Synthesis and Biological Activity of Quinolyl Acetic Acid Derivatives

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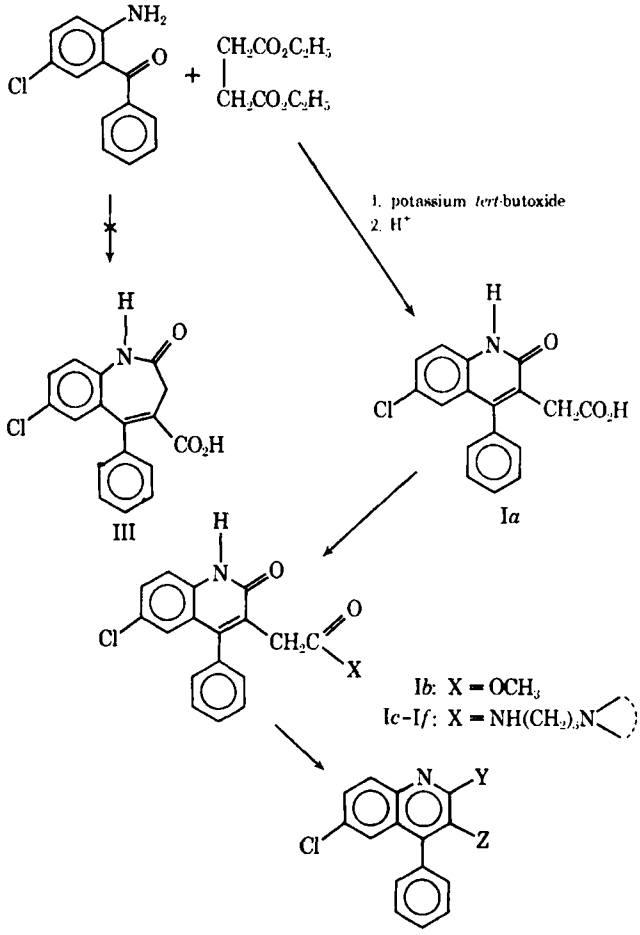
Abstract □ Derivatives of 6-chloro-4-phenyl-3-carboxymethyl-2-quinolone and 6-chloro-4-phenyl-2,3-substituted quinolines were prepared and evaluated as CNS depressants and as antibacterial agents. The compounds had no CNS activity. The quinolyl acetamides exhibited antibacterial activity against Gram-positive bacteria.

Keyphrases □ Quinolyl acetic acid derivatives—synthesis and pharmacological screening □ Quinoline derivatives—synthesis and pharmacological screening □ Antibacterial agents, potential—synthesis and screening of quinolyl acetic acid derivatives □ CNS activity—synthesis and screening of quinolyl acetic acid derivatives

The 5-chloro-2-aminobenzophenone moiety is a structural feature of several drugs affecting the central nervous system (CNS) (1–3). In addition, heterocyclic compounds containing a carbamoyl group have been reported to possess various biological activities (4–7). Consequently, as part of a program using 5-chloro-2-aminobenzophenone as a starting material for the synthesis of new nitrogen heterocyclic compounds, it was of interest to synthesize some quinolyl acetic acid derivatives (I and II), including a few quinolyl acetamides (Ic–I*f*), and to test them as CNS depressant and antibacterial agents.



IIa: Y = Cl, Z = $CH_2CO_2CH_3$
IIb: Y = OCH_3, Z = $CH_2CO_2CH_3$
IIc: Y = OCH_3, Z = CH_2CO_2H
IId: Y = OCH_3, Z = CH_3

Scheme I

5-Chloro-2-aminobenzophenone was condensed with diethyl succinate in the presence of potassium *tert*-butoxide to give 6-chloro-4-phenyl-3-carboxymethyl-2-quinolone (I*a*) in a yield of 75%. No formation was observed of a theoretically possible alternative product, the benzazepine III.

The structure of I*a* was assigned on the basis of its spectral similarity to carbostyrils and was confirmed by its facile conversion (Scheme I) to a 3-carboxymethylquinoline derivative, II*c*, which was readily decarboxylated to the corresponding 3-methylquinoline, II*d*. Loev *et al.* (8) carried out a similar condensation of 5-chloro-2-aminobenzophenone and diethyl succinate, using conditions different from those reported here. The product they obtained was also a six-membered carbostyril rather than a benzazepine, although it is unclear from their report whether they obtained a 4-phenyl-3-carboxymethyl-2-quinolone or a compound identical to I*a*. Compounds I*b*–I*f* (Table I) and II*a*–II*d* (Table II) were newly synthesized by literature methods (9–12).

PHARMACOLOGY

The compounds described in this paper were evaluated as CNS depressants by submitting them to a battery of behavioral and drug interaction tests in mice (13–21). No compound exhibited any significant CNS activity. The compounds were also tested[1] for antibacterial activity in a serial dilution test using a liquid medium[2]. The bacteriostatic values were determined after incubation for 24 hr. at 37°. Only the quinolyl acetamides, I*c*–I*f*, showed some antibacterial activity against Gram-positive bacteria. The three best results are shown in Table III.

EXPERIMENTAL[3]

6-Chloro-4-phenyl-3-carboxymethyl-2-quinolone (I*a*)—Potassium (66.3 g., 1.7 g. atom) was dissolved in *tert*-butanol (1000 ml.) at 50°, and subsequently diethyl succinate (348 g., 2 moles) and 5-chloro-2-aminobenzophenone (324 g., 1.4 moles) were added. After refluxing for 8 hr., the solvent was evaporated *in vacuo* and the residue was diluted with water, acidified with 2 *N* hydrochloric acid, and extracted with isopropyl ether. The solid material remaining in the

[1] For testing methods, refer to Table III.
[2] Merck Standard Bouillon I.
[3] Melting points were taken on a Kofler heating bench, type 7841, and are uncorrected. UV spectra were obtained on a Pye-Unicam spectrophotometer, model SP500, and the IR spectra were recorded on a Perkin-Elmer spectrophotometer, model 521, using KBr pellets. NMR spectra were obtained on Varian A-60 and T-60 spectrometers using tetramethylsilane as the internal standard and dimethyl sulfoxide as solvent. The mass spectra were recorded on a MS9 (AEI).

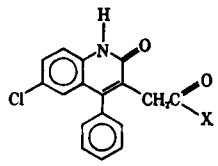
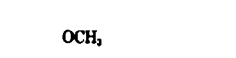
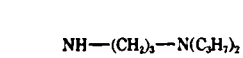


Table I—6-Chloro-4-phenyl-3-carboxymethyl-2-quinolone Derivatives (I)

Compound	X	Melting Point	Yield, %	Formula[a]	Analysis, % Calc.	Found
Ia	OH	285° dec.	75	$C_{17}H_{12}ClNO_3$	C 65.09 H 3.85 N 4.46	65.16 3.90 4.41
Ib	OCH_3	250–252°	75	$C_{18}H_{14}ClNO_3$	C 66.00 H 4.30 N 4.27	66.25 4.51 4.50
Ic	$NH-(CH_2)_3-N(C_2H_5)_2$	238°	70	$C_{26}H_{32}ClN_3O_3$	C 68.79 H 7.10 N 9.25	69.08 7.23 9.07
Id		242–244°	57	$C_{26}H_{28}ClN_3O_3$	C 68.57 H 6.44 N 9.59	68.42 6.48 9.83
Ie		246°	50	$C_{24}H_{26}ClN_3O_4$	C 65.52 H 5.95 N 9.55	65.71 6.18 9.79
If		262°	63	$C_{25}H_{29}ClN_4O_3$	C 66.30 H 6.45 N 12.37	66.44 6.60 12.28

[a] IR, NMR, and mass spectra are in agreement with the assigned structures. For spectral data, refer to the *Experimental* section.

aqueous phase was separated by filtration and washed with water and isopropyl ether. After dissolving the solid in warm 4 *N* potassium hydroxide, the solution was treated with charcoal and filtered. The filtrate was acidified with 2 *N* hydrochloric acid to give a colorless precipitate, which was collected by filtration, washed with water, and crystallized from acetic acid, yielding 329 g. (Table I); UV: $\lambda_{max}^{CH_3OH}$ 235 nm., ϵ_{molar} 4.88 × 10^4; IR: ν_{max} 1720, 1665 (CO), 1630 (C=C), 3400, 3200, and 3050 (OH, NH) $cm.^{-1}$; NMR: δ 3.17 (s, 2H, CH_2), 7.4 (m, 8 aromatic protons), and 12.1 (broad s, 1H, COOH); mass spectroscopy (200°/70 ev.): M^+ = 313.

6-Chloro-4-phenyl-3-methylcarboxymethyl-2-quinolone (I*b*)—Phosphorus oxychloride (7 ml.) was added to the solution of I*a* (84.6 g., 0.27 mole) in methanol (1000 ml.). The mixture was refluxed with stirring for 8 hr. On cooling, the solid material obtained was separated by filtration, washed with methanol, and ether (ethyl), and dried. Recrystallization from methanol afforded 66.5 g. of colorless crystals (Table I); IR: ν_{max} 1730, 1665 (CO), 1630 (C=C), 3400, and 3200 (NH) $cm.^{-1}$; NMR: δ 3.18 (s, 2H, CH_2), 3.99 (s, 3H, OCH_3), and 7.5 (m, 8 aromatic protons); mass spectroscopy (180°/70 ev.): M^+ = 327.

***N*-Substituted Basic Amides of 6-Chloro-4-phenyl-3-carboxymethyl-2-quinolone (I*c*–I*f*)**—A mixture of I*b* (163.9 g., 0.5 mole) and the corresponding amine (0.2 mole) was refluxed for 4 hr. After dilution with ligroin, the separated solid was collected and crystallized from dilute ethanol. The characteristics of I*c*–I*f* are listed in Table I.

2,6-Dichloro-4-phenyl-3-methylcarboxymethylquinoline (II*a*)—A mixture of I*b* (98.3 g., 0.3 mole), phosphorus trichloride (0.5 mole), and phosphorus oxychloride (350 ml.) was refluxed for 4 hr. The reaction mixture was cooled and poured on ice. The separated solid material was filtered, dried, and crystallized from toluene–ligroin, yielding 83 g. (Table II); IR: ν_{max} 1728 (CO) and 1632 (C=C) $cm.^{-1}$; NMR: δ 3.19 (s, 2H, CH_2), 4.0 (s, 3H, OCH_3), and 7.4 (m, 8 aromatic protons); mass spectroscopy (170°/70 ev.): M^+ = 345.

2-Methoxy-4-phenyl-6-chloro-3-methylcarboxymethylquinoline (II*b*)—A solution of II*a* (69.2 g., 0.2 mole) in benzene (500 ml.) was added to a methanol solution of sodium methoxide (8 g. sodium in 200 ml. methanol). After refluxing for 8 hr., the solvents were partially evaporated and cold water was added. The mixture was extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate, filtered, and evaporated *in vacuo* to give a residue which was crystallized from toluene–ligroin, yielding 54 g. (Table II); IR: ν_{max} 1730 (CO), 1632 (C=C), and 2830 (OCH_3) $cm.^{-1}$; NMR: δ 3.19 (s, 2H, CH_2), 3.99 (6H, $2OCH_3$), and 7.5 (8 aromatic protons); mass spectroscopy (180°/70 ev.): M^+ = 341.

2-Methoxy-4-phenyl-6-chloro-3-carboxymethylquinoline (II*c*)—A

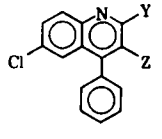


Table II—6-Chloro-4-phenyl-2,3-substituted Quinolines (II)

Compound	Y	Z	Yield, %	Melting Point	Formula[a]	Analysis, % Calc.	Found
II*a*	Cl	CH_2COOCH_3	80	185–187°	$C_{18}H_{13}Cl_2NO_2$	C 62.44 H 3.78 N 4.04	62.49 4.02 4.22
II*b*	OCH_3	CH_2COOCH_3	79	150–152°	$C_{19}H_{16}ClNO_3$	C 66.76 H 4.72 N 4.09	66.71 4.78 4.23
II*c*	OCH_3	CH_2COOH	57	208–210°	$C_{18}H_{14}ClNO_3$	C 66.00 H 4.30 N 4.27	66.30 4.52 4.47
II*d*	OCH_3	CH_3	60	253–255°	$C_{17}H_{14}ClNO$	C 71.96 H 4.97 N 4.93	71.80 5.13 4.81

[a] IR, NMR, and mass spectra are in agreement with the assigned structures. For spectral data, refer to the *Experimental* section.

Table III—Antibacterial Activity

Compound[a]	Bacteriostatic Activity, MIC[b], mcg./ml. *Staphylococcus aureus* ATCC 6538	*Streptococcus hemolyticus* SGA 380[c]	*Streptococcus fecium* SGB[c]	*Escherichia coli* ATCC 9633	*Proteus mirabilis*[c]	*Pseudomonas aeruginosa* ATCC 10145
Ic	78.2	19.6	156.00	625.0	5000.0	5000.0
Id	156.0	78.2	313.0	313.0	2500.0	2500.0
Ie	625.0	156.0	313.0	313.0	5000.0	1250.0

[a] Hydrochlorides of the compounds were used as the test substance. [b] Minimum inhibitory concentration; determined by the method described in P. Klein, "Bakteriologische Grundlagen der Chemotherapeutischen Laboratoriumspraxis," Springer-Verlag, Berlin, Germany, 1957, pp. 53ff; and R. Brunner and G. Macheck, "Die Antibiotica," 2 Bde, Verlag Hans Carl, Nuremberg, Germany, 1962. [c] Culture collection of Microbiology Department of Farbwerke Hoechst AG., Frankfurt, Germany.

mixture of II*b* (16.3 g., 0.48 mole), methanol (100 ml.), and sodium hydroxide solution (5 ml. of 50%) was refluxed for 15 hr. On cooling, the mixture was diluted with water and extracted with methylene chloride. The aqueous solution was acidified with hydrochloric acid and the obtained precipitate was filtered, washed with water, dried, and crystallized from toluene–ligroin, yielding 9 g. (Table II); IR: ν_{max} 1720 (CO), 1634 (C=C), 3350, and 3400 (OH) cm.$^{-1}$; NMR: δ 3.19 (s, 2H, CH_2), 3.99 (s, 3H, OCH_3), 7.4 (m, 8 aromatic protons), and 11.8 (broad s, 1H, COOH); mass spectroscopy (180°/70 ev.): M^+ = 327.

2-Methoxy-3-methyl-4-phenyl-6-chloroquinoline (II*d*)—Compound II*c* (32.7 g., 0.1 mole) was refluxed with quinoline (100 ml.) and copper powder (4.5 g.) for 3 hr. and worked up according to the method of Burness (12); IR: ν_{max} 1630 (C=C), 1400, 1435, 1480, 1500 (aromatic C=C), and 2825 (weak, OCH_3) cm.$^{-1}$; NMR: δ 2.29 (s, 3H, CH_3), 3.98 (s, 3H, OCH_3), and 7.4 (m, 8 aromatic protons); mass spectroscopy (170°/70 ev.): M^+ = 283.

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Determination of 6-Demethylgriseofulvin in Urine

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Abstract □ A simple UV assay is reported that is capable of measuring 1 mcg. 6-demethylgriseofulvin/ml. urine. The method utilizes the difference in the absorbance of the ionized and unionized forms of this molecule at 327 nm.

Keyphrases □ Griseofulvin metabolites—UV spectrophotometric determination of 6-demethylgriseofulvin in urine □ 6-Demethylgriseofulvin—UV spectrophotometric determination in urine □ UV spectrophotometry—determination of 6-demethylgriseofulvin

In man (1) as well as rabbit (2) and dog (3), *O*-demethylation of the antifungal agent, griseofulvin, to 6-demethylgriseofulvin is a significant route of elimination. Griseofulvin, ingested as a solution in polyethylene glycol 300, was almost quantitatively recovered (4) in the urine as 6-demethylgriseofulvin in man. While griseofulvin was readily seen in the plasma following oral administration of standard 250- and 500-mg. doses,