicted in Scheme 1.



Scheme 1

Table 1. Analgesic activity

	ED_{50} (mg/kg)
5	20
6	11.4 (10.8–11.9)
7	5.8 (2.9–11.6)
8	4.5 (2.6–12.8)
9	17.5 (14.2–21.5)
10	10.5 (8.2–13.4)
11	11.2 (10.3–12.1)
12	15.0 (9.4–24.0)
13	15.0 (12.2–18.4)
14	20
15	20
16	15.0 (12.0–18.7)
Noramidopyrine	98.0 (70.0–137.2)
Morphine	2.4 (2.0–2.9)

Biological Evaluation

All compounds were tested for their analgesic activity and acute toxicity. Results are presented in Table 1. Compounds **7** and **8** were the most potent derivatives with oral ED_{50} values of 5.8 and 4.5 mg/kg, respectively. This activity is lower than that of morphine but several times higher than that of noramidopyrine (*NAP*).

Experimental

Analgesic screening

For the hot plate test [8], groups of 10 mice were used. The animals were placed on a copper plate maintained at 56 °C. The time necessary to induce the licking reflex of the fore paws was then recorded. Two basal measurements of the pain threshold were performed before administration [9]; the measurements were carried out 30 minutes after application of the drugs.

Physical data

Melting points were determined using a Thomas Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer R-21 spectrometer (ν_{max} in cm^{-1}). ^1H NMR spectra were measured at 90 MHz on a Perkin Elmer R-32 spectrometer using tetramethylsilane (*TMS*) as an internal standard (chemical shifts in ppm). Elemental analyses were performed on a Heracus CHN Rapid Analyser; the analytical data (C, H, N) were within $\pm 0.4\%$ of the theoretical values.

2-Chloroquinoline-3-carbaldehyde (**3**)

3 was prepared according to a method reported in the literature [6].

2-Chloro-4-methylquinoline-3-carbaldehyde (**4**)

4 was synthesized analogously to **3** from acetoacetanilide (**2**) Yield: 56%; m.p.: 145–146 °C; IR (Nujol): 2850 (C–H str.), 1680 (CO str.), 1580, 1540, 1470 (Ar–C = C-str.), 795 (C–C1 str.); ^1H NMR ($CDC1_3$): 2.42 (s, 3H, 4-CH_3), 7.25–8.35 (m, 4H, Ar–H), 10.35 (s, 1H, CHO).

1-Phenyl-1H-pyrazolo [3,4-b] quinoline (**5**)

5 was prepared according to a method reported in the literature [7].

4-Methyl-1-phenyl-1H-pyrazolo[3,4-b]quinoline (**6**)

6 was synthesized analogously to **5** from **4**. Yield: 42%; m.p.: 178 °C; IR (Nujol): 1620 (C = N str.), 1585, 1540, 1490 (Ar–C = C-str.), 765 (benzene); ^{1}H NMR (Acetone-d_6): 2.45 (s, 3H, CH_3), 7.60–7.90 (m, 10H, Ar–H), 8.85 (s, 1H, 3-H).

Substituted isooxazolo[5,4-b]quinolines (**7, 8**)

Hydroxylamine hydrochloride (1.2 g, 0.01 mol) was rendered just alkaline with sodium bicarbonate and added to an ethanolic solution of 2-chloro-3-quinoline-carboxaldehyde (**3**, 0.01 mol) or 2-chloro-4-methyl-3-quinoline-carboxaldehyde (**4**, 0.01 mol) containing a few drops of acetic acid. The reaction mixture was refluxed for 1 h with stirring and then cooled. The excess of solvent was removed under vacuum. The obtained solid was filtered, washed with water, dried, and recrystallized from ethanol to yield 1.1 g (65%) of **7** (m.p.: 175 °C) and 1.1 g (65%) of **8** (m.p.: 196–198 °C).

IR (Nujol): **7** 1620 (C = N str.), 1600, 1575, 1460 (Ar–C = C); **8**: 1640 (C = N str.), 1585, 1560, 1475 (Ar–C = C str.); ^{1}HNMR (Acetone-d_6): **7:** 7.6–8.25 (m, 3H, Ar–H), 8.52 (s, 1H, 3-H); **8:** 2.45 (s, 3H, CH_3), 7.40–8.0 (m, 4H, Ar–H), 8.55 (s, 1H, 3–H).

Substituted 2-hydroxypyrimido[3,4-b]quinolines (**9, 10**)

Substituted 2-mercaptopyrimido[3,4-b]quinolines (**11, 12**)

A mixture of 2-chloro-3-quinoline-carboxaldehyde (**3**, 0.01 mol) or 2-chloro-4-methyl-3-quinoline-carboxaldehyde (**4**, 0.01 mol) and urea (0.01 mol) or thiourea (0.02 mol) in ethanol (50 ml) was refluxed while a solution of sodium hydroxide (5 mol) in 5 ml water was added dropwise during 1 h. The reaction mixture was refluxed for 3–4 h and then concentrated under vacuum. The obtained solid was filtered, washed with water, dried, and recrystallized from acetone to yield 1.5 g (80%) of **9** (m.p.: 100–102 °C), 1.5 g (76%) of **10** (m.p.: 155 °C), 1.5 g (74%) of **11** (m.p.: 119–120 °C), and 1.3 g (61%) of **12** (m.p. 62–64 °C). IR (Nujol): **9**: 3400 (OH str.), 1620 (C = N str.), 1575, 1485, 1440 (Ar–C = C) str.); **10**: 3410 (OH str.), 1610 (C = N str.), 1575, 1480, 1420 (Ar–C = C str.); **11**: 1620 (C = N str.), 1600, 1575, 1460 (Ar–C = C str.); **12**: 1620 (C = N str.), 1595, 1480, 1465 (Ar–C = C str.); ^{1}H NMR (Acetone-d_6): **9**: 7.4–8.2 (m, 6H, Ar–H), 10.25 (s, 1H, OH); **10**: 2.45 (s, 3H, CH_3), 7.2–8.1 (m, 5H, Ar–H), 10.50 (s, 1H, OH); **11**: 7.25–8.10 (m, 6H, Ar–H), 9.98 (s, 1H, SH); **12**: 2.43 (s, 1H, CH_3), 7.15–8.20 (m, 5H, Ar–H), 10.10 (s, 1H, SH).

Substituted N, N'-bis-(2-chloroquinolin-3-yl-methylene)-o-phenylenediamines (**13, 14**)

Substituted N, N'-bis-(2-chloroquinolin-3-yl-methylene)-ethylenediamines (**15, 16**)

A mixture of 2-chloro-3-quinoline-carboxaldehyde (**3**, 0.01 mol) or 2-chloro-4-methylquinoline-carboxaldehyde (**4**, 0.01 mol) and *o*-phenylenediamine (0.01 mol) or ethylenediamine (0.02 mol) in ethanol (40 ml) was refluxed for 3–4 h under constant stirring. The solvent was removed under vacuum, and the obtained solid was filtered, washed with water, dried, and recrystallized from ethanol to give 2.9 g (67%) of **13** (m.p.: 225–227 °C), 3.0 g (65%) of **14** (m.p.: 185–187 °C), 2.3 g (67%) of **15** (m.p.: 248–250 °C), and 2.0 g (48%) of **16** (m.p.: 272–275 °C).

IR (Nujol): **13**: 1640 (C = N str.), 790 (C–C str.); **14**: 1640 (C = N str.), 795 (C–C str.); **15:** 1640 (C = N str.), 790 (C–C str.); **16:** 1620 (C = N str.), 790 (C–C str.); ^{1}H NMR (Acetone-d_6): **13**: 7.20–7.75 (m, 8H, Ar–H), 8.5 (s, 2H, 2 × CH = N); **14**: 2.45 (s, 6H, 2 × CH_2), 7.20–7.75 (m, 8H, Ar–H), 8.75 (s, 2H, 2 × CH = N); **15**: 7.20–7.55 (m, 10H, Ar–H), 8.53 (s, 2H, 2 × CH = N); **16:** 2.40 (s, 4H, 2 × CH_2), 7.05–7.45 (m, 10H, Ar–H), 8.45 (s, 2H, 2 × CH = N).

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