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Nonsteroidal Antiinflammatory Agents. 2. Derivatives/Analogues of Dibenz[*b*,*e*]oxepin-3-acetic Acid

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6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepins and some related compounds have been synthesized and evaluated for antiinflammatory effect according to the carrageenan paw edema method in rats. The structure–activity relationships have been discussed among acetic acid, carboxylic acid, alcohol, and tetrazole derivatives of dibenzoxepins and acetic acid derivatives of thienobenzoxepins and of the corresponding thiepins. The 3-isopropyl alcohol **9** and 11-deoxo-3-propionic acid (**49**) were more active than indomethacin but not as active as the title compound (i.e., **43**). Carboxylic acids, tetrazoles, esters, amides, and ketones were less active than the corresponding acetic acids. Three compounds (**31**, **33**, and **34**) were evaluated for ulcerogenicity and lethality but none surpassed 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin-3-acetic acid (**41**) in therapeutic ratio.

Some compounds (**40–43**) in the series of 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepinacetic acids were already reported[1] to have favorable properties as antiinflammatory agents in comparison with indomethacin, phenylbutazone, and ketoprofen. Aultz et al.[2] have recently reported on the chemical and pharmacological studies of dibenzoxepin-2-acetic acids and their thieno and furano analogues independently of our work. In the present paper, we describe the structure–activity relationships of the following compounds which were synthesized in this institute: (1) 6,11-dihydro-11-oxodibenz[*b*,*e*]oxepinacetic acid derivatives (esters, amides, and deoxo compounds), (2) dibenzoxepins with alcohol, carboxylic acid, or tetrazole moiety in the "A" ring, (3) dibenzoxepins with the acetic acid moiety in the "C" ring (Figure 1), and (4) thienobenzoxepins and the corresponding thiepins.

Chemistry. The synthetic routes chosen for the preparation of alcohol, tetrazole, tetrazolylmethyl, butenone, and butanone derivatives (IV, VII, VIII, and **29**) of dibenz[*b*,*e*]oxepin are illustrated in Scheme I. The cyano compounds I, prepared by condensation of 2-cyanobenzyl halide with 3- or 4-hydroxyphenylalkanols, were hydrolyzed with 5 N NaOH to the corresponding carboxylic acids. After acetylation of the alcohol moiety to protect it against phosphorylation, cyclization of the acetoxy compounds II using PPE afforded the dibenz[*b*,*e*]oxepins III, which were deblocked by successive treatment with NaOH in MeOH to provide the free alcohols IV. However, an attempt to cyclize the *p*-acetoxymethyl compound II was unsuccessful and only gave an unknown compound containing phosphorus. Consequently, the synthesis of the 2-acetoxymethyldibenz[*b*,*e*]oxepin (**2**) was accomplished by brominating the 2-methyl compound and treating the resulting 2-bromomethyl compound 1 with AcONa in AcOH.

The chloromethyl compounds were prepared from the corresponding alcohols IV (n = 0) with $SOCl_2$ and converted to the cyanomethyl compounds VI (m = 1) by reaction with NaCN. Oxidation of IV (n = 0) with CrO_3 afforded the carboxylic acids V, which were converted to the corresponding cyano compounds VI (m = 0) by successive treatment with $SOCl_2$, 28% NH_4OH, and tosyl chloride–pyridine–DMF via the carboxamides. Treatment of VI (m = 0, 1) with NaN_3 gave the corresponding tetrazole derivatives VII. On the other hand, MnO_2 oxidation of IV (n = 0) provided the aldehydes which were condensed with an appropriate methyl ketone to yield VIII. The 3-butenone compound VIII (R = Me) was hydrogenated to **29**, using Pd/C as a catalyst.

Reaction of the dibenz[*b*,*e*]oxepin-2- and -3-acetic acids with diethylaminoethyl chloride gave the corresponding esters, while the other esters and amides shown in Table I were prepared from the oxepinacetic acids by treatment with $SOCl_2$ and then with alcohols, amines, or a phenol.

The phenoxymethylbenzoic acid **65**, prepared from 5-hydroxymethylphthalide with sodium phenolate, was treated with $SOCl_2$ and then cyclized to the dibenz[*b*,*e*]oxepin **37** in the presence of $AlCl_3$. Cyanation of **37** with NaCN followed by acid hydrolysis yielded **39**.

Some dibenz[*b*,*e*]oxepinone derivatives were reduced as indicated in Scheme II. Reaction of the 2-acetic acids IXm with Zn in AcOH smoothly produced the 11-methylene compounds **45** and **46**, whereas that of 3-acetic acids IXn gave many kinds of products, and heating of IXn with Zn–amalgam in HCl–toluene afforded the corresponding 11-methylene compounds **48** and **49**. Further, reduction of IXm with $NaBH_4$ and treatment of IXn with Zn in NaOH gave the corresponding 11-hydroxy compounds **44** and **47**, respectively. Various dibenz[*b*,*e*]oxepin derivatives obtained above and their intermediates are listed in Tables I–IV.

Acetic acid derivatives of thienobenzoxepins and the corresponding thiepins were synthesized by the procedure described in series 3.[3]

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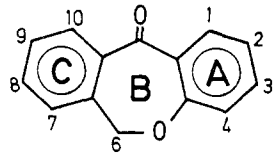
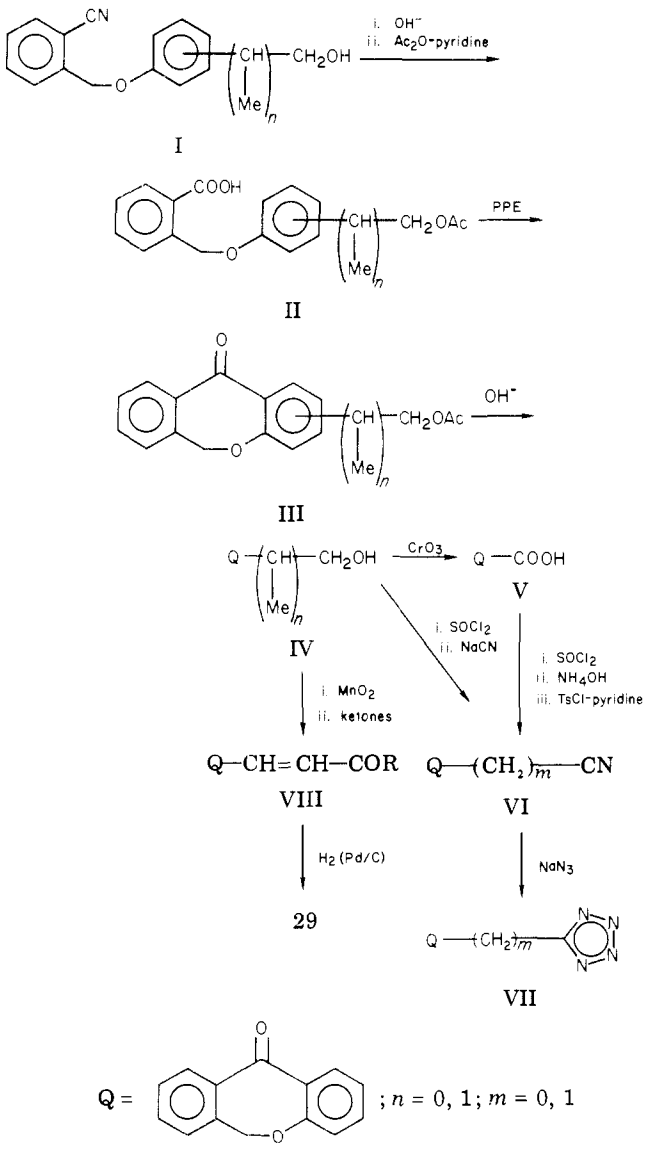
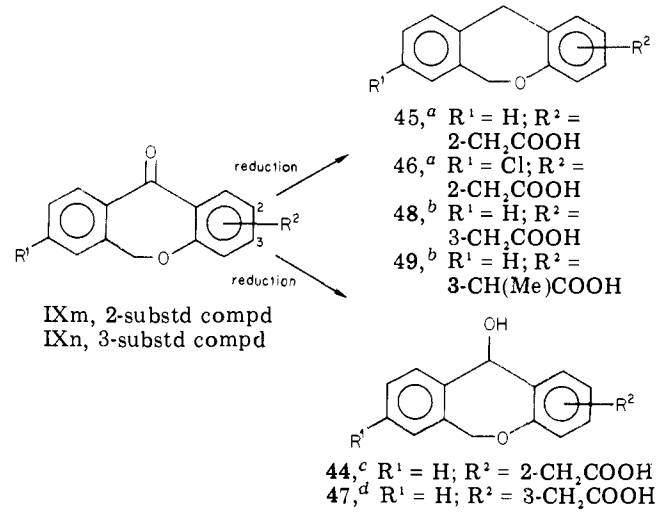


Figure 1.

Scheme I



Scheme II



45,[a] R¹ = H; R² = 2-CH_2COOH
46,[a] R¹ = Cl; R² = 2-CH_2COOH
48,[b] R¹ = H; R² = 3-CH_2COOH
49,[b] R¹ = H; R² = 3-CH(Me)COOH

IXm, 2-substd compd
IXn, 3-substd compd

44,[c] R¹ = H; R² = 2-CH_2COOH
47,[d] R¹ = H; R² = 3-CH_2COOH

[a] Zn–AcOH. [b] Zn–amalgam. [c] $NaBH_4$. [d] Zn–NaOH.

Structure–Activity Relationships. As seen in Table V, replacement of the acetic acid moiety in **40** and **41** by carboxylic acid (**12**, **13**), tetrazole (**20**, **21**), and tetrazolylmethyl (**22**, **23**) moieties decreased activity, although some compounds[4,5] with such substituents were reported to retain activity. According to Harrison et al.,[6] naproxen and naproxol, which has the 2-propanol moiety instead of the α-methylacetic acid of naproxen, are regarded as having almost the same antiinflammatory effect. However, activities of the compounds with the 2-propanol moiety (**8** and **9**) were lower than those of the corresponding acids **42** and **43**, although **8** and **9**, respectively, were effective almost equally to and considerably greater than indomethacin. Conversion of the α-methylacetic acid moiety in naproxen[7] to the butenone moiety and esterification and amidation of the acetic acid moiety in ketoprofen[4] and indomethacin[8] are known to produce no significant change in antiinflammatory activity and to decrease gastric irritability. In the case of dibenzoxepins, however, ketones **26–29** were much less potent than the corresponding acids **40–43** in inhibiting carrageenan edema. Activities of esters and amides were also lower than those of the parents (**30**, **35** vs. **40**; **31–34**, **36** vs. **41**). Relatively high activities of the alcohols **8** and **9** and esters **31** and **34** suggest a possibility that these compounds may be metabolized to the corresponding acids. The superiority of 3-substituted compounds to 2-substituted ones in anticarrageenan activity was observed not only in the acids (**40** vs. **41**, **42** vs. **43**) but also in 2-propanols (**8** vs. **9**) and esters (**30** vs. **31**).

Of these compounds, **31**, **33**, and **34** were further subjected to the gastric irritation test and measurement of LD_{50} values. These were chosen because **31** and **34** were comparatively high in anticarrageenan activities and **33** possesses the dioxolane moiety which was reported in the ketoprofen series to produce less ulceration in spite of high antiinflammatory activity.[8] Our experiments showed that compounds **31** and **33** tended to be weaker in causing gastric lesions as compared with **41**, while **34** was comparable to **41** in this effect (Table VI). LD_{50} values of **31**, **33**, and **34** were not significantly different from that of **41**. The ratios, UD_{50}/ID_{50} and LD_{50}/ID_{50}, were not so much different between **31** and **41** but much smaller in **33** and **34** than in **41**.

Compound **39** which has the acetic acid moiety at the 8 position was much less effective than **40** and **41**. This compound is related to **41** by a seemingly minor change, the reversal of the $-CH_2O-$ bridge; yet, it is only about one-tenth times as active as **41**. This change seemed to be crucial to the receptor.

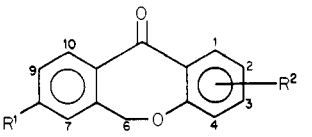
Reduction of the carbonyl moiety at the 11 position (**44–49**) lowered activity. However, it is worth noticing that **49**, in spite of lack of the 11-carbonyl group, was significantly more effective than indomethacin.

Some structural modifications were made of the "B" and "C" rings of dibenzoxepins (Figure 1) to examine their influence on activity. The tests revealed that replacement of the "C" ring by the thiophene ring (**50**, **51**, and **52**) weakened activity, as is clear from the comparison with the data of the corresponding dibenzoxepins **41**, **40**, and **43**. Conversion of –O– in **50** and **51** to –S– (**53**, **54**) did not retain potency either. Of these thieno derivatives, **50–52** and **55** had activities 0.31–0.59 times that of indomethacin.

Experimental Section

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. NMR spectra were recorded on

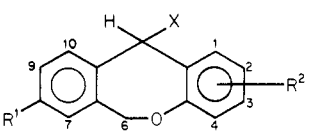
Table I. 6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin Derivatives



No.	R^1	R^2	Mp, °C	Recrystn solvent	Formula[a]
1	H	2-CH_2Br	109-110	$(i\text{-Pr})_2O$	$C_{15}H_{11}BrO_2$
2	H	2-CH_2OAc	89-92	Et_2O	$C_{17}H_{14}O_4$
3	H	3-CH_2OAc	95.5-96.5	Et_2O	$C_{17}H_{14}O_4$
4	H	2-CH(Me)CH_2OAc	Syrup		$C_{19}H_{18}O_4$
5	H	3-CH(Me)CH_2OAc	Syrup		$C_{19}H_{18}O_4$
6	H	2-CH_2OH	86-88	C_6H_6-*n*-C_6H_{14}	$C_{15}H_{12}O_3$
7	H	3-CH_2OH	79.5-80.5	Xylene-ligroine	$C_{15}H_{12}O_3$
8	H	2-CH(Me)CH_2OH	82-84	Et_2O-petr ether	$C_{17}H_{16}O_3$
9	H	3-CH(Me)CH_2OH	Syrup		$C_{17}H_{16}O_3$
10	H	2-CH_2Cl	98-101	Et_2O	$C_{15}H_{11}ClO_2$[b]
11	H	3-CH_2Cl	93-94	$(i\text{-Pr})_2O$	$C_{15}H_{11}ClO_2$
12	H	2-COOH	248-249	AcOEt	$C_{15}H_{10}O_4$
13	H	3-COOH	236-237	AcOEt	$C_{15}H_{10}O_4$
14	H	2-$CONH_2$	225.5-228	MeOH	$C_{15}H_{11}NO_3$
15	H	3-$CONH_2$	204.5-206	MeOH	$C_{15}H_{11}NO_3$
16	H	2-CN	168-169	AcOEt	$C_{15}H_9NO_2$
17	H	3-CN	138.5-139	AcOEt	$C_{15}H_9NO_2$
18	H	2-CH_2CN	120.5-122.5	AcOEt	$C_{16}H_{11}NO_2$
19	H	3-CH_2CN	130.5-131.5	EtOH	$C_{16}H_{11}NO_2$
20	H	2-Tetrazole	249-250	AcOEt	$C_{15}H_{10}N_4O_2$
21	H	3-Tetrazole	247-247.5	AcOEt	$C_{15}H_{10}N_4O_2$
22	H	2-Methyltetrazole	184.5-185.5	MeOH	$C_{16}H_{12}N_4O_2$
23	H	3-Methyltetrazole	187-188.5	EtOH	$C_{16}H_{12}N_4O_2$
24	H	2-CHO	133-134	C_6H_6-ligroine	$C_{15}H_{10}O_3$
25	H	3-CHO	169-172	C_6H_6-*n*-C_6H_{14}	$C_{15}H_{10}O_3$
26	H	2-CH=CHCOMe	101-102	C_6H_6	$C_{18}H_{14}O_3$
27	H	3-CH=CHCOMe	143.5-144.5	C_6H_6	$C_{18}H_{14}O_3$
28	H	2-CH=CHCO-C_6H_4-*p*-OMe	167-167.5	C_6H_6-ligroine	$C_{24}H_{18}O_4$
29	H	3-$(CH_2)_2$COMe	64-65	AcOEt-*n*-C_6H_{14}	$C_{18}H_{16}O_3$
30	H	2-$CH_2COO(CH_2)_2N(Et)_2 \cdot HCl$	117-119	MeOH-AcOEt	$C_{22}H_{26}ClNO_4$
31	H	3-$CH_2COO(CH_2)_2N(Et)_2 \cdot HCl$	166-168	MeOH-AcOEt	$C_{22}H_{26}ClNO_4$
32	H	3-CH_2COO-C_6H_4-*o*-COOH	128-131	Toluene	$C_{23}H_{16}O_6$
33	H	3-CH_2COOCH_2 	Syrup		$C_{22}H_{22}O_6$
34	H	3-$CH_2COOCH_2CH(OH)CH_2(OH)$	Syrup		$C_{19}H_{18}O_6$
35	H	2-CH_2CONH_2	157-159[c]	MeOH	$C_{16}H_{13}NO_3$
36	H	3-$CH_2CONHCH_2COOEt$	146-148	EtOH	$C_{20}H_{19}NO_5$
37	CH_2Cl	H	83-84	*n*-C_6H_{14}	$C_{15}H_{11}ClO_2$
38	CH_2CN	H	99-100	C_6H_6-*n*-C_6H_{14}	$C_{16}H_{11}NO_2$
39	CH_2COOH	H	176-178	$(Me)_2CO$-H_2O	$C_{16}H_{12}O_4$
40[d]	H	2-CH_2COOH	131-132.5		
41[d]	H	3-CH_2COOH	110.5-111.5		
42[d]	H	2-CH(Me)COOH	Syrup		
43[d]	H	3-CH(Me)COOH	115.5-117		

[a] The compounds were analyzed for C, H, and, where present, Br, Cl, and N; analytical results were within ±0.4% of the theoretical values unless otherwise indicated. [b] Calcd: C, 69.64; Cl, 13.71. Found: C, 69.14; Cl, 13.22. [c] Lit.[2a] mp 156-157 °C. [d] Compounds 40-43 were reported in the previous paper.[1]

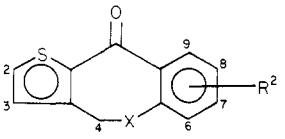
Table II. 6,11-Dihydrodibenz[*b*,*e*]oxepin Derivatives



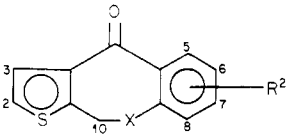
No.	R^1	R^2	X	Mp, °C	Recrystn solvent	Formula[a]
44	H	2-CH_2COOH	OH	138-140	AcOEt-*n*-C_6H_{14}	$C_{16}H_{14}O_4$
45	H	2-CH_2COOH	H	165.5-166.5[b]	C_6H_6	$C_{16}H_{14}O_3$
46	Cl	2-CH_2COOH	H	194-195	C_6H_6-*n*-C_6H_{14}	$C_{16}H_{13}ClO_3$
47	H	3-CH_2COOH	OH	127 dec	AcOEt-*n*-C_6H_{14}	$C_{16}H_{14}O_4$
48	H	3-CH_2COOH	H	151.5-153	$CHCl_3$-petr ether	$C_{16}H_{14}O_3$
49	H	3-CH(Me)COOH	H	115-117	C_6H_6-petr ether	$C_{17}H_{16}O_3$

[a] See footnote *a*, Table I. [b] Lit.[2a] mp 155-157 °C.

Table III. Thienobenzoxepin and -thiepin Analogues



50-54

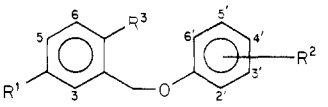


55

No.	X	R^2	Mp, °C	Recrystn solvent	Formula[a]
50	O	7-CH_2COOH	139-141	AcOEt-n-C_6H_{14}	$C_{14}H_{10}O_4S_1$
51	O	8-CH_2COOH	172-173	$CHCl_3$	$C_{14}H_{10}O_4S_1$
52	O	7-CH(Me)COOH	142-143.5	C_6H_6	$C_{15}H_{12}O_4S_1$
53	S	7-CH_2COOH	211-213	AcOEt	$C_{14}H_{10}O_3S_2$
54	S	8-CH_2COOH	202-204	AcOEt	$C_{14}H_{10}O_3S_2$
55	S	7-CH_2COOH	184-186	AcOEt	$C_{14}H_{10}O_3S_2$

[a] See footnote *a*, Table I.

Table IV. Intermediates for Table I



No.	R^1	R^2	R^3	Mp, °C	Recrystn solvent	Formula[a]
56	H	3'-CH_2OH	CN	90-91.5	i-PrOH	$C_{15}H_{13}NO_2$
57	H	3'-CH(Me)CH_2OH	CN	Syrup		
58	H	4'-CH(Me)CH_2OH	CN	77-80	Et_2O	$C_{17}H_{17}NO_2$[b]
59	H	3'-CH_2OH	COOH	135-136.5	C_6H_6-Et_2O	$C_{15}H_{14}O_4$
60	H	3'-CH(Me)CH_2OH	COOH	109-112	$(Me)_2CO$	$C_{17}H_{18}O_4$
61	H	4'-CH(Me)CH_2OH	COOH	147-149.5	$(Me)_2CO$	$C_{17}H_{18}O_4$
62	H	3'-CH_2OAc	COOH	108-108.5	$(i\text{-}Pr)_2O$	$C_{17}H_{16}O_5$
63	H	3'-CH(Me)CH_2OAc	COOH	Syrup		
64	H	4'-CH(Me)CH_2OAc	COOH	83-88	Et_2O-petr ether	$C_{19}H_{20}O_5$
65	CH_2OH	H	COOH	149-150	AcOEt-C_6H_6	$C_{15}H_{14}O_4$

[a] See footnote *a*, Table I. [b] N: calcd, 5.24; found, 4.81.

Table V. Antiinflammatory Activities of Dibenz[*b*,*e*]oxepins and Related Compounds

Compd	Antiinflam act. (carrageenan edema), ID_{50},[a] μmol/kg po	Compd	Antiinflam act. (carrageenan edema), ID_{50},[a] μmol/kg po
8	28.3 (24.6-33.5)	**39**	130.8 (93.2-206.1)
9	6.0 (4.5-9.3)	**40**	50.0 (40.2-67.4)
12	>70.8	41	12.9 (10.1-17.1)
13	>70.8	42	9.2 (6.7-14.5)
20	>64.7	43	2.7 (2.0-4.2)
21	>64.7	44	>66.6
22	>61.6	45	99.1 (79.8-131.0)
23	>61.6	46	>62.3
26	>161.7	47	>66.6
27	>161.7	48	35.0 (30.7-40.5)
28	>121.5	49	12.7 (11.1-14.5)
29	96.7 (79.2-124.5)	50	61.3 (50.7-77.7)
30	132.7 (79.0-316.9)	51	75.1 (61.3-97.0)
31	16.8 (13.4-21.5)	52	43.7 (33.0-68.3)
32	91.6 (64.4-148.1)	53	>62.0
33	100.4 (81.3-130.2)	54	>62.0
34	31.0 (24.2-43.2)	55	40.0 (34.1-47.9)
35	>67.4	Indometh-acin	23.5 (19.8-30.2)
36	>50.9		

[a] ID_{50} values were obtained from the regression line fitted by the least-squares method and their 95% fiducial limits described in parentheses were calculated according to Filler's equation.[9]

a Hitachi R-20B spectrometer (60 MHz) using Me_4Si as an internal standard.

2-Bromomethyl-6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin (1). To a stirred and irradiated (tungsten lamp) solution of 2-methyl-6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin[11] (2.00 g, 8.9 mmol) in 1,2-dibromoethane (5 mL) was added a solution of Br_2 (1.70 g, 11 mmol) in 1,2-dibromoethane (5 mL) dropwise over a period of 1 h at 150 °C. After cooling, the reaction mixture was poured into ice water and extracted with $CHCl_3$ and the washed, dried (Na_2SO_4) extract was concentrated. The residue was recrystallized from $(i\text{-}Pr)_2O$ to yield colorless crystals (0.40 g, 15%): mp 109–110 °C; NMR ($CDCl_3$) δ 4.52 (s, 2 H, $-CH_2Br$), 5.18 (s, 2 H, $-CH_2O-$), 7.05 (d, J = 10 Hz, 1 H, C-4 proton), 7.30–7.70 (m, 4 H, C-3 and C-7 to C-9 protons), 7.90 (m, 1 H, C-10 proton), and 8.36 (d, J = 3.5 Hz, 1 H, C-1 proton).

2-Acetoxymethyl-6,11-dihydro-11-oxodibenz[*b*,e]oxepin (2). A solution of 1 (7.50 g, 24.8 mmol) and AcONa (6.00 g, 73 mmol) in AcOH (25 mL) was refluxed for 1 h and concentrated

Table VI. Pharmacological Activities of 6,11-Dihydro-11-oxodibenz[b,e]oxepins

Compd	Antiinflam act. (carrageenan edema), ID_{50}, μmol/kg po	Gastric lesion, UD_{50},[a] μmol/kg po	LD_{50},[a] μmol/kg po	UD_{50}/ID_{50}	LD_{50}/ID_{50}
31	16.8 (13.4-21.5)	482.8 (521.9-724.2)	369.7 (305.5-447.4)	28.7	22.0
33	100.4 (81.3-130.2)	559.1 (329.0-950.6)	241.4 (196.1-296.8)	5.6	2.4
34	31.0 (24.2-43.2)	251.5 (125.9-503.0)	277.8 (237.5-325.1)	8.1	9.0
41	12.9 (10.1-17.1)	279.1 (169.1-460.4)	382.9 (294.5-497.8)	21.6	29.7

[a] UD_{50}, LD_{50}, and their 95% fiducial limits figured in parentheses were calculated according to Litchfield-Wilcoxon's method.[10]

in vacuo. The oily residue was poured into ice water and extracted with $CHCl_3$, and the extract was washed with 2% $NaHCO_3$ and water and dried. After removal of the solvent, the crude product was purified by silica gel chromatography using C_6H_6 and crystallized from Et_2O to yield **2** (4.75 g, 68%), mp 89–92 °C.

3-Acetoxymethyl-6,11-dihydro-11-oxodibenz[b,e]oxepin (3). A mixture of **62** (6.00 g, 20 mmol) and PPE (70.0 g) was stirred at 105 °C for 40 min and worked up in the same manner as described in the previous paper.[1] The crude product was chromatographed on silica gel using C_6H_6–ligroine (95:5) and crystallized from Et_2O to yield colorless crystals (3.50 g, 63%), mp 95.5–96.5 °C.

Similarly, **4** and **5** were prepared from **63** and **64** in 70 and 36% yields, respectively.

6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-methanol (7). To a solution of **3** (10.1 g, 35.6 mmol) in MeOH (500 mL) was added 4% NaOH (85.4 mL), and the mixture was stirred at room temperature for 19 h, concentrated to one-third in vacuo, and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water, dried, and concentrated in vacuo to a yellow oil which was crystallized from xylene–ligroine to yield colorless crystals (7.71 g, 90%), mp 79.5-80.5 °C.

Compounds **6**, **8**, and **9** were prepared similarly from **2**, **4**, and **5**, and the yields were 90, 71, and 52%, respectively.

3-Chloromethyl-6,11-dihydro-11-oxodibenz[b,e]oxepin (11). A mixture of **7** (2.51 g, 8.96 mmol) and $SOCl_2$ (70 mL) was refluxed for 1 h. After concentration, the residue was purified by column chromatography on silica gel using $CHCl_3$ to provide an orange solid. Crystallization from $(i\text{-Pr})_2O$ gave colorless crystals (1.92 g, 83%), mp 93–94 °C.

Compound **10** was prepared similarly from **6** in 58% yield.

6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-carboxylic Acid (13). To a solution of **7** (7.21 g, 30 mmol) in AcOH (30 mL) was added CrO_3 (9.00 g, 90 mmol) at a temperature below 30 °C. After the reaction mixture had been stirred at room temperature for 0.5 h, addition of water (600 mL) afforded crude product which was crystallized from AcOEt to give colorless crystals (6.74 g, 88%), mp 236–237 °C.

Compound **12** was prepared similarly from **6** in 45% yield.

6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-carboxamide (15). A mixture of **13** (3.05 g, 12 mmol) in $SOCl_2$ (70 mL) was refluxed for 1 h. After concentration in vacuo, the residue was dissolved in C_6H_6 (90 mL) and 28% NH_4OH (30 mL) was added. The reaction mixture was stirred at room temperature for 1 h. The collected precipitate was crystallized from MeOH to afford colorless crystals (2.81 g, 93%), 204–206 °C.

Compound **14** was prepared similarly from **12** in 89% yield.

6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-carbonitrile (17). A mixture of **15** (2.53 g, 10 mmol), tosyl chloride (2.85 g, 15 mmol), pyridine (3 mL), and DMF (20 mL) was stirred at 100 °C for 2 h. After treatment of the reaction mixture with water (300 mL) and $CHCl_3$, the separated $CHCl_3$ layer was dried and concentrated in vacuo to provide a solid which was crystallized from MeOH to yield colorless crystals (2.17 g, 92%), mp 138.5–139 °C.

Compound **16** was prepared similarly from **14** in 95% yield.

6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-acetonitrile (19). A mixture of **11** (1.59 g, 6.15 mmol), NaCN (0.36 g, 7.34 mmol), and Me_2SO (36 mL) was stirred at 80–90 °C for 7 h. After addition of water, the reaction mixture was extracted with $CHCl_3$. The washed and dried extract was concentrated in vacuo to an oil, which was purified by column chromatography on silica gel using $CHCl_3$–C_6H_6 (1:1). Crystallization from EtOH gave pale yellow crystals (0.42 g, 27%), mp 130.5–131.5 °C.

Compound **18** was prepared similarly from **10** in 87% yield.

3-(5-Tetrazolylmethyl)-6,11-dihydro-11-oxodibenz[b,e]oxepin (23). A mixture of **19** (0.42 g, 1.68 mmol), NH_4Cl (0.45 g, 8.38 mmol), and NaN_3 (0.55 g, 8.83 mmol) in dry DMF (8.4 mL) was stirred at 120 °C for 6 h. After removal of the solvent, the residue was suspended in water (50 mL), basified with 5% NaOH, and washed with Et_2O, and the aqueous layer was decolorized by charcoal and filtered. The filtrate was acidified to pH 2 with 10% HCl and extracted with Et_2O. The Et_2O layer was washed with water, dried, and concentrated to a solid in vacuo which was crystallized from EtOH to afford colorless crystals (0.27 g, 54%), mp 187–188.5 °C.

Compounds **20–22** were prepared similarly from **16–18**, and the yields were 77, 89, and 78%, respectively.

6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-carboxaldehyde (25). A suspension of **7** (6.83 g, 2.85 mmol) and active MnO_2 (25.0 g, 290 mmol) in C_6H_6 (110 mL) was refluxed for 3 h. The mixture was quickly filtered without suction. The precipitate was washed with C_6H_6 and the combined filtrate was concentrated. The residue was crystallized from C_6H_6–n-C_6H_{14} to give colorless crystals (4.50 g, 66%), mp 169–172 °C.

Compound **24** was prepared similarly in 62% yield from **6**.

6,11-Dihydro-2-(3-oxo-1-butenyl)-11-oxodibenz[b,e]oxepin (26). A mixture of **24** (0.50 g, 2.1 mmol), Me_2CO (25 mL), and 10% aqueous NaOH (1.4 mL) was stirred for 2.5 h and treated with water and $CHCl_3$. The organic layer was dried and concentrated in vacuo. The residue dissolved in $CHCl_3$ was chromatographed on silica gel, and elution with the same solvent afforded **26** which was crystallized from C_6H_6 to give colorless crystals (0.25 g, 43%), mp 101–102 °C.

Compound **27** was prepared similarly from **25** in 84% yield. Compound **28** was prepared from **24** by stirring with *p*-methoxyacetophenone in EtOH under reflux for 1 h in 68% yield.

3-(3-Butanoyl)-6,11-dihydro-11-oxodibenz[b,e]oxepin (29). A mixture of **27** (13.8 g, 49.6 mmol) and 5% Pd/C (4.00 g) in $(Me)_2CO$ (250 mL) was shaken with H_2 at room temperature. After cessation of H_2 uptake, the catalyst was removed by filtration and the solvent was evaporated. The residue was purified by silica gel chromatography using $CHCl_3$. Crystallization from AcOEt–n-C_6H_{14} afforded colorless crystals (7.42 g, 53%), mp 64–65 °C.

***N,N*-Diethylaminoethyl 6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-acetate Hydrochloride (31).** A mixture of **41**[1] (1.0 g, 3.7 mmol), 2-diethylaminoethyl chloride hydrochloride (0.64 g, 3.7 mmol), K_2CO_3 (1.0 g), and DMF (12 mL) was stirred for 5 h at room temperature and concentrated in vacuo. The Me_2CO solution of the crude product obtained from the $CHCl_3$ extract of the residue was treated with active charcoal, converted into the HCl salt, and crystallized from MeOH–AcOEt to afford colorless crystals (0.70 g, 41%), mp 166–168 °C.

Compound **30** was prepared similarly in 41% yield from **40** (IXm, R^1 = H; R^2 = 2-CH_2COOH).

2,2-Dimethyl-1,3-dioxolane-4-methyl 6,11-Dihydro-11-oxodibenz[b,e]oxepin-3-acetate (33). A mixture of **41** (5.00 g, 19 mmol) and $SOCl_2$ (25 mL) was refluxed for 2 h and evaporated to dryness in vacuo. To the residue were added pyridine (2.5 mL) and 2,2-dimethyl-1,3-dioxolane-4-methanol (5.36 g, 40.5 mmol) under ice cooling. The mixture was stirred for 2 h at room temperature, poured into ice water, and extracted with Et_2O. The organic layer was washed with aqueous $NaHCO_3$ and water, dried, and concentrated. Purification of the residue by silica gel chromatography using $CHCl_3$ as eluent provided a light yellow oil (4.30 g, 60%).

Compound **32** was prepared by stirring the acid halide which was obtained by the procedure described above with salicylic acid

and $(Et)_3N$ in dry toluene for 3 h in 74% yield.

2,3-Dihydroxypropyl 6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-3-acetate (34). To a solution of **33** (4.25 g, 11.1 mmol) in $MeOCH_2CH_2OH$ (40 mL) were added H_3BO_3 (4.00 g) and 2 drops of concentrated HCl. The mixture was refluxed for 0.5 h, poured into ice water, and extracted with Et_2O. The extract was washed with aqueous $NaHCO_3$ and brine solution, dried, and evaporated. The residue in $CHCl_3$ was chromatographed on silica gel, eluting with the same solvent, to give a light yellow oil (2.56 g, 70%).

6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-2-acetamide (35). A mixture of **40**[1] (1.00 g, 3.7 mmol) and $SOCl_2$ (5.0 mL) was refluxed for 0.5 h. The reaction mixture was concentrated and treated with *n*-C_6H_{14} to give the acid halide as a solid which was separated and dissolved in dry C_6H_6 (50 mL). The solution was saturated with NH_3 gas at 0 °C. The resulting precipitate was washed with 2% Na_2CO_3 and water. Crystallization from MeOH afforded colorless crystals (0.80 g, 81%), mp 157–159 °C.

Compound **36** was prepared from the acid halide by stirring with ethyl glycinate in Et_2O in 50% yield.

8-Chloromethyl-6,11-dihydro-11-oxodibenz[*b*,*e*]oxepin (37). A mixture of **65** (0.2 g, 0.8 mmol) and $SOCl_2$ (1 mL) in dry C_6H_6 (10 mL) was refluxed for 1 h and concentrated to dryness in vacuo. The oily residue was dissolved in dry 1,2-dichloroethane (10 mL), and anhydrous $AlCl_3$ (0.30 g, 2.2 mmol) was added to the solution while stirring in an ice bath. After 10 min, the reaction mixture was poured into ice water and extracted with $CHCl_3$, and the washed, dried extract was concentrated. The residue was purified by silica gel chromatography using $CHCl_3$ and crystallized from *n*-C_6H_{14} to give colorless crystals (0.20 g, 97%), mp 83–84 °C.

6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-8-acetonitrile (38). A mixture of **37** (0.23 g, 0.9 mmol) and NaCN (1.00 g, 20 mmol) in 30% aqueous dioxane (30 mL) was refluxed for 2 h. The crude product obtained from the C_6H_6 extract of the reaction mixture was chromatographed on silica gel using $CHCl_3$ and crystallized from C_6H_6–*n*-C_6H_{14} to yield colorless crystals (0.20 g, 91%), mp 99–100 °C.

6,11-Dihydro-11-oxodibenz[*b*,*e*]oxepin-8-acetic Acid (39). A mixture of **38** (0.10 g, 0.8 mmol) and HCl (1 mL) in 50% aqueous dioxane (6 mL) was refluxed with stirring for 48 h and concentrated. The residue was made basic with 2% NaOH and washed with Et_2O, and the aqueous solution was acidified with 5% HCl. The resulting precipitate was collected and crystallized from aqueous Me_2CO to yield colorless crystals (0.07 g, 33%), mp 176–178 °C.

6,11-Dihydro-11-hydroxydibenz[*b*,*e*]oxepin-2-acetic Acid (44). To an ice-cooled solution of **40**[1] (IXm, R^1 = H; R^2 = 2-CH_2COOH) (1.00 g, 3.7 mmol) in 0.5 N NaOH (10 mL) was added $NaBH_4$ (0.20 g, 5.3 mmol) under stirring for 3.5 h. After the addition of $NaBH_4$ was completed, stirring was continued for 2.5 h at room temperature. The reaction mixture was cooled with ice water and acidified with dilute HCl to pH 1–2. The precipitated crystals were collected and washed with water. Crystallization from AcOEt–*n*-C_6H_{14} yielded colorless crystals (0.93 g, 92.2%), mp 138–140 °C.

6,11-Dihydrodibenz[*b*,*e*]oxepin-2-acetic Acid (45). To a stirred solution of **40**[1] (IXm, R^1 = H; R^2 = 2-CH_2COOH) (1.00 g, 3.7 mmol) in AcOH (20 mL) was added Zn powder (3.00 g), and the mixture was refluxed for 2 h, cooled, and filtered. The filtrate was concentrated in vacuo. After addition of water to the syrupy residue, the mixture was extracted with $CHCl_3$, which was washed with water, dried, and concentrated. The residue was purified by crystallization from C_6H_6 to yield colorless crystals (0.76 g, 80%), mp 165.5–166.5 °C.

Compound **46** (mp 194–195 °C) was prepared similarly from IXm[1] (R^1 = Cl; R^2 = 2-CH_2COOH) in 84% yield.

6,11-Dihydro-11-hydroxydibenz[*b*,*e*]oxepin-3-acetic Acid (47). To a solution of **41**[1] (IXn, R^1 = H; R^2 = 3-CH_2COOH) (0.40 g, 1.5 mmol) in 10% NaOH (10 mL) was added Zn powder (0.60 g), and the mixture was stirred for 0.5 h at room temperature. After the insoluble material was removed by filtration, the filtrate was acidified with dilute HCl and extracted with AcOEt. The AcOEt layer was washed with water, dried, and concentrated. The residue was crystallized from AcOEt–*n*-C_6H_{14} to yield colorless crystals (0.22 g, 55%), mp 127 °C.

6,11-Dihydrodibenz[*b*,*e*]oxepin-3-acetic Acid (48). To a mixture of **41**[1] (IXn, R^1 = H; R^2 = 3-CH_2COOH) (0.88 g, 3 mmol), water (3.75 mL), concentrated HCl (5 mL), and toluene (7.5 mL) was added Zn–amalgam which was prepared by the reaction of Zn (5.00 g, 76.5 mg-atom), $HgCl_2$ (0.5 g, 1.8 mmol), concentrated HCl (0.5 mL), and water (7.5 mL), and the reaction mixture was refluxed for 3 h under vigorous stirring. After separation of the insoluble material by filtration, the filtrate was extracted with Et_2O. The extract was washed with water, dried, and concentrated to dryness. The residue was dissolved in AcOEt and filtered. The filtrate was purified by silica gel preparative TLC (solvent, lower layer of $CHCl_3$–MeOH–H_2O = 7:3:1) to yield crude **48**. Crystallization from $CHCl_3$–petroleum ether yielded colorless crystals (0.09 g, 12%), mp 151.5–153 °C.

Compound **49** was prepared similarly from **43** [IXn, R^1 = H; R^2 = 3-CH(Me)COOH] in 7.4% yield.

2-[*p*-(1-Hydroxy-2-propyl)phenoxymethyl]benzonitrile (58). To a stirred solution of 2-(4-hydroxyphenyl)propan-1-ol (3.04 g, 20 mmol) and Na (0.46 g, 20 mg-atom) in EtOH (20 mL) was added 2-cyanobenzyl chloride (3.03 g, 20 mmol) in EtOH (20 mL). The reaction mixture was refluxed for 2.5 h and filtered. The filtrate was concentrated to dryness in vacuo. The residue dissolved in $CHCl_3$ was washed with 2% HCl and subsequently with water and dried. Evaporation of the solvent and crystallization of the residue from Et_2O provided colorless crystals (4.00 g, 75%), mp 77–80 °C.

Similarly, **56** and **57** were obtained from reactions of 3-hydroxybenzyl alcohol and 2-(3-hydroxyphenyl)propan-1-ol with 2-cyanobenzyl chloride in 71 and 90% yield, respectively.

2-(4-Hydroxyphenyl)propan-1-ol above used was prepared by the reduction of 2-(4-hydroxyphenyl)propionic acid with $LiAlH_4$ in 88% yield as colorless crystals, mp 98–100 °C (C_6H_6). 2-(3-Hydroxyphenyl)propan-1-ol was obtained in a similar manner in 82% yield as a colorless oil, bp 151–152 °C (4 mm).

2-[*m*-(Hydroxymethyl)phenoxymethyl]benzoic Acid (59). A suspension of **56** (30.3 g, 126 mmol) in 5 N NaOH (500 mL) was refluxed for 6 h, cooled, and acidified with HCl. The resulting precipitate was collected and crystallized from C_6H_6–EtOH to give colorless crystals (25.7 g, 80%), mp 135–136.5 °C.

Similarly, **60** and **61** were prepared from **57** and **58** in 73 and 72% yield, respectively.

2-[*p*-(1-Acetoxy-2-propyl)phenoxymethyl]benzoic Acid (64). A solution of **61** (1.34 g, 5 mmol) and Ac_2O (1.53 g, 15 mmol) in dry pyridine (10 mL) was stirred for 2 h at room temperature and poured into ice water. The cooled aqueous solution was acidified with HCl and extracted with $CHCl_3$, and the washed, dried extract was concentrated in vacuo. The crude product was crystallized from Et_2O–petroleum ether to give colorless crystals (1.31 g, 80%), mp 83–88 °C.

Both **62** and **63** were prepared similarly from **59** and **60** in 89 and 95% yield, respectively.

2-Phenoxymethyl-4-hydroxymethylbenzoic Acid (65). A stirred mixture of 5-hydroxymethylphthalide[12] (0.96 g, 5.5 mmol) and sodium phenolate (0.64 g, 5.5 mmol) was heated at 200–210 °C for 1 h, cooled, and dissolved in water. The aqueous solution was acidified with 5% HCl and extracted with Et_2O. The crude product obtained by evaporation of the solvent was chromatographed on silica gel using $CHCl_3$–MeOH (50:1) and the eluate afforded a white solid which was crystallized from AcOEt–C_6H_6 yielding **65** (0.45 g, 30%), mp 149–150 °C.

Pharmacological Test Methods. Antiinflammatory activity by the carrageenan paw edema test, induction of gastric lesion, and acute toxicity were examined according to the methods described in the previous paper.[1] Animals used in these experiments were male rats of Donryu strain weighing 130–160 g.

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Folate Antagonists. 12. Antimalarial and Antibacterial Effects of 2,4-Diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines[1,2]

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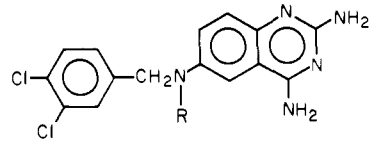
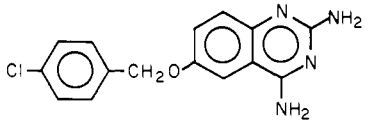
A series of 2,4-diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines was prepared via condensation of 5-chloro-2-nitrobenzonitrile or 5,6-dichloro-2-nitrobenzonitrile with the appropriate aralkyl or alicyclic thiopseudourea, reduction of the resulting 2-nitro-5-[(aralkyl or alicyclic)thio]benzonitrile with stannous chloride to the amine, and cyclization with chloroformamidine hydrochloride. Oxidation was effected with hydrogen peroxide or the bromine complex of 1,4-diazabicyclo[2.2.2]octane. These analogues when examined for suppressive activity against drug-sensitive lines of *Plasmodium berghei* in mice were not as active as 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (Ia).

Many 2,4-diaminoquinazoline antifolates have been demonstrated to possess strong antimalarial properties against sensitive and drug-resistant lines of *Plasmodium berghei* in mice, *P. gallinaceum* in chicks, and *P. cynomolgi* and *P. knowlesi* in rhesus monkeys.[3,4] Among the most potent are 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]-quinazoline (Ia), 2,4-diamino-6-[(3,4-dichlorobenzyl)-



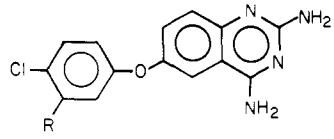
Ia, R = H
b, R = NO
c, R = CH_3

nitrosoamino]quinazoline (Ib), and 2,4-diamino-6-[(3,4-dichlorobenzyl)methylamino]quinazoline (Ic).[1,3-6] However, antimalarial activity of oxygen bioisosteres, exemplified by 2,4-diamino-6-[(*p*-chlorobenzyl)oxy]quinazoline (II), was greatly reduced.[7] Interestingly, extrusion of the



II

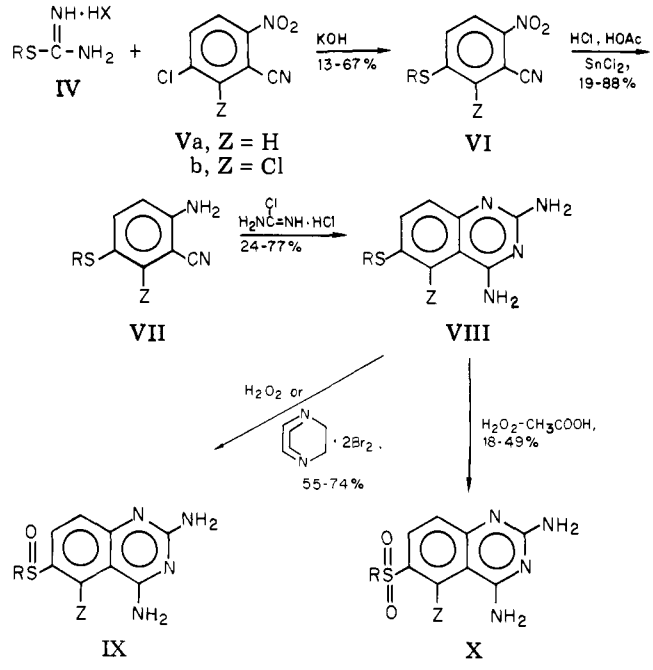
methylene bridge of II restored antimalarial activity. Thus 2,4-diamino-6-(*p*-chlorophenoxy)quinazoline (IIIa) and



IIIa, R = H
b, R = Cl

2,4-diamino-6-(3,4-dichlorophenoxy)quinazoline (IIIb) exhibited oral antimalarial effects against *P. berghei* in mice comparable with or superior to 2,4-diamino-6-[(3,4-dichlorobenzyl)amino]quinazoline (Ia).[7] Comparison of the above diaminoquinazoline antifolates with representative thio bioisosteres would therefore be of interest, and we now describe the preparation and biological activities of some 2,4-diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines.

Scheme I



Results and Discussion

Chemistry. The 2,4-diamino-6-[(aralkyl and alicyclic)thio-, sulfinyl-, and sulfonyl]quinazolines were synthesized following the route depicted in Scheme I. Condensation of 5-chloro-2-nitrobenzonitrile (Va) or

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