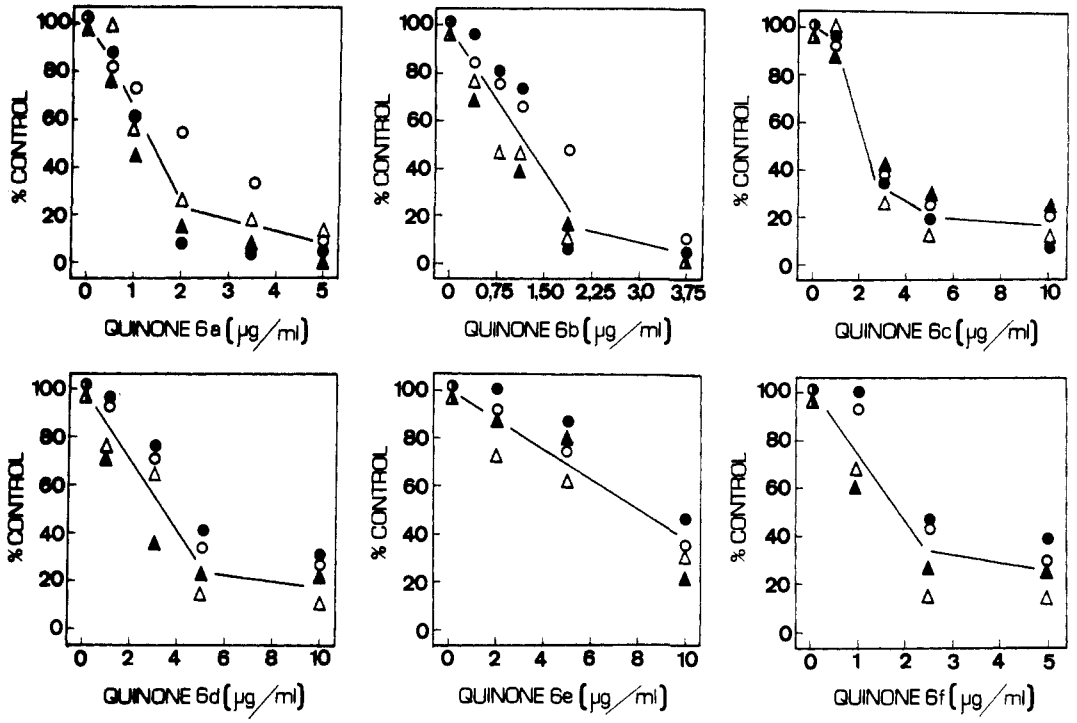

Figure 1. Effects of quinone derivatives on several cell functions. The cell suspension (1.5 mL) was incubated for 1.5 h at 37 °C in the presence of 0.2 μCi of [^{14}C]glucose (327 mCi/mmol) (Δ – Δ), 0.1 μCi of [^{3}H]thymidine (47 Ci/mmol) (▲ – ▲), 0.5 μCi of [^{3}H]uridine (30 Ci/mmol) (○–○), or 0.25 μCi of [^{3}H]proline (55 Ci/mmol) (●–●) and the corresponding quinone at the indicated concentration. Dimethyl sulfoxide (0.67% v/v) was present in the incubation mixture because of quinone insolubility in water. Samples were processed as described in the Experimental Section.

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Table III. Physical Data[a] for 1- and 2-Alkylbenzotriazoles 5 and 7

Compd	Mp, °C	Recrystn solvent	Formula[b]
5b	96-97	EtOAc-cyclohexane	$C_{10}H_{11}N_3O_2$
5d	118-120	Benzene-petr ether	$C_{11}H_{13}N_3O_2$
5e	91-92	Petr ether	$C_{12}H_{15}N_3O_2$
5f	128-129	EtOAc-Petr ether	$C_{15}H_{15}N_3$
7b	118-120	Benzene-petr ether	$C_{11}H_{13}N_3O_2$
7c	161-162	CCl_4	$C_{12}H_{15}N_3O_2$
7d	159-160	EtOAc-petr ether	$C_{15}H_{15}N_3$

[a] The NMR spectra of these compounds were as expected. [b] Analytical results for C, H, and N were within ±0.4% of the theoretical values.

The starting 2-alkylbenzotriazoles **5**, and 1-alkylbenzotriazoles **7**, were prepared following obvious modifications in the procedure described for the synthesis of 5,6-dimethylbenzotriazolylacetic acid.[23] The methyl esters **5b,d,e** and **7c,d** were prepared by passing anhydrous HCl through a methanolic solution of the corresponding acid. The physical properties of the new starting materials are listed in Table III.

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As compounds **6a–f** inhibited cell growth, we tested their effect upon DNA, RNA, and protein synthesis as well as on [^{14}C]glucose uptake. These experiments were performed to find out if the inhibition of any of these fundamental processes was responsible for the cell growth inhibition. Furthermore, these experiments appear to be necessary as preliminary steps in the study of the mode

Table I. Physical and Biological Data of 2-Alkylbenzotriazole-4,7-diones 6

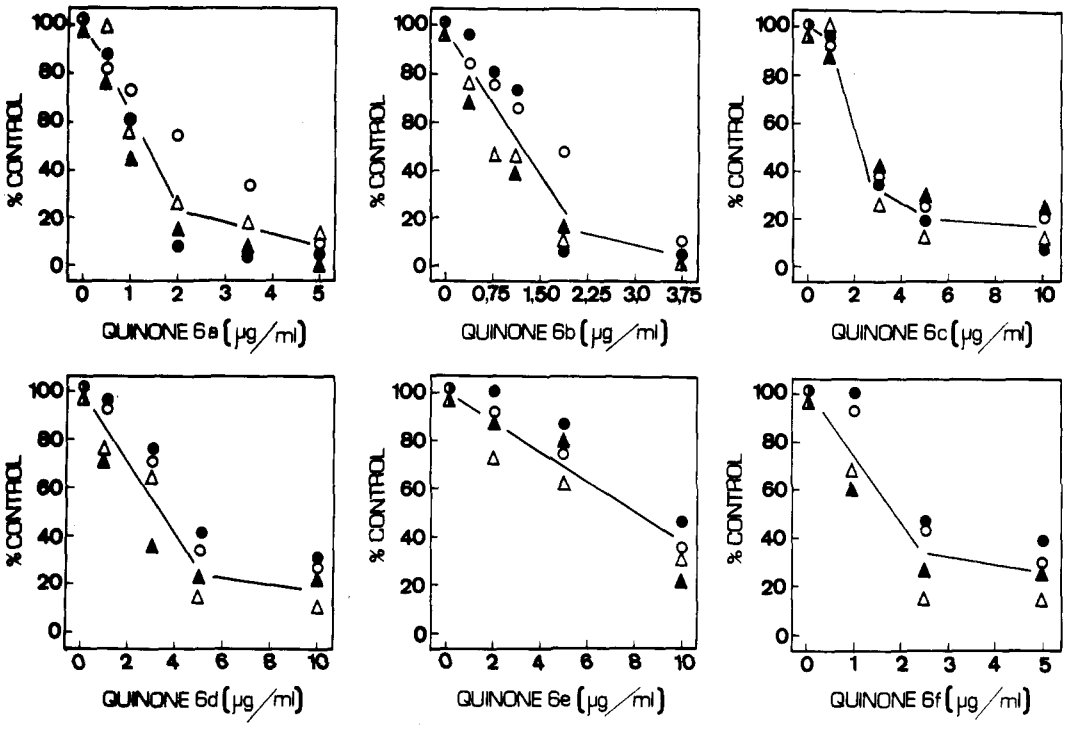
Compd	Mp, °C	Recrystn solvent[a]	Yield, %	Formula	Calcd (found) C	Calcd (found) H	Calcd (found) N	UV λ_{max} (EtOH), nm (ϵ)	NMR (δ values)	Cytostatic act., ED_{50}, μg/mL HeLa cells	Cytostatic act., ED_{50}, μg/mL KB cells
6a	193–194	A	10.5	$C_8H_7N_3O_2$	54.23 (53.98)	3.98 (4.03)	23.72 (23.77)	228 (9000), 250 (3850), 281 (750), 289 (550)	2.18 (d, 3, CCH_3, $J_{CH_3,H\text{-}6}$ = 1 Hz), 4.38 (s, 3, NCH_3), 6.70 (q, 1, H-6)	0.3	2.5
6b	Amorphous solid		17	$C_{10}H_9N_3O_4$	51.06 (50.80)	4.11 (4.21)	15.58 (15.69)	227 (16 750), 250 (13 600), 320 (1100)	2.24 (d, 3, CCH_3, $J_{CH_3,H\text{-}6}$ = 1.5 Hz), 3.84 (s, 3, OCH_3), 5.47 (s, 2, NCH_2), 6.68 (q, 1, H-6)	0.5	1.5
6c	208	B	20	$C_9H_9N_3O_2$	56.53 (56.49)	4.74 (5.00)	21.98 (22.04)	224 (19 750), 258 (16 600), 333 (600)	2.18 (s, 6, CCH_3), 4.41 (s, 3, NCH_3)	0.5	3
6d	145–146	A	15	$C_{11}H_{11}N_3O_4$	53.00 (52.66)	4.44 (4.70)	16.86 (16.58)	226 (21 000), 255 (17 000), 330 (800)	2.20 (s, 6, CCH_3), 3.84 (s, 3, OCH_3), 5.46 (s, 2, NCH_2)	1	4
6e	132–133	B	18	$C_{12}H_{13}N_3O_4$	54.75 (54.53)	4.94 (4.83)	15.96 (15.77)	229 (13 400), 256 (11 000), 340 (700)	1.99 (d, 3, $CHCH_3$), 2.16 (s, 6, CH_3), 3.72 (s, 3, OCH_3), 5.58 (q, 1, $CHCH_3$)	0.9	3.5
6f	180	B	15	$C_{15}H_{13}N_3O_2$	67.40 (67.51)	4.90 (4.99)	15.72 (15.64)	233 (20 650), 251 (15 200), 297 (1100), 340 (700)	2.11 (s, 6, CH_3), 5.67 (s, 2, CH_2), 7.32 (m, 5, C_6H_5)	0.8	3.5

[a] A, benzene–petroleum ether; B, EtOAc–petroleum ether.

Table II. Physical Data of 1-Alkyl-5,6-dimethylbenzotriazole 3-Oxides 8

Compd	Mp, °C	Recrystn solvent[a]	Yield, %	Formula[b]	UV λ_{max}, nm (ϵ) EtOH	UV λ_{max}, nm (ϵ) 4.2 N HCl	Mass spectra	NMR (δ values)
8a	197–198	A	31	$C_9H_{11}N_3O$	278 (3700), 288 (4100), 324 (8300)	287 (10 300), 286[c] (11 600)	177 (M^+, 100), 161 (M^+ – 16, 10), 147 (22), 132 (26), 103 (20), 91 (20)	2.41 (s, 6, CCH_3), 4.05 (s, 3, NCH_3), 7.65 (s, 2, H-4, H-7)
8b	200–201	B	20	$C_{11}H_{13}N_3O_3$	277 (4000), 286 (4000), 323 (7400)	287 (7400), 287[c] (7950)	235 (M^+, 70), 219 (M^+ – 16, 40), 190 (10), 175 (100), 148 (30), 132 (30), 118 (18)	2.33 (s, 6, CCH_3), 3.66 (s, 3, OCH_3), 5.50 (s, 2, NCH_2), 7.59 (s, 2, H-4, H-7)[d]
8c	127–128	A	34	$C_{12}H_{15}N_3O_3$	276 (3850), 286 (4000), 324 (7650)	287 (6900), 288[c] (8500)	249 (M^+, 55), 233 (M^+ – 16, 10), 191 (12), 190 (100), 174 (10), 131 (15), 118 (19)	1.91 (d, 3, $CHCH_3$), 2.38 (s, 3, CCH_3), 2.40 (s, 3, CCH_3), 5.28 (q, 1, $CHCH_3$), 7.21 (s, 1, H-7), 7.66 (s, 1, H-4)[d]
8d	222–224	A	16	$C_{15}H_{15}N_3O$	277 (3150), 282 (3600), 324 (7800)	288 (9300), 287[c] (9950)	253 (M^+, 7), 237 (M^+ – 16, 11), 208 (20), 194 (10), 118 (6), 91 (100)	2.32 (s, 6, CH_3), 5.44 (s, 2, CH_2), 7.05 (s, 1, H-7), 7.65 (s, 1, H-4), 7.26 (s, 5, C_6H_5)

[a] A, EtOAc–petroleum ether; B, EtOAc. [b] Analytical results for C, H, and N were within ±0.4% of the theoretical values. [c] UV data in HCl (4.2 N) of the corresponding starting products, 1-alkylbenzotriazoles 7. [d] Registered in $(CD_3)_2SO$ solution.



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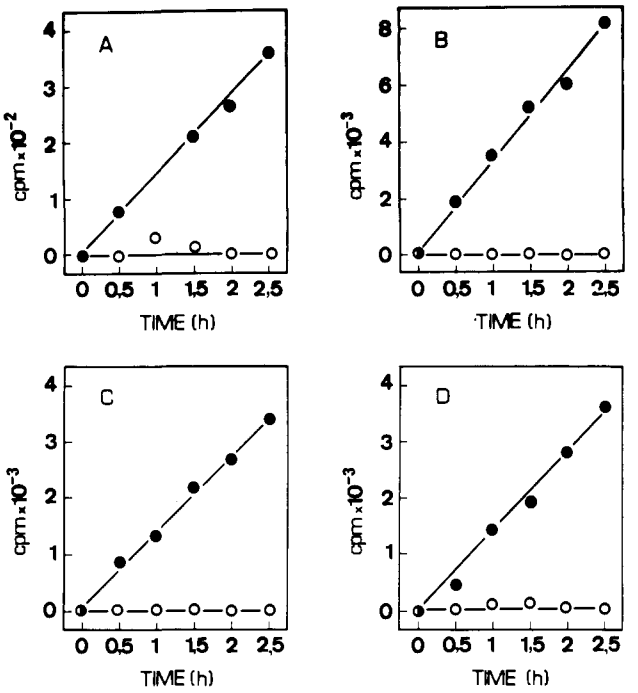

Figure 2. Irreversible effect of quinone **6b** on several cell functions. The cell suspension (37.5 mL) was incubated for 1.5 h at 37 °C in the presence (O–O) or in the absence (●–●) of 10 μg/mL of quinone **6b**. Then, the cells were washed with 37.5 mL of saline at room temperature and resuspended in 37.5 mL of fresh Minimal Medium Eagle Spinner Modified. Cells were then incubated at 37 °C in the presence of radioactive precursors at the concentrations indicated in the legend to Figure 1. Samples were taken when indicated and processed as described in the Experimental Section. Incorporation of [^{14}C]glucose (A), [^{3}H]thymidine (B), [^{3}H]uridine (C), and [^{3}H]proline (D) was studied.

of action of these compounds at the molecular level.

The quinonic compounds **6a–f** inhibited the synthesis of macromolecules (DNA, RNA, and proteins) and the uptake of [^{14}C]glucose by Ehrlich carcinoma ascites cells (Figure 1). Since the chemical structures and the biological activities of quinones **6a–f** were very similar (Figure 1), their mode of action is assumed to be the same. Therefore, only the most active example, **6b**, was used to study the reversible or irreversible nature of that mode of action. As shown in Figure 2, the synthesis of DNA, RNA, and proteins as well as the uptake of [^{14}C]glucose was inhibited irreversibly.

The four inhibitory processes for each quinone were quantitatively similar and followed the same pattern, suggesting that all of them could function analogously. Moreover, the inhibition of the uptake of [^{14}C]glucose also suggested that the common damaging cause might be related to energy metabolism. So, if compounds **6a–f** irreversibly act upon any respiratory chain step, as it has been suggested for other quinone derivatives,[2] cell respiration would then stop and, as a result, the energy-dependent synthesis of macromolecules would also stop. However, the inhibition of the four inhibitory processes could also be explained by independent actions upon each one of these processes.

No sharp quantitative differences were found among the activities of quinones **6a–f**, thus indicating that the substituents on N-2 and C-5 of the compounds assayed have no critical influence on biological activity.

Experimental Section

Chemical Methods. Melting points were observed on a Gallenkamp capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded in $CDCl_3$ solution at 60 MHz on a Perkin-Elmer R-12 spectrophotometer using Me_4Si as an internal standard. UV absorption spectra were taken with a Perkin-Elmer 350 or 402 spectrophotometer. IR spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Mass spectra were obtained in a Hitachi Perkin-Elmer RMV-GMG apparatus. Analytical thin-layer chromatography was performed on glass plates coated with a 0.25-mm layer of silica gel GF_{254} (Merck) and preparative-layer chromatography on 20 × 20 cm glass plates coated with a 2-mm layer of silica gel PF_{254} (Merck). Compounds were detected with a UV light (254 nm).

Preparation of 2-Alkylbenzotriazole-4,7-diones (6). General Procedure. A mixture of a 2-alkylbenzotriazole **5** (0.01 mol), *m*-chloroperbenzoic acid (0.025 mol), 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) (0.045 g), and anhydrous benzene (20 mL) was heated to reflux for 4 h and then cooled to room temperature. The *m*-chlorobenzoic acid which crystallized was removed by filtration and the filtrate evaporated in vacuo. The residue dissolved in a small amount of $CHCl_3$ was applied to 20 TLC preparative plates which were developed several times with the mixture EtOAc–petroleum ether (1:2). Under UV light two major bands were visible, which were removed, and the compounds extracted with EtOAc. The faster moving band was identified as the starting product. The slower was the corresponding 2-alkylbenzotriazole-4,7-dione **6**.

Preparation of 1-Alkylbenzotriazole 3-Oxides (8). General Procedure. To a solution of 0.01 mol of 1-alkylbenzotriazole **7** in 25 mL of anhydrous benzene were added 2.6 g (0.015 mol) of *m*-chloroperbenzoic acid and 0.045 g of 4,4′-thiobis(6-*tert*-butyl-3-methylphenol). The resulting mixture was refluxed for 4 h and then cooled to room temperature. The *m*-chlorobenzoic acid which crystallized was removed by filtration, and the filtrate was concentrated to 5–10 mL and applied to 20 TLC preparative plates, which were developed several times with the mixture EtOAc–EtOH–petroleum ether (1:1:2). Under UV light two major bands were visible, which were removed, and the compounds extracted. The faster moving band was identified as the starting material. The slower was the corresponding 1-alkylbenzotriazole 3-oxide **8**.

Biological Methods. Cytostatic Activity. The previously described method[24] was followed. Minimal Medium Eagle[25] (Difco, code 5675) supplemented with 10% fetal calf serum (Difco) was used. KB or HeLa cells (10^5 cells/mL) were incubated at 37 °C in Leighton tubes. After 2–3 h, the cells were attached to the glass and the compound to be tested, suspended in sterile saline containing 0.05% (v/v) Tween 80, was then added. The volume of this suspension was 10% of the final incubation mixture. Incubation was carried out at 37 °C for 72 h. As a positive control, 6-mercaptopurine was always included ($ED_{50} \sim 0.1$ μg/mL). Cell growth was estimated by measuring the cell proteins following the colorimetric method of Oyama and Eagle.[26]

Macromolecular Synthesis and [^{14}C]Glucose Uptake. The previously described method[27,28] was essentially followed. Ehrlich carcinoma ascites cells, obtained from mice bearing 7-day-old nonbloody tumors, were used. Cells were washed one to two times in saline at room temperature and then resuspended at 5 × 10^5 cells/mL in Minimal Medium Eagle Spinner Modified (Difco, code 5839) supplemented with 10% fetal calf serum (Difco). Cells were incubated with stirring in the presence of the compound to be tested and radioactive precursors, as indicated in the legend to Figure 1. At the end of the incubation period, 1 mL of the cell suspension was taken, diluted with 3 mL of cold saline (0–4 °C), and centrifuged at low speed, the supernatant being discarded. The cell pellets were lysed in 1 mL of cold water, and 1 mL of 10% trichloroacetic acid was then added. The precipitates were filtered through Whatman GF/C filters. These filters were washed three times with 2 mL of 5% trichloroacetic acid and dried, the radioactivity (cpm) being estimated in a liquid scintillation spectrometer (Packard).

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Aroyl- and Arylisoquinolineacetic Acids as Antiinflammatory Agents

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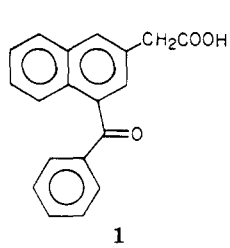
A series of 1-benzoyl- and 1-phenylisoquinolineacetic acid derivatives was prepared and tested for antiinflammatory activity. The most potent compound synthesized, 1-(4-chlorophenyl)-3-isoquinolineacetamide, was as active as phenylbutazone in the Evans blue carrageenan-induced pleural effusion assay but inactive in the adjuvant-induced arthritis model of chronic inflammation.

Since Shen[1] first outlined the structural requirements for indomethacin-type nonsteroidal antiinflammatory agents, a myriad of compounds has been synthesized and tested for this activity.[2] Reports that benzoylnaphthaleneacetic acid (1)[3] and phenylnaphthaleneacetic acid (2)[4]



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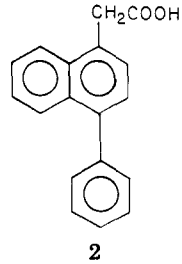

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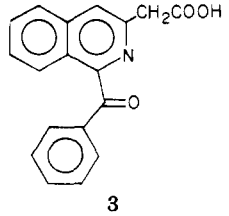

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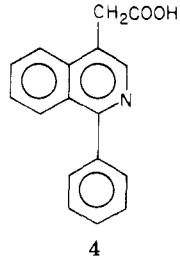

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possessed antiinflammatory activity prompted us to study various substituted isoquinolineacetic acids (3 and 4) to determine the effect on activity caused by a change from a naphthalene to a heterocyclic ring system.

Chemistry. The compounds were prepared according to Scheme I. For the synthesis of the acetic acid derivatives, the appropriate methylisoquinoline was treated with 1 mol of *N*-bromosuccinimide (NBS) to effect side-chain bromination. The crude bromomethyl compound was then treated with KCN in EtOH–H_2O and the nitrile was purified by column chromatography. The pure nitrile was stirred with concentrated H_2SO_4 to yield the desired acetamide compound. The amides were chosen for study due to the propensity of 2-pyridineacetic acids to undergo decarboxylation.[5]

The synthesis of the carboxylic acid derivatives involved treatment of the appropriate methylisoquinoline with 2 mol of NBS to give the dibromomethyl derivative. The aldehyde was prepared by heating the dibromomethyl compound with $AgNO_3$ in EtOH. The crude aldehyde was then treated with $AgNO_3$ in base according to the procedure of Shamma and Rodriguez[6] to yield the desired carboxylic acids (Table I).

Discussion

The aroyl- and arylisoquinolineacetic acid derivatives prepared fulfill the structural requirements for the hy-

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