or silyl heparin (0.1%) in water was applied and electrophoresis was run at 550 V, 18 mA, for 70 min. The spots were developed with Toluidine Blue indicator. Identical spots were obtained at about 3 cm from the points of application on the slide.

WBCT of Rat Blood. Cyclopal was given intravenously (iv) to anesthesia. An abdominal incision was made, the inferior vena cava was exposed, and 0.5 ml of blood was drawn with a 1-ml Stylex (Pharmaseal Labs., Glendale, Calif.) syringe and 26 G × 0.5 in. needle. At 20 sec from venipuncture 0.3 ml of blood was placed in a Fibrocup and the clotting time determined with a Fibrometer (B.B.L., Baltimore 18, Md).

WBCT of Rabbit Blood. Cyclopal was given iv to anesthesia and an abdominal incision made to expose the inferior vena cava. Blood samples (1.1 ml) were drawn with a 1-ml syringe and 26 G × 0.5 in. needle. Aliquots (0.5 ml) of blood were placed in disposable 12 × 75 mm culture tubes approximately 20 sec from venipuncture. The tubes were placed in a water bath (37°) and tilted every 30 sec to see if the blood was fluid. WBCT was recorded when blood was no longer fluid and would not flow up the side of the tube.

Anticoagulant Activity *in Vitro.* Heparin was dissolved in and serially diluted with saline. Aliquots (0.05 ml) were placed in disposable 10 × 75 mm culture tubes containing 0.1 ml of 0.25 *M* $CaCl_2$ in saline. Blood (9 ml) was drawn from rats into syringes containing 3.8% citrate (1 ml) and mixed. Aliquots of blood (0.9 ml) were placed in culture tubes containing the heparin and $CaCl_2$ solutions and placed on a Lab-Tek mixer (Ames Lab-Tek, Westmont, Ill.) and the time to clotting was recorded as recalcification time. Comparisons between sodium heparin and silylized heparin were made by their ability to prolong the recalcification time. Comparisons between sodium heparin and silylized heparin were made by their ability to prolong the recalcification time.

Heparin Administration. Compounds were given ig to fasted (>16 hr) animals or id by injecting through the stomach wall through the pyloric sphincter into the duodenum using a syringe and 19 G × 1 in. needle.

Suspension or Solution of Compounds. Heparin preparations were suspended in Carbowax, Tween 80, or mineral oil by sonication (<10 sec) to give a homogeneous suspension or dissolved in saline prior to mixing with a vehicle. Carbowax 1000 was warmed to approximately 40° in order to suspend the heparin.

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Chemotherapeutic Nitroheterocycles. 18.† 2-(5-Nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones Substituted by Aminoalkoxy Groups

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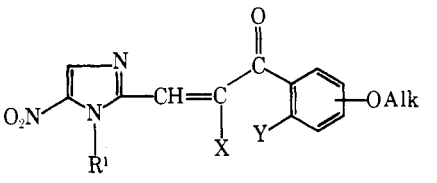
2-(5-Nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones substituted by aminoalkoxy groups and related compounds (41–69, Table II) were synthesized and their antimicrobial activities were evaluated (Table III). Some of these compounds (*e.g.*, **47**, **52**, and **59**) surprisingly exhibited a broad antibacterial spectrum including *Proteus* species and *Pseudomonas aeruginosa*. Extraordinary antitrichomonal activities could also be observed *in vitro* (MIC of compound **59**, 0.0004 μg/ml) and six of the title compounds (**48**, **49**, **52**, **58**, **64**, **66**) displayed *in vivo* activity in mice against *Trichomonas vaginalis* comparable to that of metronidazole (**70**).

In two previous papers of this series[2,3] 5-nitro-2-imidazolylmethylene derivatives of alkoxy-1-indanones (**1**), alkoxy-1-tetralones (**2**), and alkoxyacetophenones (**3**) were shown to possess considerable activity against *Trichomonas vaginalis* (*T. vaginalis*) *in vitro;* however, in general their *in vivo* efficacy in mice (subcutaneous) was disappointing. The rather poor solubility of the compounds in inorganic and organic solvents may lead to an extremely low absorption rate from the gastrointestinal tract which would explain the discrepancy between *in vitro* and *in vivo* activity.

In order to enhance the solubility we intended to introduce substituted amino groups into the alkoxy residue (OAlk in formulas 1–3) of the compounds as similar modifications within the series of 5-alkoxy-2-(5-nitro-2-furfurylidene)-1-indanones led to low MIC values against *T. vaginalis*.[4]

This communication is concerned with the synthesis and the results of the microbiological screening of 2-(5-nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones,

† For part 17 of this series, see ref 1.



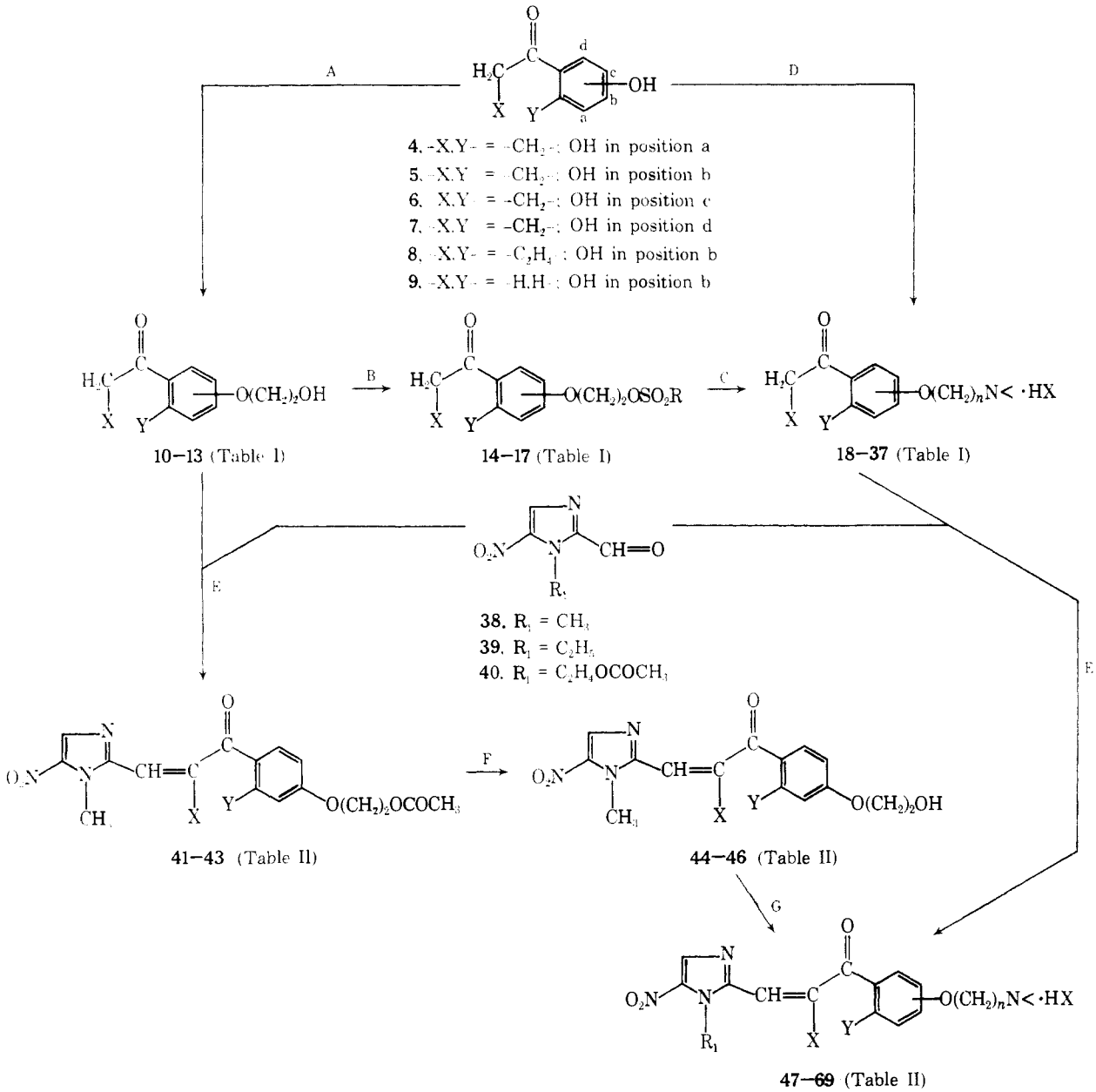
1, –X, Y– = $–CH_2–$
2, –X, Y– = $–C_2H_4–$
3, –X, Y– = –H, H–

and -acetophenones substituted by aminoalkoxy groups and some related structures (physical and chemical data are given in Table II; Table III shows the microbiological results).

Chemistry. The methods used for the synthesis of the compounds listed in Table II are given in Scheme I.

The starting materials, 4-, 5-, 6-, and 7-hydroxy-1-indanone, 6-hydroxy-1-tetralone, and 4′-hydroxyacetophenone (compounds **4–9**), were purchasable or known from the literature. Alkylation with 2-bromoethanol led to the 2-hydroxyethoxy derivatives (method A, **10–13**) which could be

Scheme I



transformed *via* tosylation‡ (method B, 14-17) followed by displacement with amines into the corresponding aminoalkoxy derivatives (method C, 20-22, 24-28, 32, 34, 35, and 37). The remaining aminoalkoxyindanones, -tetralones, and -acetophenones (18, 19, 23, 29-31, 33, and 36) were prepared by direct alkylation of the hydroxyindanones, -tetralones, and -acetophenones with the corresponding aminoalkyl chlorides (method D) (see Table I).

Most of the desired 5-nitro-2-imidazolylmethylene derivatives compiled in Table II were synthesized by condensation of the above-mentioned key intermediates (10-13 and 18-37) with the corresponding 5-nitroimidazole-2-carbaldehydes[5] (38-40) (method E). The reaction conditions (acetic acid at 100° with catalytic amounts of H_2SO_4) caused a simultaneous acetylation of free hydroxy groups; compounds 44-46 were prepared by hydrolysis of the corresponding acetoxy derivatives 41-43 (method F). Finally, 2-(1-methyl-5-nitro-2-imidazolylmethylene)-4′-(2-morpholinoethoxy)acetophenone 69 was prepared by tosylation of compound 46, followed by displacement with morpholine (method G).

Biological Activity.§ The substituted alkoxy-2-(5-nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones 41-69 shown in Table II were screened *in vitro* against gram-positive and gram-negative bacteria, fungi, and protozoa (tube dilution assay). Fungicidal activity could not be observed in any case. The minimum inhibitory concentrations (MIC values) against selected bacteria and protozoa are given in Table III.

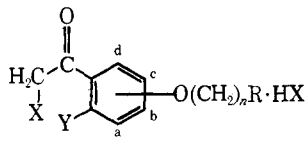
Follow-up studies against subcutaneous *T. vaginalis* infections in mice (ED_{50} determinations) were done with those compounds which were active at orally given dosages of 12.5 or 50 mg/kg, respectively. Systemic (ip) infections of mice with *Staphylococcus aureus* and *Escherichia coli* were used to evaluate the antibacterial efficacy of selected compounds *in vivo* (oral treatment with 200 mg/kg).

The indanone derivatives 41 and 44 substituted by a 2-

‡ Compound 11 [7-(2-hydroxyethoxy)-1-indanone] did not react with tosyl chloride and therefore the mesyloxy derivative 15 was prepared. The reaction of 7-hydroxy-1-indanone (7) with 2-dimethylaminoethyl chloride (method C in Scheme I) did not proceed.

§ For experimental details of the biological evaluation, see ref 2 and 4.

Table I. Substituted Alkoxy-1-indanones, -1-tetralones, and -acetophenones (10-37)



(HX = HCl, unless otherwise stated)

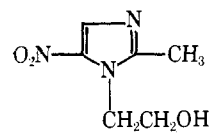
Compd	Position -X,Y- of subst		n	R	Method	Starting compd	Yield, %	Mp, °C	Recrystn solvent	Formula (analyses)
10[a,m]	$-CH_2-$	b	2	OH	A_1	5	78	130	EtOAc	$C_{11}H_{12}O_3$
11[a,m]	$-CH_2-$	d	2	OH	A_2	7	40	69	MeOH–H_2O	$C_{11}H_{12}O_3$[l]
12[a,m]	$-C_2H_4-$	b	2	OH	A_1[j]	8	78	92	C_6H_6	$C_{12}H_{14}O$
13[a,o]	-H,H-	b	2	OH	A_1[i]	9	96	66	Me_2CO–*i*-Pr_2O	$C_{10}H_{12}O_3$
14[a,m]	$-CH_2-$	b	2	OTs	B_1	10	73	99	EtOH	$C_{18}H_{18}O_5S$
15[a]	$-CH_2-$	d	2	OMs	B_2	11	44	131	*i*-PrOH	$C_{12}H_{14}O_5S$ (C, H)
16[a]	$-C_2H_4-$	b	2	OTs	B_1	12	82	111	*i*-PrOH	$C_{19}H_{20}O_5S$ (S)
17[a]	-H,H-	b	2	OTs	B_1	13	72	85	*i*-PrOH	$C_{17}H_{18}O_5S$ (S)
18[a,n]	$-CH_2-$	b	2	$N(CH_3)_2$	D	5	80	198	EtOEt[d]	$C_{13}H_{18}ClNO_2$
19[m]	$-CH_2-$	b	2	$N(C_2H_5)_2$	D	5	61	177	*i*-PrOH	$C_{15}H_{22}ClNO_2$
20	$-CH_2-$	b	2	$N(i\text{-}C_3H_7)_2$	C_1	14	57			$C_{17}H_{26}ClNO_2$[c]
21	$-CH_2-$	b	2	$N(CH_2CH{=}CH_2)_2$	C_2	14	46	136	Et_2O[d]	$C_{17}H_{22}ClNO_2$ (Cl, N)
22	$-CH_2-$	b	2	NHC_3H_7	C_2[e]	14	42	213	EtOH	$C_{14}H_{20}ClNO_2$ (Cl, N)
23[m]	$-CH_2-$	b	2	c-NC_4H_8	D[f]	5	26	188	Et_2O[d]	$C_{15}H_{20}ClNO_2$
24	$-CH_2-$	b	2	c-NC_5H_{10}	C_2	14	81	190	MeOH–Et_2O	$C_{16}H_{22}ClNO_2$ (Cl, N)
25	$-CH_2-$	b	2	c-NC_6H_{12}	C_2	14	54	179	MeOH–Et_2O	$C_{17}H_{24}ClNO_2$ (Cl, N)
26	$-CH_2-$	b	2		C_2[g]	14	59	110	MeOH[d]	$C_{19}H_{26}ClNO_2$ (Cl, N)
27	$-CH_2-$	b	2	c-$N(CH_2CH_2)_2O$	C_2	14	85	220	EtOH	$C_{15}H_{20}ClNO_3$ (Cl, N)
28[b]	$-CH_2-$	b	2	c-$N(CH_2CH_2)_2NCH_3$	C_2	14	75	238	MeOH–*i*-PrOH	$C_{16}H_{24}Cl_2N_2O_2$[k]
29	$-CH_2-$	b	3	$N(CH_3)_2$	D[h]	5	72	201	Et_2O[d]	$C_{14}H_{20}ClNO_2$ (Cl, N)
30	$-CH_2-$	a	2	$N(CH_3)_2$	D	4	51	184	Et_2O[d]	$C_{13}H_{18}ClNO_2$ (Cl, N)
31[n]	$-CH_2-$	c	2	$N(CH_3)_2$	D	6	42	210	*i*-PrOH	$C_{13}H_{18}ClNO_2$
32	$-CH_2-$	d	2	$N(CH_3)_2$	C_2	15	30	209	Et_2O	$C_{13}H_{18}ClNO_2$ (Cl, N)
33[m]	$-C_2H_4-$	b	2	$N(CH_3)_2$	D	8	62	182	Et_2O[d]	$C_{14}H_{20}ClNO_2$
34	$-C_2H_4-$	b	2	c-NC_4H_8	C_2	16	77	203	Et_2O[d]	$C_{16}H_{22}ClNO_2$ (Cl, N)
35	$-C_2H_4-$	b	2	c-$N(CH_2CH_2)_2O$	C_2	16	56	198	Et_2O[d]	$C_{16}H_{22}ClNO_3$ (Cl, N)
36	-H,H-	b	2	$N(CH_3)_2$	D	9	32	163	EtOAc	$C_{12}H_{18}ClNO_2$ (Cl, N)
37	-H,H-	b	2	c-NC_4H_8	C_2	17	49	130	Et_2O[d]	$C_{14}H_{20}ClNO_2$ (Cl, N)

[a]The substance does not contain HCl. [b]Compound 28 was isolated as the dihydrochloride. [c]Structure was confirmed by nmr. [d]The compound was insoluble even when refluxed in the solvent. [e]Six equivalents of propylamine were used. [f]Reaction time, 5 hr. [g]When 1 *N* NaOH was added to the residue after removal of the solvent, crystals precipitated which were isolated and dissolved in *i*-PrOH–EtOAc. Addition of methanolic HCl yielded 26. [h]3-Dimethylaminopropyl chloride (3 equiv) in EtOAc (not benzene) was used. Reaction time, 36 hr. [i]The product did not crystallize even if triturated with water and therefore was extracted into EtOAc. [j]Reaction time, 48 hr. [k]Cl: calcd, 20.42; found, 19.53. N: calcd, 8.07; found, 7.56. [l]C: calcd, 68.74; found, 66.30. H: calcd, 6.29; found, 6.75. [m]R. Albrecht and E. Schröder, *Justus Liebigs Ann. Chem.*, **736**, 110 (1970). [n]J. Sam and J. N. Plampin, *J. Amer. Chem. Soc.*, 82, 5205 (1960). [o]Eastman Kodak, U.S. Patent 2,816,091 (1957); *Chem. Abstr.*, **52**, 4369 (1958).

acetoxyethoxy and a 2-hydroxyethoxy group, respectively, inhibit the growth of *T. vaginalis in vitro* at 0.003 μg/ml but are inactive *in vivo*. The corresponding tetralone (**42**, **45**) and acetophenone (**43**, **46**) derivatives are considerably less active against *T. vaginalis in vitro;* however, *in vivo* the 6-(2-acetoxyethoxy)-1-tetralone derivative 42 proves to be effective (ED_{50} = 58.6 mg/kg). None of the mentioned substances (**41**-**46**) display remarkable antibacterial activity *in vitro*.

Unexpectedly, the introduction of a 2-dimethylaminoethoxy side chain into the 5 position of the indanone moiety (compound **47**) gives rise to a broad spectrum antibacterial efficacy (Table III). Additionally, the MIC value against *T. vaginalis* is extraordinary low (0.0015 μg/ml).

In general, the antiparasitic nitroimidazole derivatives, *e.g.*, metronidazole[6] (**70**), inhibit specifically the growth of anaerobic bacteria, *e.g.*, *clostridia*,[7] and do not affect those aerobic species which we use in our screening program. 2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-



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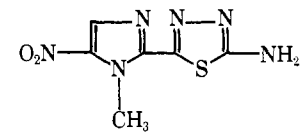

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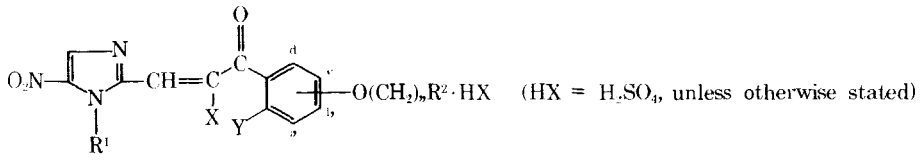
thiadiazole (**71**) is a well-known exception[8] and its antibacterial spectrum is shown for comparison at the bottom of Table III.

Compound **47** displays an appreciable *in vivo* activity (ED_{50} 25.2 mg/kg) against sc *Trichomonas* infection in mice, but no activity could be observed in mice infected with *Staph. aureus* and *E. coli*. This holds true for all other compounds of this series tested in the above-mentioned systemic bacterial infections of mice.

Chemical modification of compound **47** leads to the following structure-activity relationships.

1. Substitution of the dimethylamino group by a diethyl (**48**) or by a diisopropylamino group (**49**) results in a

Table II. Substituted Alkoxy-2-(5-nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones (41-69)



(HX = H_2SO_4, unless otherwise stated)

Compd	-X,Y-	R^1	Position of subst	n	R^2	Method	Starting compds	Yield, %	Mp, °C	Recrystn solvent	Formula (analyses)	S: calcd (found)
41[a]	$-CH_2-$	CH_3	b	2	$OCOCH_3$	E_1[b]	10 + 38	15	216	DMF	$C_{18}H_{17}N_3O_6$ (N)	
42[a]	$-C_2H_4-$	CH_3	b	2	$OCOCH_3$	E_1[b]	12 + 38	19	169	DMF	$C_{19}H_{19}N_3O_6$(N)	
43[a]	-H,H-	CH_3	b	2	$OCOCH_3$	E_1[b]	13 + 38	38	163	EtOH	$C_{17}H_{17}N_3O_6$ (N)	
44[a]	$-CH_2-$	CH_3	b	2	OH	F	41	77	260	DMF	$C_{16}H_{15}N_3O_5$ (N)	
45[a]	$-C_2H_4-$	CH_3	b	2	OH	F[c]	42	59	232	EtOH[e]	$C_{17}H_{17}N_3O_5$ (N)	
46[d]	-H,H-	CH_3	b	2	OH	F	43	93	210	EtOH[e]	$C_{15}H_{16}ClN_3O_5$ (Cl, N)	
47	$-CH_2-$	CH_3	b	2	$N(CH_3)_2$	E_1	18 + 38	29	210	DMF–EtOH	$C_{18}H_{22}N_4O_8S$ (N)	7.06 (6.50)
48	$-CH_2-$	CH_3	b	2	$N(C_2H_5)_2$	E_2	19 + 38	31	196	H_2O–*i*-PrOH	$C_{20}H_{26}N_4O_8S$ (N)	6.55 (5.66)
49	$-CH_2-$	CH_3	b	2	$N(i\text{-}C_3H_7)_2$	E_2	20 + 38	26	200	MeOH–*i*-PrOH[e]	$C_{22}H_{30}N_4O_8S$ (N)	6.29 (5.68)
50	$-CH_2-$	CH_3	b	2	$N(CH_2CH{=}CH_2)_2$	E_1	21 + 38	30	172	H_2O–*i*-PrOH	$C_{22}H_{26}N_4O_8S$ (N)	6.33 (7.00)
51	$-CH_2-$	CH_3	b	2	NHC_3H_7	E_2	22 + 38	9	244	*f*	$C_{19}H_{24}N_4O_8S$ (N)	6.85 (6.61)
52	$-CH_2-$	CH_3	b	2	c-NC_4H_8	E_1	23 + 38	30	228	MeOH–*i*-PrOH[e]	$C_{20}H_{24}N_4O_8S$ (N)	6.68 (5.39)
53	$-CH_2-$	CH_3	b	2	c-NC_5H_{10}	E_2	24 + 38	36	239	*f*	$C_{21}H_{26}N_4O_8S$ (N)	6.49 (5.75)
54	$-CH_2-$	CH_3	b	2	c-NC_6H_{12}	E_2	25 + 38	27	226	MeOH[g]	$C_{22}H_{28}N_4O_8S$ (N)	6.31 (7.12)
55	$-CH_2-$	CH_3	b	2		E_1	26 + 38	30	248	*f*	$C_{24}H_{30}N_4O_8S$[c]	6.00 (6.14)
56	$-CH_2-$	CH_3	b	2	c-$N(CH_2CH_2)_2O$	E_1	27 + 38	35	247	H_2O–EtOH	$C_{20}H_{24}N_4O_9S$ (N)	6.46 (5.13)
57	$-CH_2-$	CH_3	b	2	c-$N(CH_2CH_2)_2NCH_3$	E_2	28 + 38	66	218	H_2O–*i*-PrOH	$C_{21}H_{27}N_5O_8S$[g]	6.30 (6.18)
58	$-CH_2-$	CH_3	b	3	$N(CH_3)_2$	E_1	29 + 38	34	220	*f*	$C_{19}H_{24}N_4O_8S$ (N)	6.85 (5.92)
59	$-CH_2-$	CH_3	a	2	$N(CH_3)_2$	E_1	30 + 38	65	226	*f*	$C_{18}H_{22}N_4O_8S$ (N)	7.06 (7.33)
60	$-CH_2-$	CH_3	c	2	$N(CH_3)_2$	E_1	31 + 38	39	223	*f*	$C_{18}H_{22}N_4O_8S$ (N)	7.06 (6.12)
61	$-CH_2-$	CH_3	d	2	$N(CH_3)_2$	E_2	32 + 38	26	260	*f*	$C_{18}H_{22}N_4O_8S$ (N)	7.06 (6.12)
62	$-CH_2-$	C_2H_5	b	2	$N(CH_3)_2$	E_1	18 + 39	48	222	*f*	$C_{19}H_{24}N_4O_8S$ (N)	6.85 (6.55)
63	$-CH_2-$	$C_2H_4OCOCH_3$	b	2	$N(CH_3)_2$	E_2	18 + 40	6	195	*f*	$C_{21}H_{26}N_4O_{10}S$ (N)	6.08 (5.81)
64	$-C_2H_4-$	CH_3	b	2	$N(CH_3)_2$	E_2	33 + 38	40	206	MeOH–Et_2O	$C_{19}H_{24}N_4O_8S$ (N)	6.85 (7.05)
65	$-C_2H_4-$	CH_3	b	2	c-NC_4H_8	E_2	34 + 38	19	204	H_2O–*i*-PrOH	$C_{21}H_{26}N_4O_8S$ (N)	6.49 (6.34)
66	$-C_2H_4-$	CH_3	b	2	c-$N(CH_2CH_2)_2O$	E_1	35 + 38	52	225	MeOH[g]	$C_{21}H_{26}N_4O_9S$ (N)	6.29 (6.31)
67	-H,H-	CH_3	b	2	$N(CH_3)_2$	E_1	36 + 38	51	185	*f*	$C_{17}H_{22}N_4O_8S$ (N)	7.25 (7.37)
68	-H,H-	CH_3	b	2	c-NC_4H_8	E_2	37 + 38	58	184	*i*-PrOH[e]	$C_{19}H_{24}N_4O_8S$ (N)	6.85 (7.44)
69[d]	-H,H-	CH_3	b	2	c-$N(CH_2CH_2)_2O$	G	46	84	212	MeOH	$C_{19}H_{23}ClN_4O_5$ (N)[h]	

[a]The substance does not contain H_2SO_4. [b]Only 4 mmol of H_2SO_4 was used. [c]N: calcd, 10.48; found, 9.91. [d]The substance was isolated as the hydrochloride. [e]The compound was insoluble even when heated in the refluxing solvent. [f]The compound was heated in refluxing EtOH with a few drops of H_2SO_4, and water was added until the solution became clear. After cooling the precipitate was isolated. [g]N: calcd, 13.74; found, 12.96. [h]Cl: calcd, 8.39; found, 10.23.

Table III. Antimicrobial Activity of Compounds 41-69 (Table II)[a]

	MIC (serial dilution assay), μg/ml									
Compd	*Staph. aureus* 30-8[b]	*Strep. faecalis* 32-2	*E. coli* 1-19	*Prot. mirabilis* 2-3	*Prot. vulgaris* 2-2	*K. pneumoniae* 4-4	*Pseud. aeruginosa* 3-2	*E. histolytica* 105-2	*T. vaginalis* 100-1	ED_{50} value, mg/kg (oral treatment of mice sc infected with *T. vaginalis*)
41	–	n.t.	>3.1	–	–	–	–	>3.1	0.003	ϕ
42	–	–	–	–	–	–	–	>6.3	0.05	58.6 (35.2–103)[c]
43	>12.5	n.t.	–	–	–	–	–	>12.5	0.1	ϕ
44	>25	n.t.	>25	–	>25	>25	–	>25	0.003	ϕ
45	–	–	–	–	–	–	–	>25	0.024	ϕ
46	6.25	n.t.	>25	–	>25	–	–	>25	0.1	ϕ
47	6.3	3.1	1.6	–	1.6	6.3	6.3	100	0.0015	25.2 (19.8–33.2)
48	12.5	6.3	6.3	–	3.1	25	25	>100	0.003	3.46 (1.99–5.36)
49	50	50	12.5	–	100	>100	–	25	0.0015	4.67 (0.844–7.16)
50	–	–	–	–	–	–	–	50	0.012	15.8 (10.2–26.8)
51	>6.3	>6.3	1.6	–	3.1	>6.3	>6.3	>6.3	0.006	n.t.
52	6.3	3.1	1.6	–	3.1	12.5	25	100	0.006	2.90(0.954–5.30)
53	25	12.5	6.3	–	25	–	–	50	0.0015	10.9 (6.96–15.0)
54	>100	12.5	6.3	–	12.5	–	–	50	0.0008	ϕ
55	–	–	–	–	–	–	–	>100	0.0008	ϕ
56	>50	>50	>50	–	>50	>50	>50	50	0.012	25.7 (17.6–34.2)
57	6.3	3.1	6.3	>100	3.1	50	25	50	0.012	n.t.[d]
58	12.5	1.6	3.1	–	1.6	25	12.5	>100	0.0008	2.57 (0.67–3.55)
59	3.1	3.1	0.8	50	1.6	25	12.5	25	0.0004	19.1 (13.9–25.9)
60	6.3	6.3	1.6	–	12.5	25	25	>100	0.012	ϕ
61	>3.1	>3.1	>3.1	–	>3.1	>3.1	>3.1	>3.1	0.012	n.t.
62	25	6.3	12.5	–	25	–	–	100	0.003	11.2 (7.56–16.6)
63	50	25	25	–	>50	50	–	>50	0.2	n.t.
64	100	100	50	–	6.3	100	50	>100	0.05	5.18 (1.81–9.72)
65	100	50	100	–	100	>100	–	50	0.025	n.t.[e]
66	>100	–	–	–	–	–	–	100	0.05	3.19 (1.67–5.05)
67	25	50	50	–	12.5	100	–	>100	0.05	ϕ
68	25	25	50	–	50	–	–	>100	0.1	n.t.[f]
69	12.5	25	–	–	12.5	–	–	>100	0.2	33.5 (24.8–44.2)
70[g]	–	n.t.	–	–	–	–	–	100	1.6	3.86 (3.19–4.84)
71[h]	25	n.t.	12.5	50	0.2	1.6	–	>50	0.05	5.94 (3.61–14.61)

[a] Symbols and abbreviations: –, a preliminary paper disk assay revealed no activity at a level of 200 μg/disk; n.t., not tested; >6.3, >25, etc, the compound was insoluble at higher concentrations (in μg/ml) and no activity could be observed below or at this point (concentrations >100 μg/ml were not investigated); ϕ, a preliminary *in vivo* test at a dose level of 12.5 mg/kg (compounds 41, 43, 45, and 46, 50 mg/kg) did not show a significant effect. [b] Strain no., collection of Department of Chemotherapy, Schering AG. [c] Range of confidence at the 95% level in parentheses. [d] Compound 57 was active at the 12.5 mg/kg dose level. However, oral toxicity in mice was relatively high (LD_{50} *ca.* 0.5–1 g/kg) and therefore ED_{50} was not determined. [e] Toxic at the 12.5 mg/kg dose level. [f] Active at the 12.5 mg/kg dose level, but toxic with 200 mg/kg. [g] Metronidazole, see ref 6. [h] 2-Amino-5-(1-methyl-5-nitro-2-imidazolyl)-1,3,4-thiadiazole, see ref 8.

decrease of antibacterial activity *in vitro*, whereas the MIC against *T. vaginalis* is hardly influenced. The antitrichomonal ED_{50} values of compound **48** (3.46 mg/kg) and **49** (4.67 mg/kg) are in the range of metronidazole (**70**, 3.86 mg/kg).

The diallylamino group (compound **50**) abolishes antibacterial and diminishes antitrichomonal activity, whereas the monopropylamino derivative **51** is obviously more effective against bacteria and parasites. Its rather low solubility made it impossible to test the compound in concentrations higher than 6.3 μg/ml.

Within a small set of compounds (**52**-**55**) the amino group nitrogen is part of a heterocycle. The pyrrolidine derivative **52** gives rise to the lowest antibacterial MIC values compared to compounds containing larger ring systems. The MIC's against *T. vaginalis* are nearly constant in this series, but the remarkable *in vivo* activity of compound **52** (ED_{50} 2.9 mg/kg) is decreased by ring enlargement.

The morpholino (**56**) and the 4-methylpiperazino derivatives (**57**) are less trichomonicidal; the latter possesses similar antibacterial potency compared to compound **52**.

2. Lengthening of the side chain of compound **47** leads to compound **58** and causes a slight decrease in antibacterial activity, whereas the MIC against *T. vaginalis* is not changed. The *in vivo* activity against *T. vaginalis* is remarkable (ED_{50} 2.57 mg/kg).

Extremely low MIC values against bacteria and *T. vaginalis* are observed if the basically substituted side chain is fixed to position 4 of the 1-indanone moiety (position a in the general formula at the top of Table II); *e.g.*, 4-(2-dimethylaminoethoxy)-2-(1-methyl-5-nitro-2-imidazolylmethylene)-1-indanone (**59**) inhibits the growth of all our test bacteria within a concentration range of 0.8-50 μg/ml including *Proteus mirabilis* and *Pseudomonas aeruginosa*. Against *T. vaginalis* the MIC value is 0.0004 μg/ml for **59**, but the ED_{50} value (19.1 mg/kg) against *T. vaginalis* in mice is rather disappointing.

Derivatives bearing the 2-dimethylaminoethoxy group in position 6 (**60**) and 7 (**61**) of the 1-indanone ring system are less active (positions c and d in the general formula at the top of Table II).

3. The residue R^1 at the imidazole N atom of all derivatives mentioned so far was represented by a methyl group. Replacement of the methyl group in compound **47** by an ethyl group lowers the antibacterial activity. The antitrichomonal effect is similar to that of **47** *in vitro* and *in vivo*. The introduction of a 2-acetoxyethyl side chain as residue R^1 results in a marked decrease in antimicrobial activity (compound **63**).

4. In another series the indanone moiety was replaced by the tetralone or acetophenone systems. Generally these modifications diminish the antitrichomonal activity *in vitro* and nearly eliminate the antibacterial activity as can be seen by comparison of compounds **47**, **52**, and **56** with compounds **64**–**66** and **67**–**69**. This is in marked contrast to the low antitrichomonal ED_{50} values of the tetralone derivatives **64** (5.18 mg/kg, compared with 25.2 mg/kg of **47**) and **66** (3.19 mg/kg, compared with 25.7 mg/kg of **56**). These findings correspond to previous observations in the series of 2-(5-nitro-2-imidazolylmethylene)-1-indanones and -tetralones[3,9] which show some tetralone derivatives superior *in vivo*, whereas the corresponding indanone derivatives display much better *in vitro* activity.

Experimental Section

General. Where analytical results are indicated only by symbols of the elements, values for those elements were within ±0.4% of the calculated values. The salts **47**–**68** compiled in Table II do not always contain accurately stoichiometric amounts of H_2SO_4; therefore the S values for all these compounds are given in the table. Melting points are uncorrected and taken on a Tottoli melting point apparatus (W. Büchi, Switzerland).

Substituted Alkoxy-1-indanones, -1-tetralones, and -acetophenones (10–37, Table I). Method A_1. 5-Hydroxy-1-indanone (**5**, 0.1 mol) was dissolved in a solution of sodium (0.1 mol) in 130 ml of ethanol. 2-Bromoethanol (0.2 mol) and KI (1 g) were added, and the mixture was refluxed for 72 hr. After removal of EtOH *in vacuo*, the residue was triturated with H_2O (2.2 l.) and the product (**10**) was collected.

Method A_2. A mixture of 7-hydroxy-1-indanone (**7**, 0.1 mol), K_2CO_3 (38 g), and 2-bromoethanol (0.2 mol) was stirred at 100° for 4 hr under a nitrogen atmosphere. After removal of excess 2-bromoethanol a saturated NaCl solution was added and the product was extracted with EtOAc. The organic layer was concentrated *in vacuo* and the residue was dissolved in $CHCl_3$. For separation of starting material, this solution was stirred for 3 hr with 10 *N* NaOH. The organic layer again was concentrated *in vacuo* and the residue was recrystallized from MeOH–H_2O (1:1) to yield **11**.

Method B_1. A pyridine (200 ml) solution of 5-(2-hydroxyethoxy)-1-indanone (**10**, 0.1 mol) and tosyl chloride (0.11 mol) was stirred at room temperature for 3 hr. The solution was poured onto ice–H_2O and the solid (**14**) collected.

Method B_2. A pyridine (300 ml) solution of 7-(2-hydroxyethoxy)-1-indanone (**11**, 0.1 mol) and mesyl chloride (0.13 mol) was stirred at room temperature for 20 hr. After pouring onto ice–H_2O the mixture was acidified with 5 *N* HCl and the solid (**15**) was collected.

Method C_1. A mixture of 5-(2-tosyloxyethoxy)-1-indanone (**14**, 10 mol) and diisopropylamine (80 mmol) was refluxed for 4 days. After removal of excess amine *in vacuo*, the residue was partitioned between 0.5 *N* NaOH (150 ml) and EtOAc and the organic layer was extracted with 5 *N* HCl. The acidic aqueous solution was made alkaline with 5 *N* NaOH and the product was again extracted into EtOAc. After removal of the organic solvent, methanolic HCl was added to the residue and the mixture concentrated to dryness. The crude product (**20**) was used for the next step.

Method C_2. A solution of 5-(2-tosyloxyethoxy)-1-indanone (**14**, 10 mmol) and diallylamine (40 mmol) in EtOH (100 ml) was refluxed under a nitrogen atmosphere for 5 hr. After removal of the solvent the residue was partitioned between 1 *N* NaOH (100 ml) and EtOAc. The organic layer was concentrated to dryness and the residue was dissolved in ether. Addition of ethereal HCl yielded the product (**21**).

Method D. A benzene (90 ml) solution of 2-dimethylaminoethyl chloride (0.14 mol, freshly prepared from its hydrochloride in the usual manner) was added to a solution of 5-hydroxy-1-indanone (**5**, 0.1 mol), NaOEt (0.1 mol), and KI (0.1 g) in 100 ml of EtOH. The mixture was refluxed for 20 hr. After removal of the solvent *in vacuo* and addition of brine, the product was extracted into EtOAc. Concentration of the organic layer *in vacuo* to dryness and addition of ethereal HCl yielded the hydrochloride **18**.

Substituted Alkoxy-2-(5-nitro-2-imidazolylmethylene)-1-indanones, -1-tetralones, and -acetophenones (41–69, Table II). Method E_1. A mixture of 1-methyl-5-nitroimidazole-2-carbaldehyde (**38**, 10 mmol), 5-(2-dimethylaminoethoxy)-1-indanone hydrochloride (**18**, 10 mmol), H_2SO_4 (11 mmol), and 10 ml of AcOH was stirred at 100° for 6 hr. After cooling to room temperature the precipitate (**47**) was filtered off and washed with MeOH.

Method E_2. 1-Methyl-5-nitroimidazole-2-carbaldehyde (**38**, 10 mmol) and 6-(2-dimethylaminoethoxy)-1-tetralone hydrochloride (**33**, 10 mmol) were treated as described in method E_1. The reaction mixture was concentrated *in vacuo* and the residue was triturated with MeOH–*i*-PrOH. Filtration and washing with MeOH yielded the product (**64**).

Method F. A suspension of 5-(2-acetoxyethoxy)-2-(5-nitro-1-methyl-2-imidazolylmethylene)-1-indanone (**41**) in EtOH (80 ml) and concentrated HCl (40 ml) was refluxed for 2 hr. After cooling the precipitate (**44**) was isolated by filtration.

Method G. 4′-(2-Hydroxyethoxy)-2-(1-methyl-5-nitro-2-imidazolylmethylene)acetophenone hydrochloride (**46**, 10 mmol) was triturated with a 20% solution of $NaHCO_3$ in H_2O and the product was filtered off and dried. It was suspended in pyridine (40 ml) and 20 mmol of tosyl chloride was added. The mixture was stirred at room temperature for 4 hr and subsequently poured onto ice–H_2O (400 ml) to yield 4 g (85%) of 2-(1-methyl-5-nitro-2-imidazolylmethylene)-4′-(2-tosyloxyethoxy)acetophenone, mp 146° (*i*-PrOH). *Anal.* ($C_{22}H_{21}N_3O_7S$) N, S.

A solution of this compound (10 mmol) and 40 mmol of morpholine in EtOH (35 ml) was refluxed for 4 hr. After concentration *in vacuo* 100 ml of H_2O and 16 ml of 2 *N* NaOH were added and the mixture was extracted with EtOAc. Removal of the solvent and trituration with methanolic HCl yielded compound **69**.

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