A mixture of **36** (1 g, 0.0054 mol) and *S*-methylthiourea sulfate (1.01 g, 0.0054 mol) in 65% EtOH (30 ml) was refluxed for 24 hr until no more methyl mercaptan was evolved. The solvent was removed from the reaction mixture and the residue treated with 50% NaOH solution (25 ml). The separated oil was extracted with C_6H_6 (3 × 50 ml), the combined extracts were dried (Na_2SO_4), and solvent was removed to get the product as a thick oil.

3-Ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decan-2-one 8-Oxide (57). A solution of **28** (1.5 g, 0.007 mol) in H_2O (2 ml) was treated with 30% H_2O_2 (2 ml) and the reaction mixture stirred for 1 hr at 60°. Excess of H_2O_2 was decomposed by adding $KMnO_4$ solution to the reaction mixture and concentrated under reduced pressure, and the residue was extracted with hot C_6H_6 (3 × 50 ml). The combined extracts were dried (Na_2SO_4), the solvent was removed, and the residue was crystallized from C_6H_6–petroleum ether.

3,8-Dibenzyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (27). A mixture of **16** (20 g, 0.06 mol) and Et_3N (18 ml, 0.128 mol) in dry $CHCl_3$ (200 ml) was added dropwise with stirring to $COCl_2$ (15 ml) kept below −20° when a vigorous exothermic reaction took place and a thick mass of Et_3N·HCl separated out. After the addition was over, the reaction mixture was stirred for an additional 12 hr at room temperature and solvent removed in vacuo. The residue was taken up in dry C_6H_6 (200 ml), the insoluble Et_3N·HCl filtered off, and the solvent removed from the filtrate to get the product as an oil.

3-Ethyl-8-methyl-1,3,8-triazabicyclo[4.4.0]decane-2-thione (34). A solution of $CSCl_2$ (3.1 ml, 0.035 mol) in dry $CHCl_3$ (25 ml) was added dropwise under stirring to an ice-cold mixture of **17** (6 g, 0.035 mol) and Et_3N (9.8 ml, 0.07 mol) in dry $CHCl_3$ (100 ml) and the reaction mixture stirred for 1 hr at room temperature and then refluxed for 1 hr. Solvent was removed in vacuo and the residue taken up in dry C_6H_6 (100 ml). The insoluble Et_3N·HCl was filtered off, the solvent removed from filtrate, and the residue distilled under reduced pressure. Using this procedure compounds **33** and **35** were also made.

3-Benzyl-8-carbethoxy-1,3,8-triazabicyclo[4.4.0]decan-2-one (32). A solution of ethyl chloroformate (2 ml, 0.02 mol) in C_6H_6 (10 ml) was added dropwise to a cold solution of **27** (1.4 g, 0.004 mol) in C_6H_6 (40 ml) and the reaction mixture refluxed for 24 hr. The solvent was removed in vacuo, the residue cooled in ice and treated with 50% NaOH solution (10 ml), and the separated oil extracted with C_6H_6 (3 × 25 ml). Removal of the solvent from combined extracts yielded the product as an oil.

3-Benzyl-1,3,8-triazabicyclo[4.4.0]decan-2-one (31). A mixture of **32** (1 g, 0.003 mol) and 48% HBr solution (20 ml) in glacial AcOH (20 ml) was refluxed for 24 hr. The solvent was removed from the reaction mixture, the residue treated with 50% NaOH solution (25 ml), and the separated oil extracted with C_6H_6 (3 × 20 ml). The combined extracts were dried (Na_2SO_4) and solvent was removed to get the product as an oil.

Acknowledgments. The authors thank Drs. A. B. Sen and R. K. Chatterjee of the division of chemotherapy of this Institute for providing the antifilarial screening results, Dr. B. N. Dhawan and his associates for antiinflammatory data, and the staff of our Instrumentation Services for various spectroscopic and analytical data. One of us (S.S.) thanks CSIR, New Delhi, for the award of a junior research fellowship.

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Potential Bioreductive Alkylating Agents. 5. Antineoplastic Activity of Quinoline-5,8-diones, Naphthazarins, and Naphthoquinones

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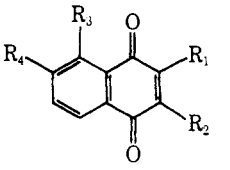
A number of 2-chloromethyl and 2-bromomethyl derivatives of naphthoquinones, quinolinediones, and naphthazarins were designed and synthesized as potential bioreductive alkylating agents, and the antitumor activity of these compounds was assessed in mice bearing Sarcoma 180 ascites cells. The results indicated that, with the exception of 3-benzamido-2-chloromethyl-1,4-naphthoquinone, which was inactive, all newly synthesized naphthoquinones possessed strong antitumor activity against this neoplasm. 6,7-Bis(bromomethyl)quinoline-5,8-dione had moderate inhibitory activity against Sarcoma 180 at its optimal daily dosage level of 15 mg/kg. 3-Bromo-2-bromomethyl- and 3-bromo-2-chloromethylnaphthazarin produced a moderate extension of the life span of tumor-bearing mice; whereas, in contrast, 6,7-dimethyl analogs of these agents were inactive when employed in daily doses up to 40 mg/kg of body weight.

The synthesis of a series of benzo- and naphthoquinone derivatives with common structural features (**1**), which were designed to generate a reactive species in cells, have been reported previously.[1-5] These agents were found to be potent inhibitors of (a) the growth of rodent tumors,[1-3] (b) the synthesis of DNA and RNA in these neoplastic cells in vitro,[1,2] and (c) the coenzyme Q-mediated beef heart mitochondrial enzymes, NADH-oxidase and succinoxidase.[2,4] The mechanism by which these compounds exert their cytotoxicity has been postulated[6] to involve the enzymatic reduction of the quinone ring in vivo, presumably by an NADPH-dependent quinone reducing system analogous to that acting on mitomycin C,[7-9] to form a dihydroquinone, which spontaneously generates the reactive species, an *o*-quinone methide (**2**); this reactive intermediate may then act to alkylate cellular components. Chemical evidence[10] has been obtained to substantiate the existence of an *o*-quinone methide from 2,3-dimethyl-5,6-bis(acetoxymethyl)-1,4-benzoquinone (**3**).

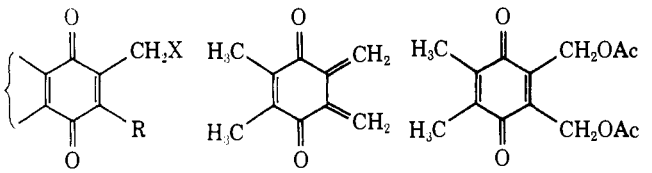
As part of a study to develop new antineoplastic agents of this class with (a) greater therapeutic potency and (b) better water solubility (in salt form), the synthesis of a

Table I



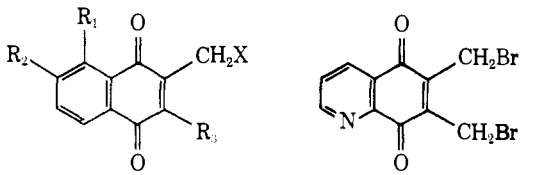
R_1	R_2	R_3	R_4	Mp, °C	% yield	Recrystn solvent	Elemental analyses	Uv, λ max (nm), EtOH
$-CH_2Cl$	$-SC_6H_5$	-H	-H	146–148	57	EtOH	C, H, Cl	204 (53,333), 250 (30,667)
$-CH_2Cl$	$-SC_2H_5$	-H	-H	65–68	14	EtOH	C, H, Cl	204 (19,000), 215 (17,800), 258 (19,600)
$-CH_2Cl$	$-NHC(=O)C_6H_5$	-H	-H	179–182	28	EtOH	C, H, N, Cl	205 (30,357), 248 (19,643), 254 (18,929), 280 (18,214)
$-CH_2Cl$	$-C_6H_5$	-H	-H	119–120	52	EtOH	C, H, Cl	208 (27,667), 230 (17,333), 260 (33,333), 268 (39,333)
$-CH_2Cl$	$-CH_2Cl$	-H	-Cl	137–140	17	EtOH	C, H, Cl	205 (22,500), 255 (16,500), 260 (16,250)
$-CH_2Cl$	$-CH_2Cl$	-Cl	-H	107–110	12	EtOH	*a*	207 (26,897), 235 (13,448), 256 (12,759)
$-CH_2Cl$	$-CH_2Cl$	$-CH_3$	-H	143–145	12	Ligroine	C, H, Cl	202 (17,209), 227 (18,837), 250 (17,442)
$-CH_2Cl$	$-CH_2Cl$	-H	$-CH_3$	108–110	14	Ligroine	C, H, Cl	207 (18,214), 250 (15,536)
$-CH_2Br$	-Br	-H	-H	118–120		EtOH		208 (15,510), 252 (20,612)
$-CH_2Br$	-Cl	-H	-H	126–128	54	EtOH	C, H, Cl, Br	204 (21,875), 247 (13,130), 253 (13,750), 275 (13,750)

[a] Calcd for $C_{12}H_7O_2Cl_3$: C, 49.74; H, 2.42; Cl, 36.75. Found: C, 49.31; H, 2.42; Cl, 36.06.



1 2 3

number of 2-chloromethyl or 2-bromomethyl derivatives of naphthoquinones (**4**), quinolinediones (**5**), and naphthazarins (**6**) was carried out and is described in the present report.



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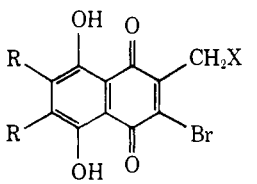
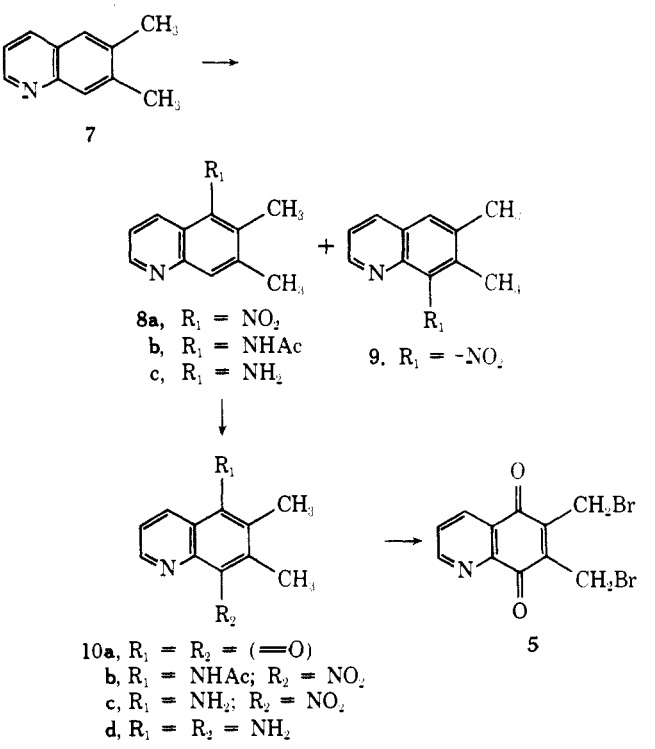


6

X = Cl, Br

Chemistry. 2-Chloromethylnaphthoquinones (**4**) were prepared by direct chloromethylation of the appropriate naphthoquinones according to the procedure of Thomson.[11] The syntheses of the starting quinones for the chloromethylation reaction have been documented.[12-20] 2-Bromomethylnaphthoquinones were formed by bromination of the corresponding 2-methylnaphthoquinones, employing NBS as the brominating agent. The physical properties of the naphthoquinones are listed in Table I.

Scheme I



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8a, $R_1 = NO_2$
b, R_1 = NHAc
c, $R_1 = NH_2$

9. $R_1 = -NO_2$

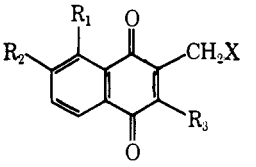
10a, $R_1 = R_2 = (=O)$
b, R_1 = NHAc; $R_2 = NO_2$
c, $R_1 = NH_2$; $R_2 = NO_2$
d, $R_1 = R_2 = NH_2$

5

The synthesis of 6,7-bis(bromomethyl)quinoline-5,8-dione (**5**) was achieved as shown in Scheme I. Nitration of 6,7-dimethylquinoline[21] (**7**), using a mixture of nitric and sulfuric acids as the nitrating reagent, gave mainly 5-nitro-6,7-dimethylquinoline (**8a**), with the 8-nitro isomer **9** as a minor product. The separation of these two isomers was achieved by fractional crystallization from a mixture of benzene and ligroine.

5-Nitro-6,7-dimethylquinoline (**8a**) was reduced catalyti-

Table II. Effects of Naphthoquinone Derivatives on the Survival Time of Mice Bearing Sarcoma 180 Ascites Cells



R_1	R_2	R_3	X	Optimal dosage, mg/kg[a]	Av Δ wt, %[b]	Av survival, days ± SE[c]	T/C[d]
Control					+13.9	12.7 ± 0.3	
H	H	Br	Br	10	+0.6	29.8 ± 5.0	2.3
H	H	Cl	Br	10	−1.3	29.8 ± 3.2	2.3
CH_3	H	CH_2Cl	Cl	5	−2.9	21.0 ± 2.4	1.7
H	CH_3	CH_2Cl	Cl	5	−2.9	19.4 ± 1.5	1.5
Cl	H	CH_2Cl	Cl	2.5	−2.2	25.0 ± 3.6	2.0
H	Cl	CH_2Cl	Cl	10	−3.0	21.0 ± 1.0	1.7
H	H	C_6H_5	Cl	15	+1.0	29.7 ± 3.2	2.3
H	H	$NHC(=O)C_6H_5$	Cl	10	+20.6	13.0 ± 0.5	1.1
H	H	SC_2H_5	Cl	15	−4.1	30.4 ± 6.0	2.4
H	H	SC_6H_5	Cl	20	−7.8	23.2 ± 5.3	1.8

[a] Administered once daily for 6 consecutive days beginning 24 hr after tumor implantation. [b] Average weight change from onset to termination of drug treatment. [c] Each value represents results from five to ten mice. [d] T/C represents the ratio of the survival time of treated to control animals.

cally to 5-amino-6,7-dimethylquinoline (**8c**), which was then treated with Fremy's salt to give 6,7-dimethylquinoline-5,8-dione (**10a**) in high yield. Compound **10a** was also prepared in lesser yield by an indirect approach which involved reductive acetylation (**8b**), nitration (**10b**), hydrolysis (**10c**), catalytic reduction (**10d**), and ferric chloride oxidation (**10a**) as shown in Scheme I. Treatment of compound **10a** with *N*-bromosuccinimide in carbon tetrachloride gave the desired 6,7-bis(bromomethyl)quinoline-5,8-dione (**5**) in good yield.

Attempts to prepare 6-bromomethylquinoline-5,8-dione using the same bromination procedure failed to give the desired product.

The preparation of 3-bromo-2-bromomethyl-6,7-dimethylnaphthazarin (**6a**) was accomplished by the steps shown in Scheme II employing an established method.[22] The starting material, 1′,4′-dimethoxy-2′,3′-dimethyl-1,2-benzocycloheptene-3,7-dione (**13**), was obtained by methylation of 1′,4′-dihydroxy-2′,3′-dimethyl-1,2-benzocycloheptene-3,7-dione (**12**), which in turn was prepared by reaction of 2,3-dimethyl-1,4-dihydroquinone (**11**) and glutaric acid in a molten mixture of aluminum chloride and sodium chloride. Reaction of benzocycloheptenedione **13** with 4 equiv mol of bromine in acetic acid gave the corresponding tetrabromo derivative **14**, which lost 1 mol of bromine in warm pyridine solution to form the cyclopropyl intermediate **15a**. The NMR spectrum of **15a** showed the geminal coupling constant between the two cyclopropyl ring protons to be J = 4.0 Hz, which is in agreement with the reported value for the geminal coupling constant of cyclopropyl protons.[23] Treatment of the cyclopropyl derivative **15a** with a mixture of boiling hydrobromic acid and acetic acid resulted in the formation of 3-bromo-2-bromomethyl-6,7-dimethylnaphthazarin (**6a**).

Biological Evaluation. The antitumor activity of these compounds was assessed in mice bearing Sarcoma 180 ascites cells. The results (Table II) indicated that, with the exception of the 3-benzamido-2-chloromethyl-1,4-naphthoquinone, which was inactive against Sarcoma 180, all newly synthesized naphthoquinones demonstrated strong antitumor activity. Compounds with a 5- or 6-chloro substituent

Scheme II

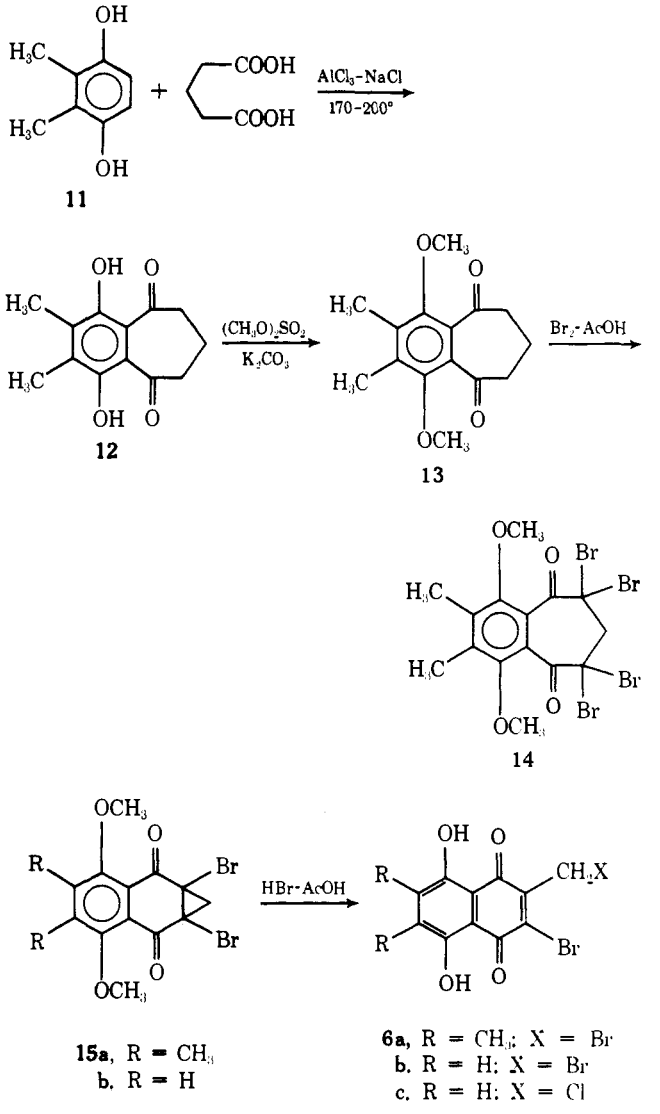


Table III. Effects of Quinoline-5,8-diones and Naphthazarin Derivatives on the Survival Time of Mice Bearing Sarcoma 180 Ascites Cells

Compd	Optimal dosage, mg/kg[a]	Av Δ wt, %[b]	Av survival, days ± SE[c]	T/C[d]
Control		+10.3	13.5 ± 0.4	
5	15	-4.5	21.8 ± 5.2	1.6
10d	20	+6.3	10.6 ± 0.8	0.8
6a	40	-0.8	9.0 ± 0.4	0.8
6b	30	-19.1	19.6 ± 2.3	1.5
6c	10	-6.0	18.2 ± 3.0	1.3
15b	20	+12.6	12.2 ± 0.5	0.8

[a] Administered once daily for 6 consecutive days beginning 24 hr after tumor implantation. [b] Average weight change from onset to termination of drug treatment. [c] Each value represents results from five to ten mice. [d] T/C represents the ratio of the survival time of treated to control animals.

(electron withdrawing) on the benzene ring of the naphthoquinones appeared to possess equal antitumor activity to the corresponding 5- or 6-methyl-substituted (electron donating) analogs. The 3-bromo- and 3-chloro-2-bromomethylnaphthoquinones were essentially equiactive in this neoplastic cell line, prolonging the life span of tumor-bearing mice from about 13 days for untreated control animals to approximately 30 days. Although the optimal daily dosage level of 15 mg/kg of 3-phenyl-2-chloromethyl-1,4-naphthoquinone was about equal in activity to that of 3-chloro- or 3-bromo-2-bromomethylnaphthoquinone, this compound produced satisfactory antitumor activity over a wider range of dose levels, suggesting a higher therapeutic index.

The antineoplastic potencies obtained with the active compounds reported in this paper are within the same order of magnitude as those reported for the parent compounds of this series, i.e., 2-chloromethyl-, 2-bromomethyl-, and 2,3-bis(chloromethyl)naphthoquinones.[2] Recently, a correlation between the redox potential of the quinone ring of this class of compounds and their antineoplastic activities was reported.[24] The similarities in antineoplastic activity between naphthoquinone derivatives are consistent with their closely related redox potentials.

6,7-Bis(bromomethyl)quinoline-5,8-dione (**5**) demonstrated moderate antitumor activity at the optimal daily dosage level of 15 mg/kg, prolonging the life span of Sarcoma 180 bearing mice from 13.5 days for untreated tumor-bearing animals to about 22 days (Table III). 6,7-Dimethylquinoline-5,8-dione, a precursor of **5** which lacks alkylating side chains, was inactive.

Although the chemical synthesis of the 3-bromo-2-bromomethylnaphthazarin (**6b**) and 3-bromo-2-chloromethylnaphthazarin (**6c**) has been reported,[22] the biological activities of these materials as antineoplastic agents have not been explored. These two compounds produced similar moderate extensions of the life span of tumor-bearing mice at optimal dosage levels. Substantial host toxicity, as measured by body weight loss, occurred during treatment with these agents. The newly synthesized dimethylnaphthazarin analog **6a** was inactive under the same conditions at dosage levels up to 40 mg/kg. In a similar manner, the cyclopropyl intermediate **15b** proved to be inactive.

Experimental Section

Biological Methods. Antineoplastic Activity. Compounds were tested for antineoplastic activity in CD-1 mice bearing Sarcoma 180 ascites cells. Complete details of the biological methods have been described earlier.[25]

Chemical Methods. All melting points were measured on a calibrated Thomas-Hoover capillary melting point apparatus. Analyses were performed by the Baron Consulting Co., Orange, Conn. Spectral data were obtained using a Perkin-Elmer 257 grating ir spectrophotometer and Varian T-60A spectrometer and were as expected. The latter instrument used Me_4Si as an internal standard. Where analyses are indicated only by symbols of elements, analytical results obtained for those elements are within ±0.4% of the theoretical values.

Chloromethylation of Naphthoquinones. Naphthoquinones (0.01 mol) with substituents at the 2, 5, or 6 positions were dissolved or suspended in 25 ml of AcOH. Formalin (37%, 10 ml) was added and HCl gas was passed into the mixture for 2–3 hr. The mixture was allowed to stand at room temperature overnight and was poured into 200 ml of ice water. The precipitate was collected, washed with H_2O, dried, and recrystallized from a solvent to give the desired products (Table I).

5-Nitro-6,7-dimethylquinoline (8a). 6,7-Dimethylquinoline (**7**, 7.5 g, 0.05 mol) in 60 ml of H_2SO_4 was nitrated by the dropwise addition of an acid mixture (4 ml of concentrated HNO_3 in 15 ml of H_2SO_4) with cooling using a salted ice bath to keep the temperature about 0°. The mixture was stirred at this temperature for 1 hr and then poured into ice water. The clear solution was made alkaline by addition of concentrated NH_4OH. The precipitate was collected, washed with H_2O, and dried. Fractional crystallization from a mixture of benzene and ligroine gave initially 0.6 g of 8-nitro-6,7-dimethylquinoline (**9**, mp 191–193°) and then 5.5 g (55%) of 5-nitro-6,7-dimethylquinoline (**8a**), mp 140–141°. Anal. ($C_{11}H_{10}N_2O_2$) C, H, N.

5-Acetamido-6,7-dimethylquinoline (8b). To 5-nitro-6,7-dimethylquinoline (**8a**, 6.2 g, 0.03 mol) in AcOH (200 ml) was added 30 ml of Ac_2O and 3.0 g of iron powder. The suspension was heated and stirred at 60° for 20 min and filtered, and the precipitate was washed with AcOH. The filtrate and the washings were combined and lyophilized to dryness. The solid residue was dissolved in 150 ml of $CHCl_3$, washed with a solution of $NaHCO_3$, dried over Na_2SO_4, and evaporated to dryness to yield white crystals. Recrystallization from acetone gave white needles (4.2 g, 65%), mp 201–203°. Anal. ($C_{13}H_{14}N_2O$) C, H, N.

5-Acetamido-6,7-dimethyl-8-nitroquinoline (10b). To 5-acetamido-6,7-dimethylquinoline (**8b**, 1.6 g, 7.5 mmol) in 10 ml of concentrated H_2SO_4 was added dropwise an acid mixture (1 ml of concentrated HNO_3 in 5 ml of concentrated H_2SO_4), with cooling in a salted ice bath. The temperature was kept at 0° for 1 hr and then poured into ice water. The solution was made alkaline by the addition of ammonia and the precipitate was collected, washed with H_2O, dried, and recrystallized from EtOAc to give microcrystals (1.5 g, 77%), mp 198–200°. Anal. ($C_{13}H_{13}N_3O_3$) C, H, N.

5-Amino-6,7-dimethyl-8-nitroquinoline (10c). 5-Acetamido-6,7-dimethyl-8-nitroquinoline (**10b**, 1 g, 3.9 mmol) was refluxed in 25 ml of concentrated HCl for 2.5 hr. The red solution that formed was concentrated under reduced pressure and diluted to 25 ml with H_2O. The solution was made alkaline by the addition of NH_4OH. The precipitate which formed was collected and recrystallized from benzene to give brown crystals (0.4 g, 47%), mp 202–205°. Anal. ($C_{11}H_{11}N_3O_2$) C, H, N.

6,7-Dimethylquinoline-5,8-dione (10a). Method 1. 5-Amino-6,7-dimethyl-8-nitroquinoline (**10c**, 1 g, 4.6 mmol) and 0.5 g of 10% Pd/C were suspended in 100 ml of EtOH; the mixture was hydrogenated under 30 psi of pressure for 2 hr. The catalyst was removed by filtration and the solvent was evaporated to dryness under reduced pressure. The gummy residue was dissolved in dilute HCl, and $FeCl_3$ (2 g) in a small volume of H_2O was added. After stirring at room temperature for 3 hr, the solution was neutralized by addition of $NaHCO_3$ and the mixture was extracted several times with $CHCl_3$. The $CHCl_3$ extracts were combined, dried, and evaporated to dryness. The brown residual solid was chromatographed on a column of silica gel, using EtOAc as eluent, to give yellow crystals. Recrystallization from benzene and ligroine gave yellow needles (0.4 g, 46%), mp 164–166°.

Method 2. 5-Amino-6,7-dimethylquinoline (**8c**, 1.8 g, 0.01 mol) in 500 ml of acetone was added with stirring to a solution of Fremy's salt (13 g in 500 ml of 0.05 *M* KH_2PO_4). The solution was stirred at room temperature overnight, diluted with 1 l. of H_2O, and extracted with $CHCl_3$ three times. The $CHCl_3$ extracts were combined, dried over Na_2SO_4, and evaporated to dryness. The yellow solid was recrystallized from benzene to yield 1.5 g (80%) of yellow needles, mp 165–167°.

Compounds obtained from methods 1 and 2 were identical in ir and NMR spectra. Anal. ($C_{11}H_9NO_2$) C, H, N.

6,7-Bis(bromomethyl)quinoline-5,8-dione (5). 6,7-Dimethylquinoline-5,8-dione (**10a**, 0.27 g, 1.4 mmol), *N*-bromosuccinimide (0.43 g, 2.8 mmol), and catalytic amounts of benzoyl peroxide were refluxed in 25 ml of CCl_4 overnight. The mixture was filtered and the filtrate was evaporated to dryness. The yellow oily residue was crystallized from ethyl acetate and petroleum ether to give yellow microcrystals (150 mg, 30%), mp 127–129°. Anal. ($C_{11}H_7NO_2Br$) C, H, N, Br.

1′,4′-Dihydroxy-2′,3′-dimethyl-1,2-benzocycloheptene-3,7-dione (12). To a molten mixture of anhydrous $AlCl_3$ (300 g) and sodium chloride (100 g) at 180° was added, in small portions with stirring, a mixture of 2,3-dimethylhydroquinone (22 g, 0.16 mol) and glutaric acid (21 g, 0.16 mol); the temperature was not allowed to exceed 195°. The mixture was cooled and decomposed with water (1 l.) and concentrated HCl (500 ml), and the precipitate which formed was collected. Recrystallization from ethanol gave 20 g (53%) of yellow crystals, mp 82–83°. Anal. ($C_{13}H_{14}O_4$) C, H.

1′,4′-Dimethoxy-2′,3′-dimethyl-1,2-benzocycloheptene-3,7-dione (13). Ketone 12 (5 g, 0.02 mol), anhydrous potassium carbonate (6.5 g, 0.04 mol), and dimethyl sulfate (8 g, 0.06 mol) were refluxed in 50 ml of dry acetone for 8 hr. The mixture was filtered and the filtrate was evaporated to dryness. The oily residue was crystallized from ethyl acetate and ligroine to give colorless crystals (3.2 g, 61%), mp 79–81°. Anal. ($C_{15}H_{18}O_4$) C, H.

2,3-Dibromo-1,2,3,4-tetrahydro-5,8-dimethoxy-6,7-dimethyl-2,3-methylene-1,4-dioxonaphthalene (15a). Bromine (6.4 g, 0.04 mol) in 5 ml of AcOH was added slowly with stirring to benzocycloheptenedione 13 (2.62 g, 0.01 mol) in AcOH (30 ml). Stirring was continued overnight at room temperature. The yellow tetrabromo precipitate 14 was collected, washed with AcOH followed by EtOH, and dried (3.5 g). The tetrabromo derivative was dissolved in 20 ml of warm pyridine and was allowed to stand at room temperature overnight. The resulting brown suspension was added to 100 ml of diluted HBr. The precipitate which formed was collected and dissolved in 60 ml of EtOAc, filtered, and evaporated to dryness. The gummy residue was purified by column chromatography (silica gel) using as eluent EtOAc and ligroine (1:5, v/v). Recrystallization from ethanol gave pale yellow crystals (0.6 g, 14%): mp 165–166°; NMR ($CDCl_3$) δ 2.25 (s, 6), 2.33 (d, J = 4 Hz, 1), 2.70 (d, J = 4 Hz, 1), and 3.82 (s, 6); ir (KBr) 1690 cm^{-1} (–C=O). Anal. ($C_{15}H_{14}Br_2O_4$) C, H, Br.

3-Bromo-2-bromomethyl-6,7-dimethylnaphthazarin (6a). Compound 15a (0.7 g) in 20 ml of glacial AcOH which contained 3 ml of concentrated HBr was boiled for 10 min. The resulting brown mixture was poured into ice H_2O. The precipitate was collected, dried, and recrystallized from EtOAc and ligroine to give brown crystals (0.2 g, 30%), mp 205° dec. Anal. ($C_{13}H_{10}Br_2O_4$) C, H, Br.

Acknowledgment. This research was supported in part by U.S. Public Health Service Grant CA-02817 from the National Cancer Institute.

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Studies in Antifertility Agents. 8. Seco Steroids. 2. 5,6-Secoestradiol and Some Related Compounds

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Three-ring β-secoestradiols, 2α,3β- and 2β,3β-2-ethyl-3-(*p*-hydroxyphenyl)-6β-methyl-*trans*-bicyclo[4.3.0]nonan-7β-ols, have been synthesized and some of them shown to possess significant antiimplantation activity in rats.

The relationship between estrogenic, antiestrogenic, and antifertility activity, in particular postcoital antifertility activity, has been the subject of considerable discussion.[1] A critical estrogen–progesterone balance is necessary for implantation of the blastocyst and its subsequent development, and any alteration in this balance may lead to termination of pregnancy. Compounds which are able to alter the estrogen–progesterone ratio level in the uterine milieu possess the inherent possibility of acting as postcoital antifertility agents. Thus, while estrogens are at one phase or another essential in the normal process of mating and early pregnancy, they prevent conception at practically all stages in most mammalian species. In our search for new postcoital antifertility agents secoestrones seemed of potential interest, as these could either mimic, compete with, and dis-

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